Protocol
Informed Consent Form
Statistical Analysis Plan
for
NCT03842995

South-seq: Deoxyribonucleic Acid (DNA) Sequencing for Newborn Nurseries in the South

Manual of Operations and Procedures (MOOP) for DNA Sequencing for Newborn Nurseries in the South (SouthSeq)

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
3.c.4	Probands who met inclusion/exclusion criteria but passed away prior to sample collection can be included	Expands the pool of eligible probands
3.b	Update staff roster, organization, and responsibilities	Staff have been added and removed from the project
Appendix 3	Updated site consents	Modified genomic data sharing section
Appendix 7	Amended enrollment, ROR (in-person) and (at-home)	Amended to become more sensitive to families of deceased probands

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Abbreviations

ACMG	American College of Medical Genetics and Genomics
CAP/CLIA	College of American Pathologists/Clinical Laboratory Improvement Amendment
COA	Children's of Alabama
CSER2	Phase II of the Clinical Sequencing Evidence-Generating Research
DCC	Data Coordinating Center
DSMB	Data Safety Monitoring Board
EMR	Electronic Medical Record
FACToR	The Feelings About genomic Testing Results
FAQ	Frequently Asked Questions
FTP	File Transfer Protocol
GC	Genetic Counselor
GCOS	Genetic Counseling Outcome Scale
GCP	Good Clinical Practice
GG	Genome Gateway
HA	HudsonAlpha
HRQoL	Health-Related Quality of Life
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IRB	Institutional Review Board
IUGR	(Symmetric) Intrauterine Growth Restriction
IVH	Intraventricular Hemorrhage
MOOP	Manual of Operating Procedures
NEC	Necrotizing Enterocolitis
NGHRI	National Human Genome Research Institute
NICU	Neonatal Intensive Care Unit
NIH	National Institutes of Health
NOA	Notice of Award
PHI	Protected Health Information
PI	Principle Investigator
PII	Personally Identifiable Information
ROP	Retinopathy of Prematurity
ROR	Return of Results
SOP	Standard Operating Procedures
UAB	University of Alabama at Birmingham
UMMC	University of Mississippi, Medical Center
VRC	Variant Review Committee
WIRB	Western Institutional Review Board
WGS	Whole Genome Sequencing

1. INTRODUCTION

The National Human Genome Research Institute (NHGRI), National Institutes of Health (NIH) must ensure compliance with federal laws and regulations, including procedures and policies to protect the safety of all participants in the clinical studies it supports. In preparing to implement a study, the Principal Investigators (PI) must be aware of the terms of award outlined in their Notice of Award (NOA) with respect to required reporting, data and safety monitoring oversight, and Institutional Review Board (IRB) approval.

The role of the manual of operating procedures (MOOP) is to facilitate consistency in the SouthSeq study implementation and data collection across study visits and participants. Use of the MOOP increases the likelihood that the results of the study will be scientifically credible and provides reassurance that participant safety and scientific integrity are closely monitored.

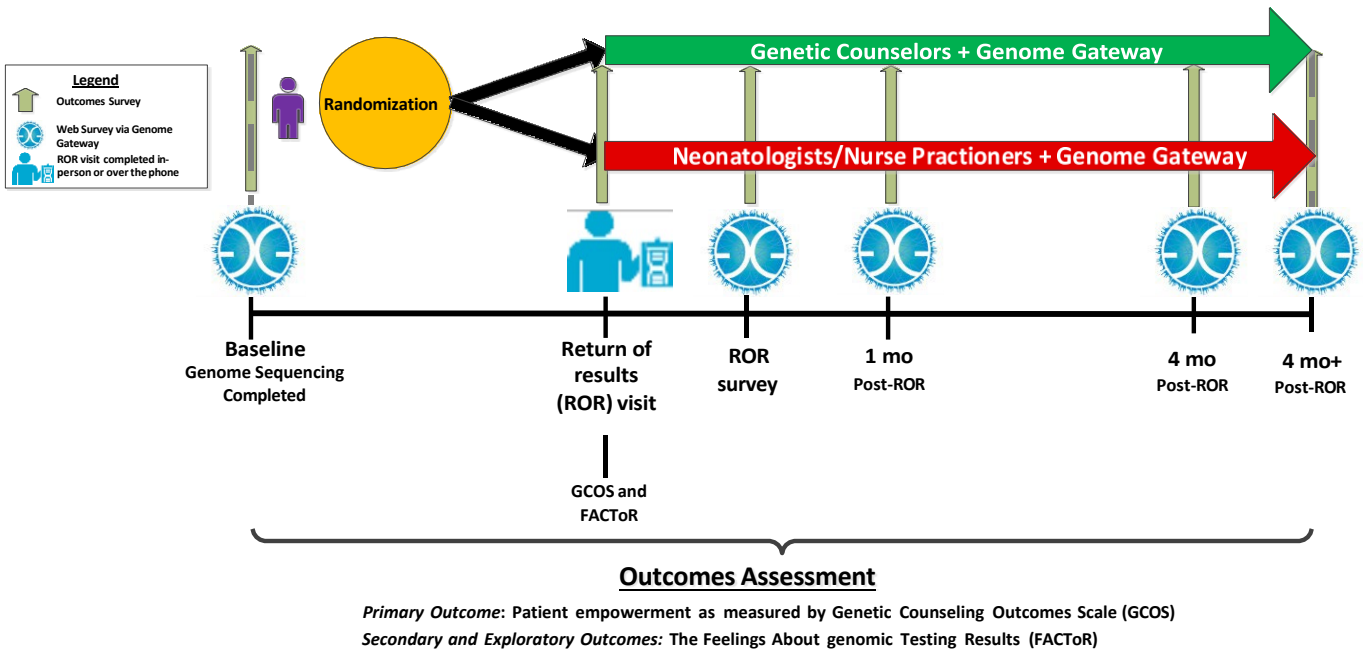
2. OVERVIEW

The University of Alabama at Birmingham (UAB), in partnership with HudsonAlpha (HA) Institute for Biotechnology, will serve as the Clinical Coordinating Center and the Data Coordinating Center for SouthSeq. The SouthSeq MOOP should serve as the study manual to help study staff in executing study procedures. This MOOP (and its appendices) include the protocol, survey forms, and site-specific Informed Consent Forms (ICFs). The SouthSeq MOOP is a dynamic document that will be updated throughout the study to reflect any protocol or ICFs amendments, as well as the refinement of the study forms and procedures. Any edits or changes to the MOOP will be noted in track changes with an updated version number and date; electronic copies will be sent via email to site research nurse/coordinators and archived on Freedcamp (freedcamp.com).

3. MOOP CONTENTS AND ORGANIZATION

3.a Study Flow Diagram

Figure 1. Participant Level Timeline



3.b Staff Roster, Organization and Responsibilities

Table 1. Study Roster

Name	Role	Address	Phone #	Email
HudsonAlpha				
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University of Alabama at Birmingham/ Children's of Alabama				
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Ashley Moellinger, MSN, CPNP-AC	CV Pediatric nurse practitioner, nurse in the CVICU	Children's of Alabama	205-638-3450	Ashley.Moellinger@childrensal.org
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* Will be point of contact regarding results for site genetic counselors (GCs)/ neonatal intensive care unit (NICU) staff, study coordinator, reviewing variants, writing letters, uploading letters, assigning learning, and reviewing records

[#] Point of contact for any study related questions

3.b.1 Organization

In this multi-site clinical trial, sites will be supervised by HudsonAlpha and by the site PI at each respective site (UAB, the University of Mississippi Medical Center [UMMC], Woman's Hospital (Baton Rouge), and Children's Hospital of New Orleans) according to the established monitoring standard operating procedures (SOPs). HA, in collaboration with the Clinical Trials Team at UAB, will oversee the clinical trial to assure satisfactory data recording, adherence to the study protocol, and Good Clinical Practice (GCP), as well as monitor recruitment utilizing reports generated by the physician/team leaders at each site. The staff listed in the study roster will be responsible for all aspects of the clinical trial. This includes but is not limited to the following:

- Finalizing the study protocol and protocol modifications
- Development of the Manual of Operating Procedures (MOOP) and its maintenance
- Participant randomization
- Development and implementation of the data flow and data tracking
- Development of procedures for data entry, error identification, and error correction
- Quality control procedures
- Submitting for Internal Review Board (IRB) review and approval

- Creating reports - enrollment, participant status (e.g., withdrawals)
- Maintaining the study binder (regulatory and clinical documents)
    - ICF and W9 form will be uploaded to genome gateway and hardcopies will be stored in the hardcopy study binder
    - All other forms can be maintained within the electronic study binder or on Genome Gateway
- Preparation of all study materials: recruitment materials, tracking documents, official reports
- Identifying, recruiting, screening, and enrolling participants
- Obtaining ICF from each participant
- Protecting participants' rights
- Collecting study data and following participants through study completion
- Compliance and accountability with the administration of the study intervention
- Communicating questions, concerns, and/or observations to the PIs

All of the above activities will be carried out by the SouthSeq team on a weekly basis, or more frequently as needed, and will be monitored by the PIs and co-investigators. In the event a problem is identified by either study site PI or staff, a teleconference/webinar will be scheduled to review the issue. These teleconferences/webinars will be organized by Candice Finnila, PhD, SouthSeq Clinical Project Manager, and specific staff as designated by Dr. Finnila. Organized teleconferences/webinars will include discussions of overall recruitment status and identified barriers to recruitment experienced by the site with the study teams at HA and UAB. If the site study team members are unable to participate on the teleconference call, information about recruitment barriers and recruitment status can be shared via email in advance of the clinical trials team weekly meeting.

The study will be conducted under the auspices of the IRBs at UAB, UMMC, Woman's Hospital (Baton Rouge), and Children's Hospital of New Orleans. UAB's IRB will serve as the main reviewer in accordance with the reliance agreements. Before initiating the clinical trial within the SouthSeq study, the site PI will have written and dated full approval from the responsible IRB for the protocol. In the event changes/amendments to the protocol or other study materials (e.g. participant-related documents, study advertisements) are made, approved amendments will be submitted to the respective sites, as notification of changes. The UAB IRB has approved Genome Gateway as the electronic data entry system.

Site investigators will also promptly report to Dr. Finnila all protocol deviations in the study, all unanticipated problems involving risks to human subjects or others, and any protocol deviations, to eliminate immediate hazards to subjects. The UAB IRB will be promptly notified when necessary.

(1) HudsonAlpha (HA) Institute for Biotechnology

The HudsonAlpha Institute for Biotechnology is a non-profit research institute located in Huntsville, AL. As part of the SouthSeq project, HudsonAlpha is responsible for intake of participant samples, with follow through to development of a College of American Pathologists/Clinical Laboratory Improvement Amendment (CAP/CLIA)-certified genetic Sanger report and a family-friendly report (see appendix 1) created by the genetic counselors (GC) at HudsonAlpha that will be returned to the proband's (neonate being sequenced) family. More specifically, HudsonAlpha is charged with the handling and processing of proband samples, isolating genomic DNA, preparing sequencing libraries, conducting whole genome sequencing (WGS), completing genomic data analysis, curating and annotating identified genetic variation, interpreting genetic variants, sending variants for validation in a CAP/CLIA-certified independent laboratory, overseeing and leading variant review committee (VRC) meetings, and writing genetic counseling letters that will accompany delivery of technical Sanger reports to participant families.

Genome Gateway

Genome Gateway, a web interface developed by HudsonAlpha, will be used to facilitate communication, education and the sharing of information between the study staff and study participants. Genome Gateway provides a simple user interface that is intuitive and easy to navigate for participants, healthcare providers, and researchers. It is hosted on a HIPAA-compliant platform with a secure, unique login system, physical and data security, and disaster recovery and backup.

Genome Gateway was initially created to provide support to patients and healthcare providers during clinical appointments, including a dynamic family history tool that creates a pedigree, tailored learning articles (modules) assignable per individual, secure messaging and customized questionnaire deployment. Current account types are listed below:

- Admin Account: An administrative account for the user(s) who require global access to the website, including access to a back-end console website used for management of functions within the user-facing site. This account provides the highest level of permissions and is restricted to a small number of users, who are responsible for addition of website content and management of the data and workflow within Genome Gateway.

- Patient Account: An account for study participants (or parents in the case of SouthSeq). This account gives access to their personal settings and demographic information, allows entry of family history information, completion of surveys, and access to learning modules. For SouthSeq, participants can also access files and messages sent to them by study staff. Patients can also reply to messages.

- Provider Account: An account for study personnel who interact with the patients as providers. This can include neonatologists, nurse practitioners, clinical geneticists, research study coordinators, research nurses, and GCs. Providers can access participant profiles (including personally identifiable information [PII]/ patient health information [PHI]), complete surveys regarding participants ("administered surveys"), and send messages and files to participants and other research staff. Providers also have access to learning modules.

- Researcher Account: An account for study personnel who need access to de-identified data for research purposes, but who do not interact directly with participants. Researchers can access completed administered surveys, but only in a de-identified manner. Researchers can also send/receive messages to/from other study personnel.

Whole Genome Sequencing (WGS)

At least 1 mL of blood will be drawn from each newborn participant into a 4mL EDTA tube (blood collection method and location of venipuncture will be left up to the clinical staff, but should be combined with routine care if possible). Blood will be shipped as soon as possible following study enrollment/specimen collection. Blood tubes that are not shipped day of venipuncture will be stored at 4^{o}C until shipment. If the newborn has had a blood transfusion, they can still be enrolled and a blood sample can still be collected. Isolation of genomic DNA from whole blood will be performed in the HudsonAlpha Clinical Services Laboratory (CSL) using the QIA symphony instrument (Qiagen). Sequencing libraries will be constructed from genomic DNA using the CSL's custom whole genome library preparation protocol. Sequencing will be completed on the Illumina HiSeq X or NovaSeq sequencing platform. DNA library fragments will be sequenced from both ends (paired) with a read length of 150 base pairs. WGS will be completed to an approximate depth of 30X, with

requirement that at least 80% of base positions reach 20X coverage. Genetic variation will be called using GATK3 (Broad Institute) and variants will be loaded into a custom software analysis application (Codicem, HudsonAlpha) which will annotate variants with relevant information in order to aid in variant curation and interpretation. Variant classification will be determined according to the guidelines set forth by the American College of Medical Genetics and Genomics (Richards *et. al.*, 2015, PMID: 25741868). Variants that are classified as pathogenic, likely pathogenic, or of uncertain significance will be included in a research report and PerkinElmer, EGL-Eurofins, or HudsonAlpha CSL will perform Sanger confirmation, where validation will take approximately 28 days. Variants of interest to the analysts will be discussed by the Variant Review Committee (consisting of neonatologists, medical geneticists, nurse coordinators, GCs, research scientists, ethicists, etc.) to determine whether they should be returned. Variants deemed to be returnable to participants will be written into a genetic counseling report generated by GCs at HudsonAlpha, which, along with the CAP/CLIA-certified Sanger validation report, if available, will be returned to the participant family by a GC or healthcare provider, and placed in the proband's medical record.

(2) University of Alabama at Birmingham (UAB) Women & Infants Center and Children's of Alabama (COA)

Located in the largest metropolitan region in Alabama, UAB Women & Infants Center has a 120 bed level IV NICU with ~1,500 admissions per year and is physically connected to Children's of Alabama (COA), which has a 40 bed NICU and a 20 bed cardiovascular ICU, with ~400 admissions per year. The Division of Neonatology is directed by Dr. Wally Carlo (UAB Site PI), and includes 15 attending neonatologists. The NICU is also the site of an active medical genetics consultation service including Dr. Anna Hurst. A chart review of 2017 UAB admissions indicated that 47% were African American and 8% were Hispanic.

(i) Responsibilities

- Identify potential participants in the nursery or inpatient setting using the inclusion/exclusion criteria outlined in the study protocol
- Obtain consent from interested participants
- Collect W9 from parents/caregivers, so they may be paid for their participation in the clinical trial
- Collect blood specimens from the enrolled proband and parents, if available
- Assistance in creation and set-up of Genome Gateway account for the parents/caregivers
- Direct participant (parent or caregiver) to complete baseline survey and family history questionnaire/pedigree via Genome Gateway
    - The research nurse will complete assigned surveys in Genome Gateway. These surveys are focused on clinical phenotypes, previous genetic testing, prenatal testing (if known) and the enrollment process.
- May call parents/caregivers when surveys are not completed within specific time frames.
- Ship samples to the HudsonAlpha Clinical Services Laboratory and submit them for sequencing via online portal
- Schedule participant family for a return of results (ROR) appointment with a genetic counselor/healthcare provider based on randomization assignment. Coordinate the ROR appointment day logistics including space, personnel, audio recording, and asking families to complete initial follow-up survey in Genome Gateway
    - If travel to the site is an issue, a phone call may be scheduled to return genetic results (though this is not the preferred method)
- Place the clinical Sanger report, along with the family-friendly genetic counseling letter in the child's medical record so that clinicians have access to the finding(s)

(3) Clinical Trials Group at UAB

The clinical trials group is one of the most active academic clinical investigational programs at the UAB. The group has played a pivotal role in the advancement of healthcare, patient care, and access to treatments.

(i) Responsibilities

- Development of clinical trial's objectives, design, and methods
- Oversight of the scientific and technical direction of the trial
- Submit and process W9's for payment from parents/caregivers at all participating sites
- Track survey completion and payments
- Ensure compliance with GCP principles, quality management, and oversee monitoring systems
- Ensure protocol compliance

(4) University of Mississippi Medical Center (UMMC)

The UMMC, located in Jackson, MS provides tertiary care for the entire state, with a 102 bed level IV NICU and ~950 admissions per year. The Division of Neonatology and Newborn Medicine is directed by Dr. Renate Savich (UMMC site PI) and includes 14 neonatologists. Dr. Brian Kirmse is Chief, Division of Pediatric Genetics. A unique population is the Mississippi Band of Choctaw, a group of ~10,000 individuals that mostly reside in the central portion of Mississippi, and who are disproportionately affected by both chronic disease and congenital anomalies. The demographics of NICU population at this site include 41% African American, 3% Choctaw, and 3% Hispanic patients.

(i) Responsibilities

- Identify potential participants in the nursery or inpatient setting using the inclusion/exclusion criteria outlined in the study protocol
- Obtain consent from interested participants
- Collect W9 from parents/caregivers, so they may be paid for their participation in the clinical trial
- Collect blood specimens from the enrolled proband and parents, if available
- Assistance in creation and set-up of Genome Gateway account for the parents/caregivers
- Direct participant (parent or caregiver) to complete baseline survey and family history questionnaire/pedigree via Genome Gateway
    - Research nurse will complete assigned surveys in Genome Gateway. These surveys are focused on clinical phenotypes, previous genetic testing, prenatal testing (if known) and the enrollment process.
- May call parents/caregivers when surveys are not completed within specific time frames.
- Ship samples to the HudsonAlpha Clinical Services Laboratory and submit them for sequencing via online portal
- Schedule participant family for a return of results (ROR) appointment with a genetic counselor/healthcare provider based on randomization assignment. Coordinate ROR appointment day logistics including space, personnel, audio recording, and asking families to complete the baseline surveys in Genome Gateway
    - If travel is an issue, a phone call may be scheduled to return genetic results (though this is not the preferred method)
- Place the clinical Sanger report along with the family-friendly genetic counseling letter in the child's medical record so that clinicians will have access to the finding(s)

(5) Woman's Hospital (Baton Rouge)

Located in Baton Rouge, LA Woman's Hospital has an 84 bed Level IIIc NICU with ~1100 admissions per year. The Division of Neonatology is directed by Dr. Steve Spedale (Woman's Hospital Site PI), and includes 10 attending neonatologists and

11 neonatal nurse practitioners. The Genetics consultation service is directed by Dr. Duane Superneau and there is a full-time in-house GC, Hillary Wienpahl. The demographics of the NICU population at this site include 43% African American and 3% Hispanic infants.

(i) Responsibilities

- Identify potential participants in the nursery or inpatient setting using the inclusion/exclusion criteria outlined in the study protocol
- Obtain consent from interested participants
- Collect W9 from parents/caregivers, so they may be paid for their participation in the clinical trial
- Collect blood specimens from the enrolled proband and parents, if available
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    - If travel is an issue, a phone call may be scheduled to return genetic results (though this is not the preferred method)
- Place the clinical Sanger report along with the family-friendly genetic counseling letter in the child's medical record so that clinicians will have access to the finding(s)

(6) Children's Hospital of New Orleans

Children's Hospital, located in New Orleans, LA, has a 36 bed level IV NICU with ~200 admissions per year, and has a 20 bed cardiovascular ICU, with ~65 admissions per year. The Division of Neonatology is directed by Dr. Brian Barkemeyer (Site PI), and includes 8 attending neonatologists through an affiliation with Louisiana State University Health Sciences Center – New Orleans with plans to hire 2 more neonatologists by July 2019. Through this partnership, Children's Hospital trains the largest group of future neonatologists and pediatricians in Louisiana. The demographics of the NICU population at this site include 37% African American and 12% Hispanic infants.

(i) Responsibilities

- Identify potential participants in the nursery or inpatient setting using the inclusion/exclusion criteria outlined in the study protocol
- Obtain consent from interested participants
- Collect W9 from parents/caregivers, so they may be paid for their participation in the clinical trial
- Collect blood specimens from the enrolled proband and parents, if available
- Assistance in creation and set-up of Genome Gateway account for the parents/caregivers
- Direct participant (parent or caregiver) to complete baseline survey and family history questionnaire/pedigree via Genome Gateway

    - Research nurse will complete assigned surveys in Genome Gateway. These surveys are focused on clinical phenotypes, previous genetic testing, prenatal testing (if known) and the enrollment process.
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    - If travel is an issue, a phone call may be scheduled to return genetic results (though this is not the preferred method)
- Place the clinical Sanger report along with the family-friendly genetic counseling letter in the child's medical record so that clinicians will have access to the finding(s)

(7) University of Louisville & Norton Children's Hospital

Norton Children's Hospital, located in Louisville, KY provides tertiary care for much of Kentucky and Southern Indiana. NCH features a 101 bed level IV NICU that covers over 1100 admissions per year. The NICU is staffed by two neonatology groups. The University of Louisville, Division of Neonatology with its 24 neonatologists staffs the NICU at NCH, a Neonatal Follow-up Program, and several other NICUs in the region. Norton Children's Neonatology with 14 neonatologists staffs the NICU at NCH, a High Risk Neonatology Follow-up Clinic, and several other NICUs in the region. The demographics of the NICU population at NCH includes 19% African American and 4% Hispanic patients. A second NICU at the University of Louisville Hospital offers a secondary recruitment site if needed.

(i) Responsibilities

- Identify potential participants in the nursery or inpatient setting using the inclusion/exclusion criteria outlined in the study protocol
- Obtain consent from interested participants
- Collect W9 from parents/caregivers, so they may be paid for their participation in the clinical trial
- Collect blood specimens from the enrolled proband and parents, if available
- Assistance in creation and set-up of Genome Gateway account for the parents/caregivers
- Direct participant (parent or caregiver) to complete baseline survey and family history questionnaire/pedigree via Genome Gateway
    - Research nurse will complete assigned surveys in Genome Gateway. These surveys are focused on clinical phenotypes, previous genetic testing, prenatal testing (if known) and the enrollment process.
- May call parents/caregivers when surveys are not completed within specific time frames.
- Ship samples to the HudsonAlpha Clinical Services Laboratory and submit them for sequencing via online portal
- Schedule participant family for a return of results (ROR) appointment with a genetic counselor/healthcare provider based on randomization assignment. Coordinate ROR appointment day logistics including space, personnel, audio recording, and asking families to complete the baseline surveys in Genome Gateway
    - If travel is an issue, a phone call may be scheduled to return genetic results (though this is not the preferred method)
- Place the clinical Sanger report along with the family-friendly genetic counseling letter in the child's medical record so that clinicians will have access to the finding(s)

3.c Communication Plan

As this protocol is currently being carried out at multiple sites (HudsonAlpha, UAB, UMMC, Woman's Hospital (Baton Rouge), and Children's Hospital of New Orleans it is strongly recommended that each site meets as a group to at a minimum biweekly to discuss the ongoing progress of the study.

Topics of discussion at each meeting may include:

- Recruitment progress
- Enrollment and ROR progress/status
- Issues or concerns with the study and possible solutions (e.g., Genome Gateway concerns)
- Other study updates

Additionally, the clinical project manager (Dr. Candice Finnila) will keep the overall study and clinical trial investigators informed of the weekly progress of the study work group meetings via email updates that include the following information:

- Screening log (maintained by each site's research nurse/coordinator and compiled by Dr. Finnila)
- Consort diagram detailing number of participants enrolled (updated via Freedcamp website twice/month)
    - Including demographics and enrollment site
    - Update on the study findings to be returned (overall diagnostic rate and number of primary and secondary findings)
- Other study updates
- Review status of data collection, including pending surveys, timeliness of the data, completeness of data, and data elements requiring possible adjudication, verification, or further explanation.

In addition, meetings will be conducted within and among various study working groups and personnel to discuss the on-going progress of the study, as well as any urgent topics. Specifically:

- PI Meeting: These meetings will occur as needed and attendees include Drs. Bruce Korf, Greg Cooper, Greg Barsh, Candice Finnila and Kevin Bowling. This group will meet to discuss items required by the funding group and other high-level items that might impact the study.
- SouthSeq Leadership: attendees include Drs. Bruce Korf, Greg Cooper, Greg Barsh, Maria Danila, Kevin Bowling, and Candice Finnila. This group meets weekly to discuss topics that require high-level decisions and involve direction of the study and clinical trial.
- SouthSeq Operations: attendees include PIs, research nurses, GCs, and representation from the clinical trial team from UAB and analysis group from HudsonAlpha. These meetings will be held ad hoc for the duration of project. The purpose of the call is to discuss any topics that may impact multiple study sites and troubleshoot potential resolutions.
- Clinical Trials: attendees include Dr. Maria Danila, Dr. Elizabeth Rahn, Dr. Candice Finnila, Kelly East, Dr. Kyle Brothers, Dr. Sara Knight, Jeff Foster, Dr. Renate Savich, Dr. David Redden, Josh Melnick, weekly for duration of project for the purpose of discussing the clinical trial portion of the study. Site research nurses/coordinators may request call-in information if they would like to attend.
- GC Virtual Huddle: attendees include all HudsonAlpha GCs and site-specific GCs, bi-weekly for duration of project, purpose of the call is to discuss the progress of returning results, challenging cases, and trouble-shoot any genetic counseling issues that arise.

- Qualitative: attendees include Dr. Sara Knight, Dr. Kyle Brothers, Carla Rich, Dr. Maria Danila, Dr. Elizabeth Rahn, Dr. Candice Finnila, Kelly East, Whitley Kelley, Dr. Renate Savich, Dr. Ashley Cannon, and Jaimie Richards weekly for the duration of project, purpose of the call is to discuss qualitative dimensions of the study including key informant interviews, semi-structured interviews with parents, cognitive interviews, and deliberative engagement events.
- Education and Training: attendees include Kelly East, Dr. Elizabeth Rahn, Dr. Sara Knight and Dr. Maria Danila, bi-weekly until patient education and provider training materials are finalized (then this call will transition to an as-needed basis), purpose of the call is to discuss the progress of the development and testing of patient/provider education and training materials.
- Variant Review Committee (VRC): attendees include medical geneticists, neonatologists, other clinical specialists, nurses, GCs, ethicists, research scientists, and PIs (Drs. Korf, Cooper, and Barsh). These meetings will most likely be held on a weekly basis, depending on the number of reports requiring discussion, and will be site specific. At these meetings genetic variations will be discussed in the context of clinical phenotype, and variant sign-off will occur. It is at a VRC meeting where decisions will be made as to what variants are returned to participant families, and to what extent it is believed that the genetic findings describe the participant's phenotype.

3.c.1 Participant Recruitment

The goal of SouthSeq study is to recruit and enroll 1,500 newborns (probands) with signs suggestive of a genetic disorder being treated at hospitals in which African Americans and rural populations are highly represented. The SouthSeq clinical trial will recruit and enroll parents or caregivers from 800 newborns enrolled in the parent SouthSeq study. Recruitment will draw from the five major pediatric institutions (UAB/Children's of Alabama, UMMC, Woman's Hospital (Baton Rouge), Children's Hospital of New Orleans, and the University of Louisville/Norton's Children Hospital. A central goal of this project is to expand the access of genomic medicine to underrepresented minorities and/or medically underserved communities, which feature prominently in the South.

Families with newborns will be recruited, in addition to families with stillborn babies, directly from the four pediatric sites meeting the study eligibility criteria. Families can be approached perinatally and can consent to participate prior to birth. The inclusion and exclusion criteria will be reviewed with potential participants and the informed consent will be obtained by the site study coordinator. Study procedures will not begin until the signed informed consent forms have been obtained. Consent must be obtained from any parent/caregiver who thinks they might ever participate in the clinical trial.

Study primary investigators will meet as part of a monthly operations meeting to discuss topics relevant across all recruitment sites. In the event a problem is identified by either study site PI or staff, a teleconference/webinar or a direct conversation with a PI or coordinator will be scheduled to review the issue.

In addition to the robust set of learning available within Genome Gateway, a one-page flyer has been created to provide a high-level overview of the study (see Appendix 5), and will be used for participant recruitment and to help build awareness for the study. Basic information about the study will also be housed on the public facing website: hudsonalpha.org/southseq.

3.c.2 Proband Eligibility Criteria

Inclusion Criteria:

An infant receiving care in the nursery or other inpatient setting, e.g. surgical and/or cardiac intensive care unit during their first hospital admission or first 12 months of life, AND meeting one of the following criteria:

a) A pattern of congenital anomalies consistent with a genetic, i.e, syndromic cause, and for which the primary care team does not know of an obvious etiology. "Obvious etiology" refers to a genetic, infectious, or environmental cause that has been or can be rapidly confirmed by history and/or laboratory testing, e.g. Trisomy 21, TORCH infection, fetal hydantoin exposure.
b) A major medical condition such as seizures, neurological abnormality (hypotonia, hypertonia), metabolic abnormality, or conjugated hyperbilirubinemia for which the primary care team does not know of an obvious etiology. As noted above, "obvious etiology" refers to a genetic, infectious, or environmental cause that has been or can be rapidly confirmed by history and/or laboratory testing, e.g. intraventricular hemorrhage associated with significant prematurity, seizures associated with an inborn error of metabolism for which a molecular diagnosis can be confirmed.
c) Parent or caregiver must be willing to participate and answer clinical trial surveys

Exclusion Criteria:

a) A pattern of findings and/or abnormalities consistent with known or strong suspicion for a chromosomal aneuploidy (Ts13, 18, 21, Monosomy X).
b) Isolated anomalies known to have a low diagnostic yield for Mendelian causes, e.g. gastroschisis, hydronephrosis.
c) A pattern of findings and/or abnormalities consistent with confirmed teratogenic exposures, e.g. hydantoin, valproate.
d) A pattern of findings and/or abnormalities consistent with confirmed congenital infection, e.g. TORCH.
e) Parent or caregiver is not available or willing to participate and answer clinical trial surveys**

**Families who choose not to participate in the clinical trial (randomization and surveys) can still be enrolled in the study (WGS and ROR). This option will not be advertised, but if someone specifically asks if the surveys are required, it is acceptable to say no.

Notes:

1. Patients with suspected Down syndrome or life-threatening whole chromosome aneuploidies in which acute clinical care depends on a diagnosis, e.g. Ts13 or Ts18, will not be enrolled, but patients with congenital anomalies for which a clinical chromosomal microarray would otherwise be obtained may be enrolled.
2. Patients with a history of potential teratogenic exposures or congenital infection may be eligible for inclusion if there are congenital anomalies and/or conditions that are not explained by the potential teratogen or infection. In this situation, one of the study investigators should be consulted.
3. "Pattern of findings and/or abnormalities" refers to established principles for medical genetics, in which general guidelines are "2 or major congenital anomalies", "1 major and 2 or more minor anomalies", "1 major anomaly and an unexplained major medical condition", or "1 major anomaly and a first degree relative with the same anomaly", with examples (not intended to be exhaustive) indicated below.

Major	**Minor**	**Medical Conditions**
Structural malformations likely to require surgical intervention or be of significant functional effect	*Physical variants that are a departure from normal development but only have a cosmetic effect*	*Medical conditions not explained by prematurity (such as NEC, ROP, IVH)*

Structural brain malformations (holoprosencephaly, schizencephaly)	Abnormal hair whorls (position or number -- absent, triple, multiple)	Seizures
Cleft lip and palate	Abnormal fontanelles (third sagittal, metopic)	Cataracts
Severe micrognathia	Preauricular pits or tags	Unexplained Hypoglycemia
Macroglossia	Atypical ear formation or placement (microtia, cupped, crumpled, low-set)	Conjugated (direct) hyperbilirubinemia
Structural heart defect	Epicanthal folds	Hearing Loss (confirmed)
Congenital diaphragmatic hernia	Cleft/bifid uvula	Ichthyosis
Structural renal anomaly	Neck webbing	Hypotonia
Coloboma – iris or retina	Supernumerary nipple	Myopathy
Tracheoesophageal fistula	Sacral dimple	Arthrogryposis
Symmetric IUGR	Syndactyly	Hepatic dysfunction
Anotia	Single transverse palmar crease	Apnea (central or obstructive)
Omphalocele	Clinodactyly	
Vertebral anomalies	Hypospadias	
Limb deficiency or shortening	Abnormal pigmentation	
Ambiguous genitalia	Dysmorphic findings not otherwise mentioned	
Biliary atresia		
Imperforate anus		
Heterotaxy		

3.c.3 Screening Log

The primary intent for completing a screening log (see appendix 11) is to report trial results and to assess the generalizability of findings. It is important to maintain consistency and accuracy when completing the log. Each potential participant will be assigned a screening ID:

- UAB Screening IDs: 10001 through 10999
- UMMC Screening IDs: 20001 through 20999
- Woman's Hospital (Baton Rouge) Screening IDs: 30001 through 30999
- Children's Hospital of New Orleans Screening IDs: 40001 through 40999
- University of Louisville Screening IDs: 50001 through 50999

It is important to complete all fields and if the proband's parents/caregivers don't participate it is important to complete a decliner survey (see appendix 2). **The decliner survey can be completed post-encounter by a research nurse /coordinator using their judgment to determine the reason(s) for not participating.**

The Screening Log will only include those that are approached for participation. General information about the number of individuals admitted to the hospital can be collected later.

Sections of Screening Log to be completed:

- Proband demographics (sex, ethnicity, race)
- Date of consent (if enrolled)
- SouthSeq ID (if enrolled)
- Eligible for enrollment (if not, provide a reason)
- Completion of decliner survey (if needed) – this is optional to the family
- Completion of W9 (form needed for participant payments)*

The Screening Log will be kept by each site's research nurse/coordinator and will be sent monthly to Dr. Finnila to compile a study wide list of screened participants.
*Please make sure the participant writes legibly and is using their legal name to ensure prompt payment.

3.c.4 Participant Enrollment

Newborns with possible congenital anomalies will be screened to determine if they satisfy inclusion and exclusion criteria. Parents or caregivers of the newborn (i.e. proband) will be enrolled in the clinical trial (includes WGS) once ICF is signed. Mothers, under 18 years or older, may consent for themselves and their children to participate. In addition, probands may be included that have passed away prior to sample collection.

Consent of at least one parent/caregiver is necessary for enrollment of the proband and participation in the clinical trial, but if the other parent/caregiver will potentially complete any surveys it is crucial to have them sign a consent form, complete a W9 form, and complete the enrollment survey. Prior to enrollment the study objectives will be explained to potential participants. After answering questions posed by the potential participating family, and before any protocol-specified procedures are initiated, participants must sign the ICF. A copy of the signed and dated ICF will be provided to the family via Genome Gateway unless they prefer a paper copy. Basic demographic information and reason(s) for exclusion must be logged for all individuals who sign the ICF, but withdraw before receiving WGS. During the enrollment visit, the following procedures will be performed.

- Review inclusion/exclusion criteria
- Review, signing and noting the date Informed consent form (ICF)
- Documentation date of birth (proband and parent(s)/caregiver(s))
- Documentation parent/caregiver self-reported race/ethnicity
- Creation of Genome Gateway account
- Collection contact information for enrolled parent/caregiver
- Collection of information for a non-household contact, if participant is willing, asked in enrollment survey via Genome Gateway
- Completion of W9 (payment for survey completion) form by any parent/caregiver who will complete a survey
- Administration of the baseline survey (Site specific to determine how much help is given to participating families)
- Encouraging review of initial online learning topics in Genome Gateway

Families that are approached but decline to participate will be asked to complete a decliner survey. **The survey includes basic demographic information and the reason for not participating (to be completed by research nurse/coordinator)** (see Appendix 2: Decliner Survey). The reason(s) for not participating are documented and transferred from the survey (or based on what the coordinator was told) to the clinical trial Screening Log. The form can be filled out at the coordinator's discretion. It can be done at the time of the patient encounter or completed after depending on comfort level and time availability. The decliner survey will be completed on paper and uploaded to Genome Gateway. Steps for uploading documents to Genome Gateway can be found 3.f.2 section 1.

3.c.5 Participant Retention

After enrollment, the site study coordinator will contact potential family participants in a variety of ways (messaging through Genome Gateway platform, by mail, by phone and in-person) for optimal retention. Retention efforts begin with recruitment and are an ongoing process and congeniality, respectfulness and friendliness in interactions with participants is important in this endeavor. To increase retention research the nurse/coordinator responsible for recruitment will be responsible for accommodating the scheduling needs of all participants. The following major principles and commonly used strategies to maximize retention and minimize loss to follow-up will be employed during the trial, some examples are included here:

- Stressing the idea that participants have an active role in the research and are part of the research team
- Enhancing participants understanding of the study's mission and the protocol
- Building relationship with the participant and focusing on participant satisfaction, with the study staff taking a central role on this effort
- Actively discuss with participants any questions and concerns pertaining to their newborn's condition
- Identifying potential problems and key retention factors, and developing intervention strategies regarding retention

It is highly recommended that the ROR visit be conducted in-person. The research nurse/coordinator will contact the participants to schedule their ROR visit.

1. The study site staff will phone the participant up to 2 times to offer times for the in-person ROR
2. In case the participant is not reached by phone, the research coordinator will call the non-household contact
3. In case the non-household contact is not reached by phone, the research coordinator will send the participant a certified letter (appendix 14) (includes family friendly WGS results letter). If the family has questions, the phone number to the HA genetic counselor assigned to the recruiting site will be provided.

In the event, a study participant parent or caregiver participant does not return to the clinical trial site for an in-person return of results appointment, then:

4. The study site staff will phone up to 2 times to offer results disclosure over the phone
5. Call the non-household contact (see contact schedule above)
6. Send a certified letter that includes the family-friendly WGS results letter, and have the Sanger results letter added to the medical record. The report is also available within Genome Gateway.

3.d Informed Consent and HIPAA

3.d.1 Informed Consent (IC) Process

One of the study research nurses/coordinators involved in the enrollment visit will carry out the process of IC. During the enrollment visit, the study participant (i.e. parent or caretaker of the infant who will have WGS testing) will review the ICF and then the research study coordinator obtaining consent will explain each section. During this process, individuals will be informed of all study aspects so that they can make an informed decision. Participants will then confirm their willingness to participate in the research study by signing the ICF. **Consent of at least one parent/caregiver is required for the newborn to be enrolled and participate in the clinical trial, but both parents/caregivers are recommended if both are involved in care of proband.** The participant will be given as much time as they need to read and ask questions about the ICF. The newborn's parent or participant's legally authorized representative will be informed that he/she is not obligated to participate in the study and that it is strictly voluntary. The individual or participant's legal authorized representative will be informed that that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her newborn's subsequent medical treatment or relationship with the treating physician.

- A frequently asked questions pamphlet (FAQ) has been provided to the study coordinators to help answer common patient questions. This is available in the Genome Gateway learning section as well as a hard copy/electronic file. This FAQ will be a live document and will continue to be modified as additional questions arise. This document is not IRB-approved and should not be given to participant families.

The IC process will ensure that there is no penalty for not participating in a clinical trial and that treatment for the newborn will not be compromised if families choose to not participate, or if they cease participation at any time. By signing the ICF, the participant authorizes the use of their newborn's PHI, indicates that they understand the study and its benefits and risks, and agrees to all other aspects of the study outlined in the form.

A signed version of the ICF will be kept by the study staff in the study binder and on Genome Gateway. Copies of the signed ICF and W9 form will be uploaded to Genome Gateway. See section 3.f.2, section 1 for details on uploading documents to Genome Gateway. These documents will be added to the particular participant's "files" section.

The ICF contains or assures the following:

- Disclosure of relevant information to participants about the research
- The participant's comprehension of the information
- The participant's voluntary agreement to participate in the clinical trial without coercion or undue influence
- Disclosure of any appropriate alternative procedures and their risks and benefits
- Disclosure of the extent of confidentiality that will be maintained
- Statement of compensation and/or medical treatment available if injury occurs
- Name, address, and telephone number of the participants

During the study period, if there is a change in any of the study procedures that may affect the participant, the ICF will be revised and approved by the UAB IRB and then the supporting sites will be notified. Per NIH policy, the signed consent forms will be scanned into Genome Gateway and kept as part of the study record for at least 7 years after completion of the study and stored electronically in servers housed within the UAB School of Medicine and HudsonAlpha (sites will maintain all forms till completion of the study. After completion, all sites will send their paper materials to UAB for storage). Participants can withdraw their consent and revoke their data authorization at any time by informing the local study coordinator or investigator (if this occurs, please contact HudsonAlpha and Dr. Finnila). For participants that withdraw their consent, no further data will be collected via surveys and the recruitment site will be notified. If results have not yet been returned at the time of withdrawal, no results will be reported. In this case, the participant's Genome Gateway account will be disabled, and the study team will be notified not to contact them.

3.d.2 Informed Consent Form

See appendix 3 for the informed consent forms (site-specific)

3.e Study Intervention

In this non-inferiority trial, we aim to compare technology-assisted community-based WGS result delivery by healthcare providers with formal genetic counseling by genetic counselors (GCs). The clinical trial will include parents/caretakers of newborns who undergo WGS. We estimate that 800 parents/caregivers will be enrolled into the clinical trial. Given the complexity of secondary findings and their implications, the parents of all children with secondary findings in the American College of Medical Genetics and Genomics (ACMG) gene list will be provided with formal genetic counseling (standard of care) and will thus be excluded from the clinical trial. We estimate that ~1.5% of sequenced probands will have such findings. Families enrolled before and after the trial period, (the trial is slated to end in January 2021, contingent on whether a no cost extension is to be awarded) will receive results from a GC.

3.e.1 Participant Randomization

Randomization will occur centrally once the WGS results are available and clinical summaries of results are created, ~45-90 days after enrollment, using a computer-generated random number generator. The unit of randomization will be at the family level. Permuted block randomization with varying block size will be utilized. Randomization will be stratified by site and type of WGS result (positive/inconclusive/no finding). Participating families will be assigned to one of the two study arms in a 1:1 ratio. The randomization status of a participant family will be communicated to a site at the same time that the results and clinical summary/family-friendly report are provided to the site, and the site is notified that results are ready to be returned. The Randomization Binder will be kept by Kelly East, lead GC at HudsonAlpha, and will be communicated to the sites by uploading the result file within GG to the site coordinator and to the disclosing health care provider, if known. When files are uploaded, a note will be made of the randomization status. The randomization status of each case will also be documented and tracked in a secure, password-protected excel file outside of Genome Gateway, which will not be accessible to the rest of the study team.

3.e.2 Implementation of the Intervention

Participants in both study arms will be provided with a similar set of resources and genetics learning topics (see section 3.e.3 appendix 4 for resources and learning topics available on Genome Gateway) at the screening/enrollment visit to supplement in-person genetics consultation. Following randomization, parents will be scheduled for a WGS results delivery visit, 3 months (+/- 1 month) after enrollment by the research nurse/coordinator at each site. WGS result delivery visits will be coordinated when possible with a NICU follow-up appointment (if available at the site) to minimize additional visits and burden to the participants. In the case when an infant has yet to be discharged from the NICU, the study visit for the return of results and the assessments associated with this visit will occur in the hospital. In a case where the child dies prior to WGS result availability, or is no longer inpatient, an outpatient study visit with the parents should be scheduled for return of results. In rare instances where extenuating circumstances would prohibit a parent from attending an in-person return of results, results may be disclosed over the phone. Importantly, return of results over the phone should be limited to individuals who have extenuating circumstances prohibiting return to the hospital and not preferentially to those with certain WGS result types (e.g., negative). At the WGS results delivery visit, the clinician (either trained healthcare provider or GC, depending on the arm) will explain to parents the:

1. Type of WGS result (positive/inconclusive/no finding)
2. Level of diagnostic certainty of the result
3. Recurrence risk, if known

4. Implications, if any, for family members
5. Recommended next steps for follow-up and continued medical management in light of result (e.g. typical management guidelines for a certain condition, follow-up testing)
6. Support resources available

Genetic Counselor's at HudsonAlpha will prepare and provide a family-friendly report of WGS results for both study arms (see appendix 1 for family –friendly report example). All families will be oriented to Genome Gateway and encouraged to review learning topics appropriate to their diagnostic findings, which will be assigned to them following result disclosure by a HudsonAlpha Genetics Counselor.

Study investigators will audio record the return of results sessions, whether in-person or over the phone, so that GCs at HA can check for minor, major, and high-risk errors in communication of the WGS findings that will be corrected, appropriately. (see appendix 13 for the audio recording process)

(1) Results (ROR) Recordings

Prior to the WGS result disclosure participants will be reminded that the interaction will be recorded using a digital audio recorder, and their GG account username/password will be needed post-ROR for completion of the GCOS and FACToR measures. They will be reminded that the purpose of the recording is to help the study team understand how the results are described and what questions and topics come up during the discussion. Participants will be reminded that the recordings will only be used by the SouthSeq study and no identifiable information will be shared outside of the study team.

Participants are given an opportunity to opt-out of the recording, but their results would have to be delivered by a GC. This can cause a delay if the participant is scheduled to have results delivered by a trained healthcare provider. Participants will not be given a copy of the recording. However, if they self-select to record the session on their own device that is permissible.

The GC or physician conducting the results disclosure will begin by verbally introducing the people attending the return of results session. This introduction/preamble will be scripted (appendix 13), the audio recording is begun and the family ID is stated clearly on the recording, as well as the name of the clinician doing the disclosure.

The parents/caregivers are counseled on the genetic test results, and when the interaction is finished, the recording is stopped. The digital recording file is uploaded in Genome Gateway to the designated HudsonAlpha GC (based on site) by the site study coordinator within 72 hours (3 business days) for positive or VUS results and within 7 business days for negative results. Errors will not be tracked within the GC arm, but only within the trained healthcare provider arm. Below are the HudsonAlpha GCs assigned to each clinical site:

Birmingham, AL (UAB): Meagan Cochran, MS, CGC
Jackson, MS (UMMC): Whitley Kelley, MS, CGC
Baton Rouge, LA (BR): Veronica Greve, MS, CGC
New Orleans, LA(LSU): Veronica Greve, MS, CGC
University of Louisville (UL): Meagan Cochran, MS, CGC

The GG platform is built to accept all types of files including audio files. The file should be named following this format SITE_PARTICIPANT ID.filetype (ex. UAB_00034.mp3).

Files from the GC (control arm) disclosures will be stored for future analysis. Files from the trained health care provider (experimental arm) will be reviewed by a HA genetic counselor for error tracking. At least one genetic counselor will review each disclosure. For the first 10 disclosures, the cases will be reviewed by all 4 HA genetic counselors (Kelly East, Whitley Kelley, Meagan Cochran, and Veronica Greve) to monitor for inter-rater consistency in error tracking. Typically, the HA genetic counselor designated to a site will be the individual doing the review/error tracking for all experimental arm disclosures at that site except for when she is not available and another team member will support this work.

Errors will be tracked within GG utilizing a participant-specific questionnaire that is assigned to the GC completing the review. This questionnaire will ask about the length of the recording, the name of the clinician doing the disclosure, and whether any errors were noted as well as the contents of the error. The questionnaire will ask separately about each error type (safety error, major error, minor error). See section 3.g.1 and figure 2 for a breakdown of error types.

3.e.3 Intervention Materials

(1) Educational Materials for the Parents/Caregivers on Genome Gateway

Educational materials have been created for parents/caregivers to provide background information about the goals of SouthSeq study and about what to expect as a participant in the clinical trial. Materials also cover background information about genomics, the types of results that may be received through WGS, and the potential impact of those results.

Educational content is provided to the parent in multiple formats including text, 2D graphics, videos, and animations. Content is provided as a series of small sections (i.e., learning topics). Effort has been taken to develop educational content that is understandable to participants who may have a low literacy level.

The primary delivery mechanism for the educational content is the Genome Gateway web platform. Genome Gateway serves as the single source for participating families to review their designated learning topics. Participating families will be given an account and automatically assigned a series of brief learning topics at enrollment. HudsonAlpha genetic counselors will assign all additional learning topics (tailored based on results) manually after ROR at the same time that an electronic version of the result report and letter are uploaded to the participant's files. The topics will vary on the type of WGS result returned but will be assigned in a consistent manner across all patients. Each site has been provided with two iPads for the participating families to use for enrollment and viewing of the educational materials.

(2) Educational Materials/Training for the Healthcare Providers

Educational materials for the healthcare providers that will be involved in disclosing WGS results will be in the form of 1) in-person training, 2) materials hosted in Genome Gateway for enduring/just-in-time access.

A half-day in-person training will occur at each site prior to the launch of the clinical trial. Contents of this training will include background information and logistics about SouthSeq, WGS, Genome Gateway and the clinical trial. The majority of the training will focus on the delivery of WGS results. The training will consist of a few short didactic talks, hands on learning activities, small group discussion, and role-plays. Additional training sessions will be conducted remotely over the phone with a HudsonAlpha GC to allow providers to work through the training materials and care for patients, as well as onboarding of new study personnel when necessary. **A provider should not return results until fully onboarded (e.g. trained with the protocol).**

Fact sheets about each training topic have been developed as part of the training materials and are available for later reference (see appendix 6). All training materials will be organized and hosted within Genome Gateway and assigned to the healthcare providers for enduring access.

Providers who will be disclosing results to participants as part of the clinical trial must attend the in-person training or participate in a "make-up" training, consisting of watching recordings of didactic portions of the training and a virtual workshop/conference call with a HudsonAlpha GC to cover the discussion, hands-on, and role-play portions of the training.

The family-friendly report that will be developed for each case (by a HA genetic counselor) will also provide just-in-time education to the providers about a specific result and what it means – and provide a road map for topics to discuss with the participant.

If providers have questions regarding the study and specific results, they will be instructed to reach out to a HudsonAlpha GC for assistance, rather than their own site-specific GC. This will allow for centralized tracking and management of questions and issues that come up across all the sites and limit compromises to the clinical trial.

3.e.4 Study Outcomes

The **primary hypothesis for this non-inferiority trial** is that there will be no clinically relevant difference in parental empowerment, as a measure of health-related quality of life between parents in the Experimental (trained healthcare provider) arm when compared to the Standard of Care (genetics providers) arm. The primary study outcome is parental **empowerment** (McAllister *et. al*., 2011, PMID: 21255005)**,** which will be measured at the WGS return of results (ROR) visit, ~3 months after enrollment (see appendix 7 for survey measures). To ensure completion of the primary outcome, parents or caregivers will be asked to complete the parental empowerment measure on-site (or over the phone) immediately after the return of results. The remaining measures included in the ROR visit will be available to complete via Genome Gateway at their convenience.

The **Secondary hypotheses** will be that the active treatment arm (trained healthcare providers) will be non-inferior to the control arm (GCs) in terms of **personal utility** (Li *et. al*., 2017, manuscript in submission) and **uncertainty** (Bieseker *et. al*., 2017, PMID: 27925165) (see appendix 7 for survey measures). In addition to assessing quantitative outcomes, we will also assess qualitative outcomes, including the **diagnostic "journey"** parents experienced during their child's stay in the nursery or inpatient setting, the **emotions** they experienced while waiting for genomic results and upon receiving these results, **parents' reasons** for wanting a genetic diagnosis, and whether those **expectations** were met.

3.e.5 Data Collection

Data will come from all 4 clinical sites via self-administered surveys conducted online using Genome Gateway, or via paper surveys (scanned into Genome Gateway) in case of technical failure, lack of computer access or poor computer literacy. Organization of surveys and time points is indicated in Table 2 and Figure 1 (organized with most important measures located at beginning of survey). If parents do not respond to initial requests to complete follow-up surveys, they will be sent three automated reminder messages within two weeks of each study visit using the messaging feature of the Genome Gateway platform. (Genome Gateway is able to send reminders once the survey has been assigned by the research nurse or coordinator the reminder can be sent as a text/email/or message in Genome Gateway).

1. The study site staff will phone the participant up to 2 times to offer times for the in-person ROR
2. In case the participant is not reached by phone, the research coordinator will call the non-household contact

3. In case the non-household contact is not reached by phone, the research coordinator will send the participant a certified (includes family friendly WGS results letter). If the family has questions, the phone number to the HA genetic counselor assigned to the recruiting site will be provided.

The use of these different data sources and modes for data collection provide some redundancy to assure that all outcomes are appropriately ascertained, creates a pragmatic approach for the study, and minimizes burden to the parents (relief from frequent contacts with the study team outside of scheduled follow-up visits). The data sources and approaches proposed are based on the considerable experience of the UAB clinical trial team and our collaborators in building comprehensive data capture platforms, collecting survey results, and linking to administrative data sources.

Table 2. Study Outcome Instruments, Key Covariates, and Measurement Times

	Instrument	Timing of Assessment				
		Enrollment	ROR	1 m post ROR*	4 m post ROR*	4m + 2 wk post ROR
Informed Consent Form (ICF)		x				
Outcome of Sequencing			x			
Sociodemographic	Age, race/ethnicity, marital status, education, socioeconomic status, insurance status	x	x	x	x	
Empowerment	GCOS† (McAllister *et.al*, 2011)	x	x**			
Worry/Positive Psychological Effects with Genetic Testing	FACToR¢		x**	x	x	
Satisfaction	Adapted from PACE (Patient Assessment of Communication Effectiveness) (Mazor *et al.,* 2016)		x	x		
Knowledge	GKA‖ (Schmidlen *et. al*., 2016)	x				
Child's Health	VAS∞	x	x	x	x	
Uncertainty	PUGS‡ (Bieseker *et. al*., 2017)	x	x			
Personal Utility	PrU$^{\Delta}$ (Li *et. al*., 2017)		x		x	
Medical Activation	Medical Actions and non-Med/Patient-Initiated Actions Attributable to Genomic Testing					x
Healthy literacy	Health Literacy Screening Questions (Chew et. al., 2004)	x				
Numeracy	SNS◊ (Fagerlin *et. al*., 2007), (Zikmund-Fisher *et. al.,* 2007)	x				
General Health	Adapted from SF-12¿ (Ware *et. al.,* 1996)	x	x	x	x	
Social support	MOS¶ (Sherbourne *et. al*., 1991)	x	x	x	x	
Understanding	Novel Measure		x	x	x	
Family Communication						x
Information Seeking			x	x	x	

ENR: Enrollment * Post WGS (whole genome sequencing); †Genetic Counseling Outcome Scale; ‡Parental Perceptions of Uncertainties in Genomic Sequencing; ¢The Feelings About genomic Testing Results #Genetic Counseling Satisfaction Scale; ‖Genetic Knowledge Assessment; ∞Visual Analog Scale $^{\Delta}$ Parental Personal Utility Scale; ◊Subjective Numeracy Scale; §National Health and Nutrition Examination Survey;¿12-Item Short Form Survey; ¶Medical Outcomes Study. In green, primary analyses. ** GCOS and FACToR need to be completed in-person (or over the phone) immediately after ROR delivery before leaving session.

(1) Primary Outcomes

The main outcome to be assessed as part of this randomized controlled clinical trial will be **parental empowerment** as measured at the main time point for our study (i.e., immediately after the ROR visit). Parental empowerment will be measured using the validated Genome Counseling Outcome Scale (GCOS), which contains 24, 7-point Likert type items, with higher scores representing greater empowerment. The GCOS-24 that we are using for our participants measures patient reported outcomes (PRO) and has been proposed as a measure to evaluate routine clinical genetics services (McAllister et. al., 2011, PMID: 21255005).

(2) Secondary Outcomes

To avoid survey fatigue and undue emotional burden, not all secondary or exploratory outcome instruments will be administered at each time point. The secondary outcomes assessed at the main time point (WGS ROR visit) for this study are: **personal utility** and **parental uncertainty**. Personal utility will be assessed using the parental personal utility scale (PrU). Parental uncertainty will be assessed using the Parental Perceptions of Uncertainties in Genomic Sequencing (PUGS).

(3) Exploratory Outcomes

Genetic knowledge and background genetic education will be addressed using the Genetic Knowledge Assessment (Schmidlen et. al., 2016, PMID: 26306685). The Genetic Knowledge Assessment (GKA) is a questionnaire containing 15 true/false knowledge items and 4 education background questions. In addition, we will assess parental subjective understanding of their child's results by asking respondents to rate their agreement.

(4) Covariates

Beyond the primary, secondary, and exploratory outcomes described above, a schedule of other data being collected for use in various analyses is provided in table 2.

The FACToR measure needs to be completed, alongside GCOS, in-person (or over the phone) immediately after ROR delivery before leaving session.

3.f Participant Evaluations and Follow-Up

3.f.1 Timeline and Visit Schedule

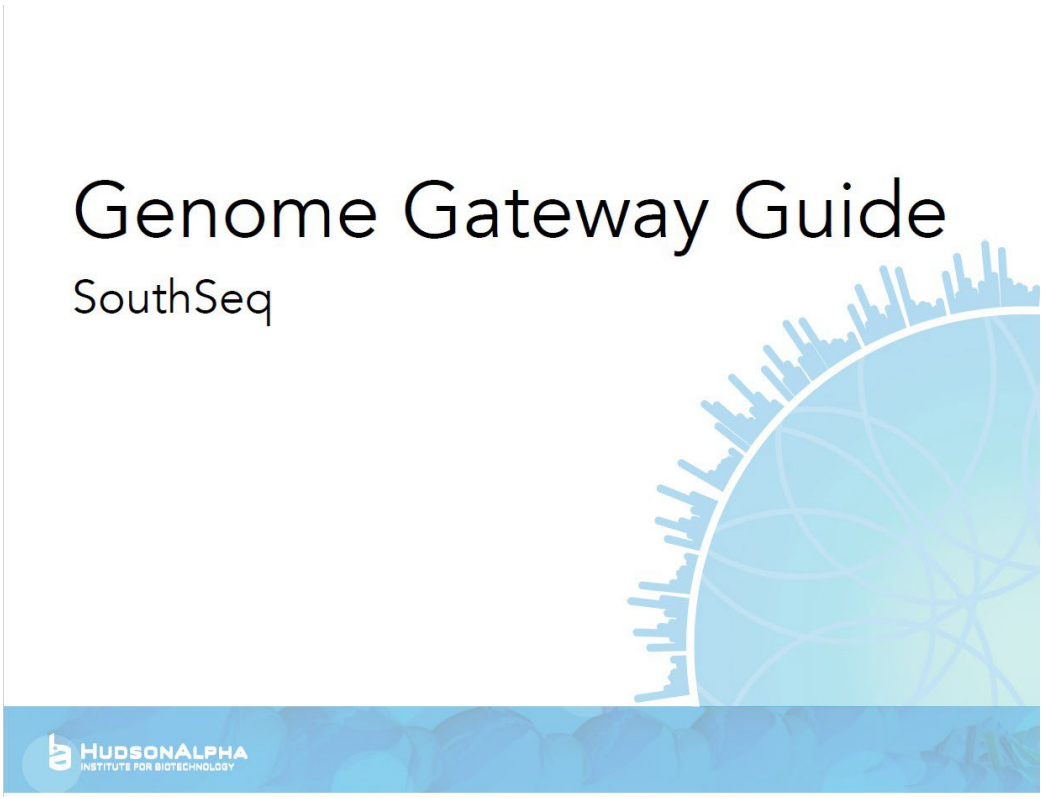
3.f.2 Scope

(1) Screening/Enrollment Visit

- Potential newborns (probands) will be identified via electronic medical record (EMR) review or referral from clinical care team
- Research nurse/coordinator will complete screening log and will assign a screening ID (see section 3.c.3 above)
    - Will review inclusion and exclusion criteria in protocol
    - Will communicate with site genetics staff to help determine eligibility
- May email physician or nurse practitioner caring for newborn to notify them that the family will be approached for study
- It is important to note that WGS does not replace standard clinical genetic testing (e.g. microarray)
- Research nurse approaches families for consent
    - Talk in-person in private area of the hospital (e.g. patient room, conference room)
    - Call or phone to arrange a meeting time for working and/or long distance families
    - Maintain contact for undecided families
    - Explain study procedures and mention secondary findings
    - After the consent form is signed (only parents/caregivers who have consented can participate in the clinical trial) blood specimens are collected from the proband and parents, if available
        - If both parents/caregivers express interest in participating, both parents/caregivers should be consented and complete their own surveys

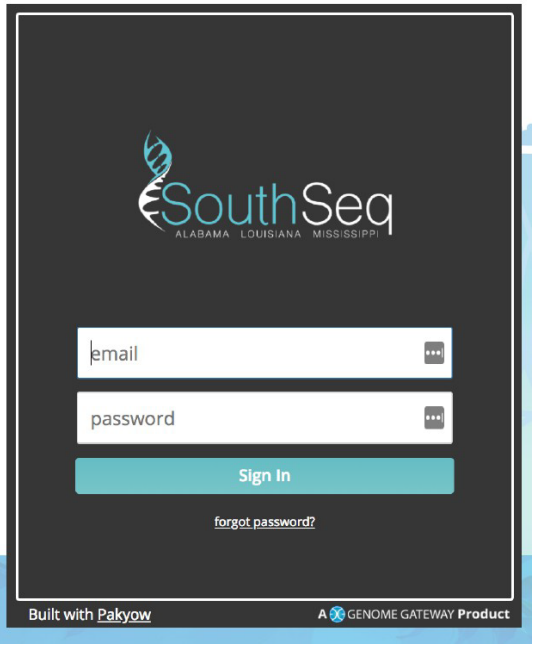
- Families are supplied with an iPad (two will be ordered for your site for use in this study) to complete Genome Gateway registration, the enrollment/baseline survey, and family history questionnaire/pedigree in Genome Gateway at enrollment.
    - The research nurse will not assist the parents/caregivers as much as possible with answering questions on the enrollment survey unless a technical issue arises.

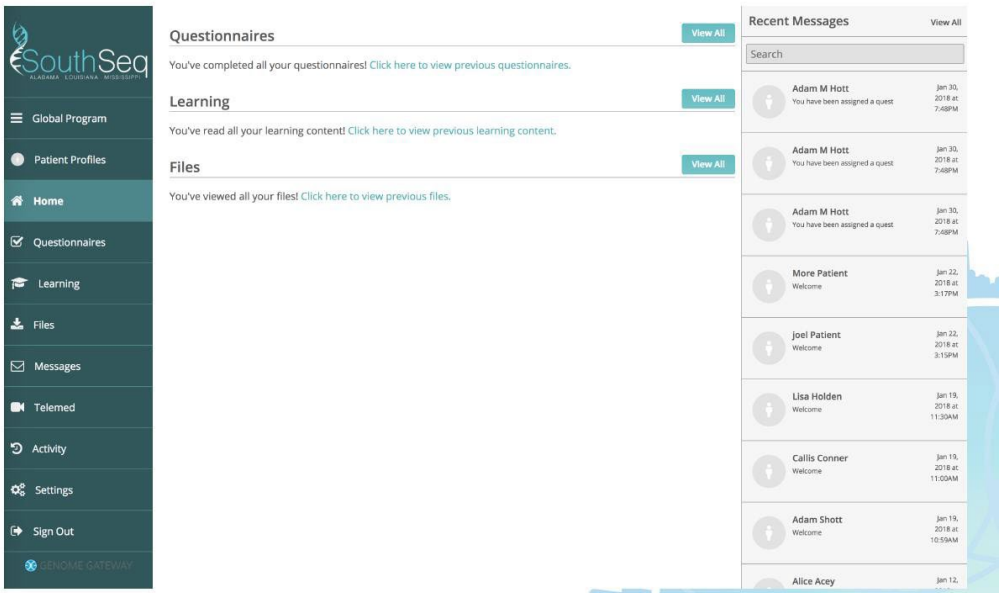
Detailed instructions regarding Genome Gateway participant registration and navigation are below:



participants.southseq.org

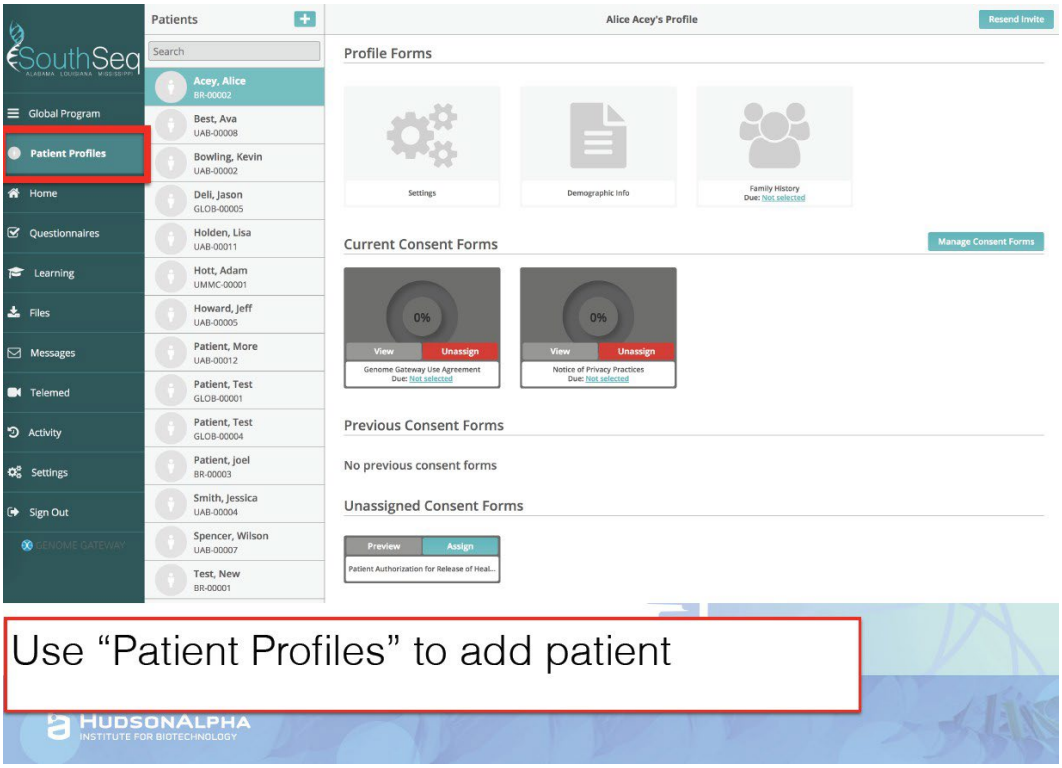
Use provider account login information



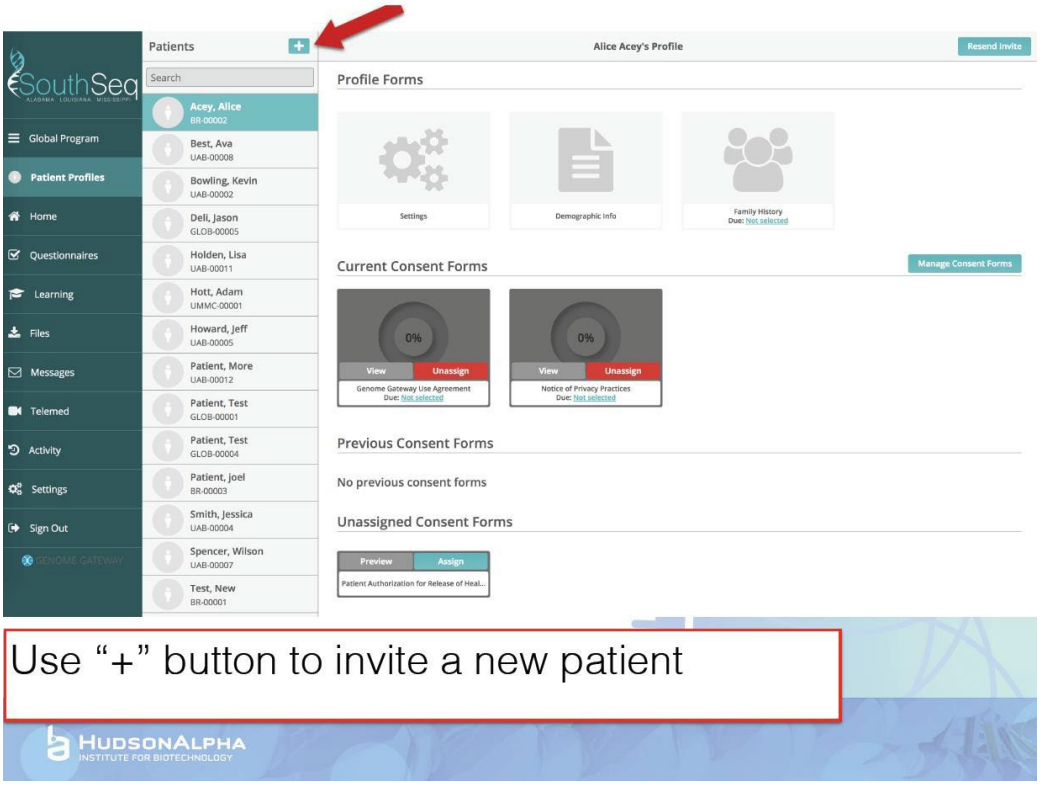


Home Page for Navigation

- After logging-in to Genome Gateway, you will need to create a new patient account

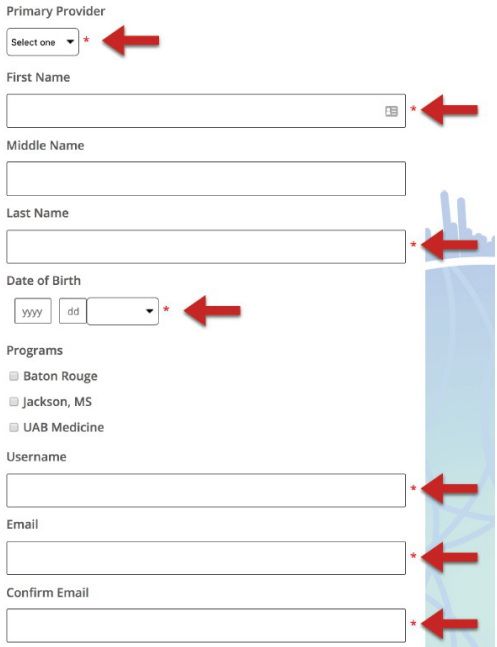


Use “Patient Profiles” to add patient



Use “+” button to invite a new patient

Add patient information to create user account. Required fields are indicated by "*"



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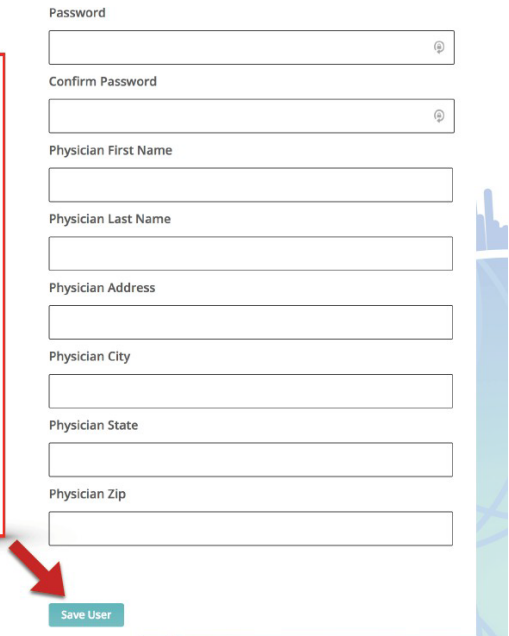
DO NOT create password

(patient will set this up on their end when they open their account for the first time)

Click "Save User" to create the account. An email will be generated inviting the patient to Genome Gateway



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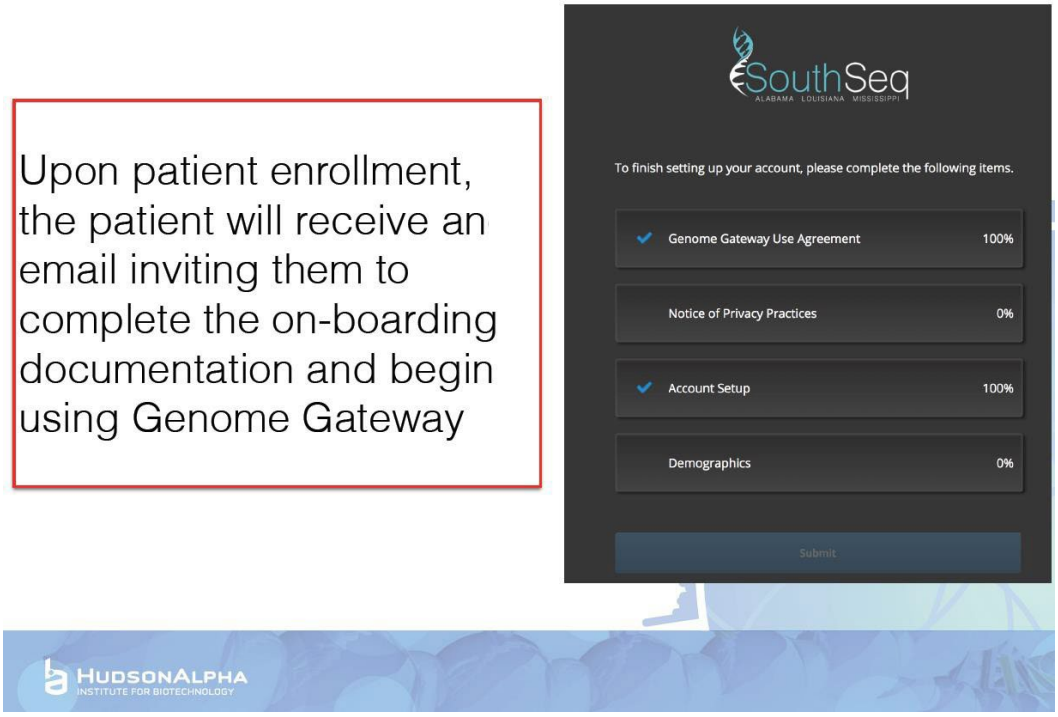
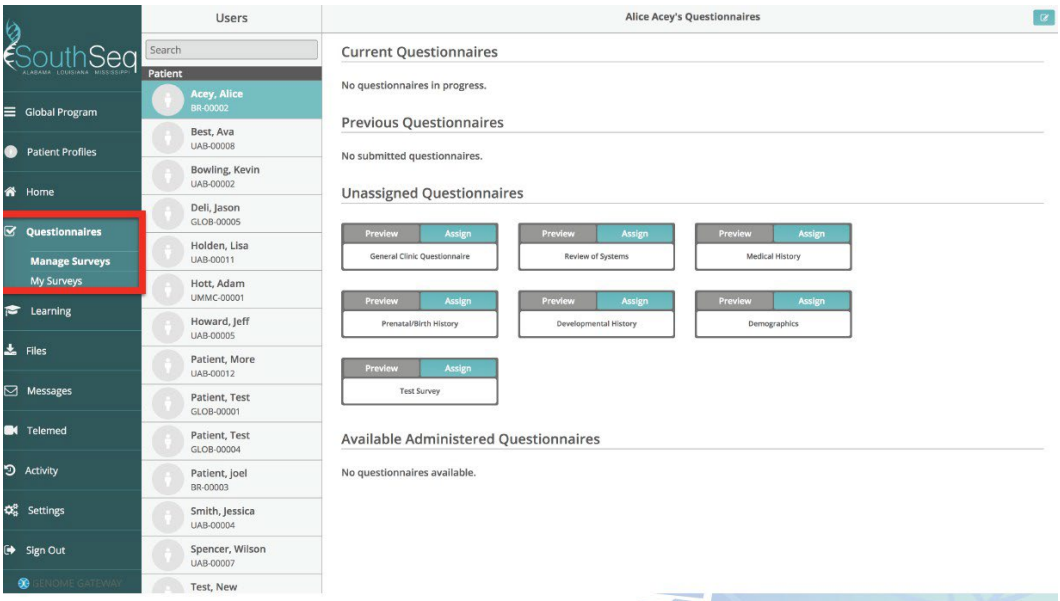


Notes for research nurse/coordinator:

- Each participant will need to be enrolled into a study site by selecting from the site list when filling out the patient enrollment
- Each participant will need to be associated with a primary provider (varies by site -physician currently overseeing care for proband). Can be selected when filling out patient information
- Study IDs will be automatically assigned to participants once a Genome Gateway account is created
    - Don't forget to add study ID to the screening log
- The study IDs will be visible under participants' names on any screen with that information
- The study ID number will also be printed on the blood sample tube labels

Patient Questionnaires



Navigate to "Questionnaires" from the homepage

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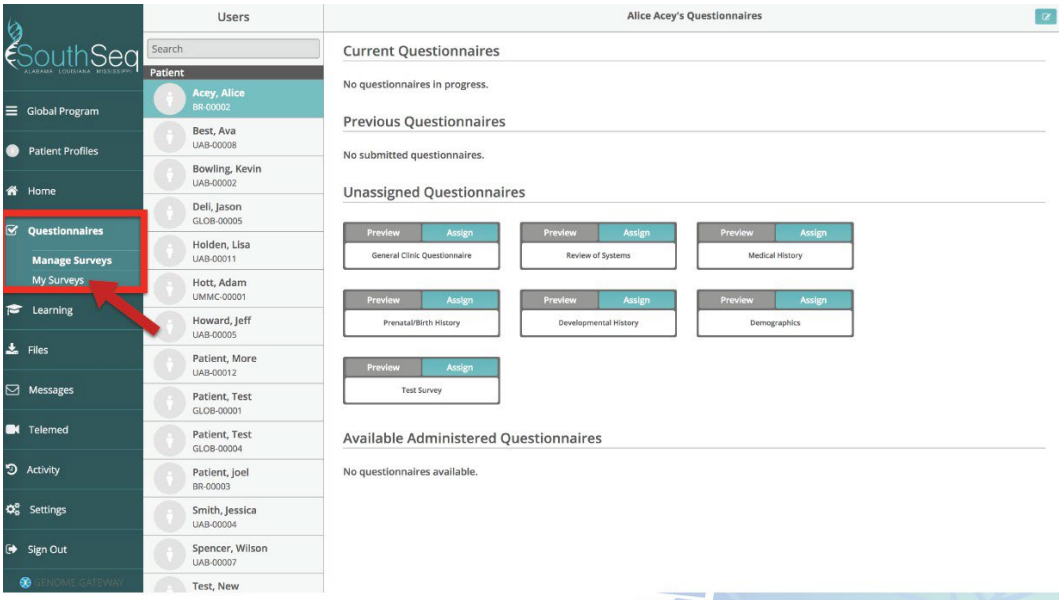

Complete the Questionnaires assigned to you by selecting "My Surveys"

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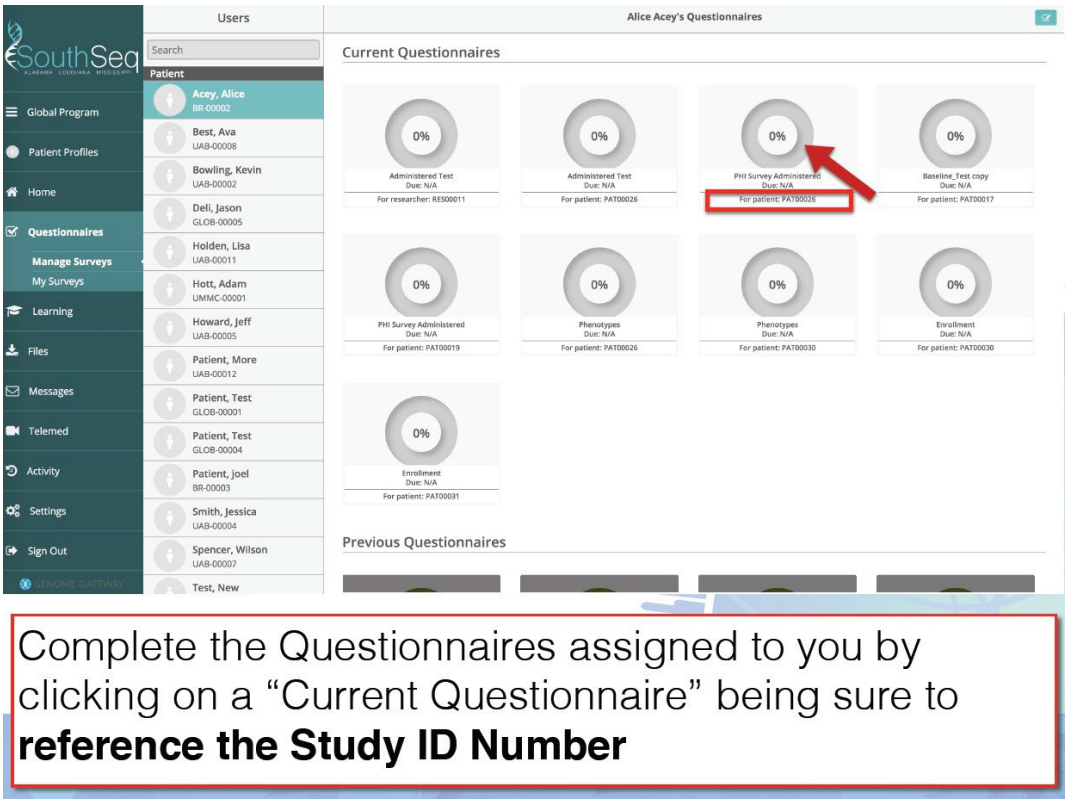
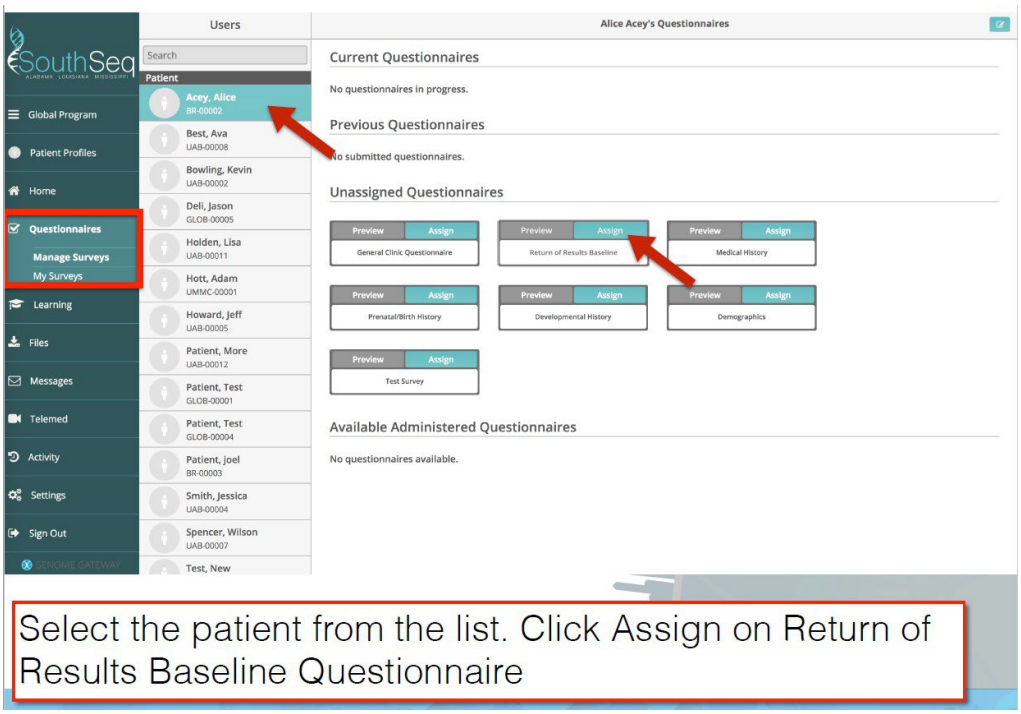
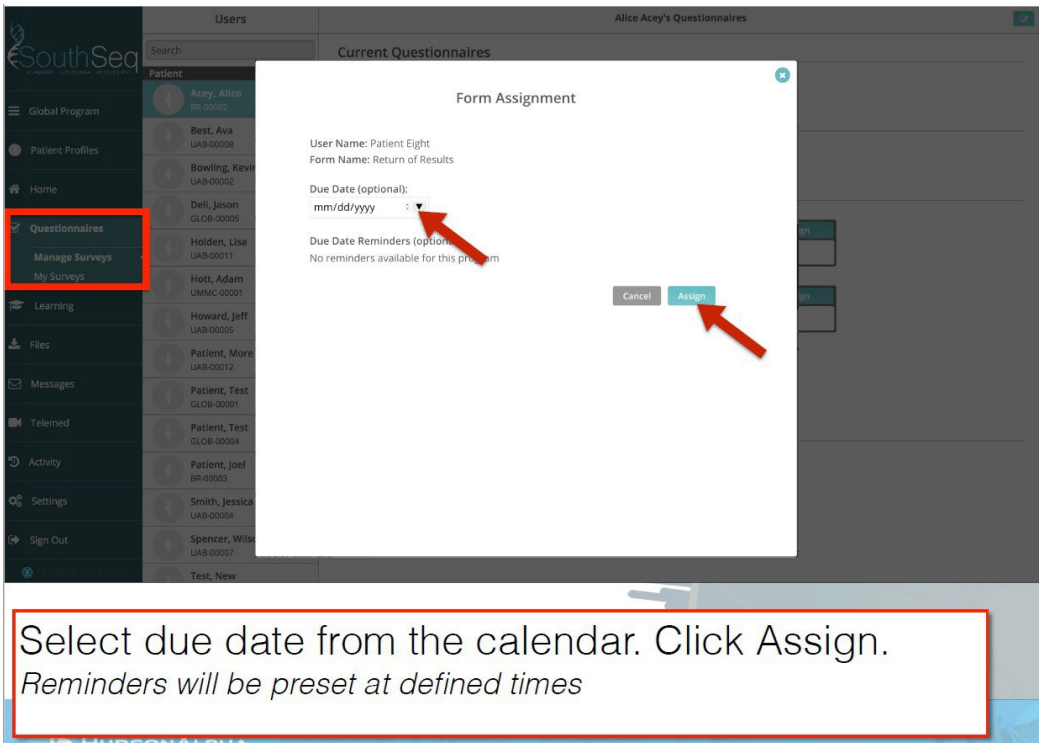


- Research nurse will complete assigned surveys in Genome Gateway.
    - These surveys are focused on phenotypes, previous genetic testing, prenatal testing (if known) and the enrollment process. (see screenshot steps below)
    - This information will be accessible to the analysis team at HudsonAlpha.

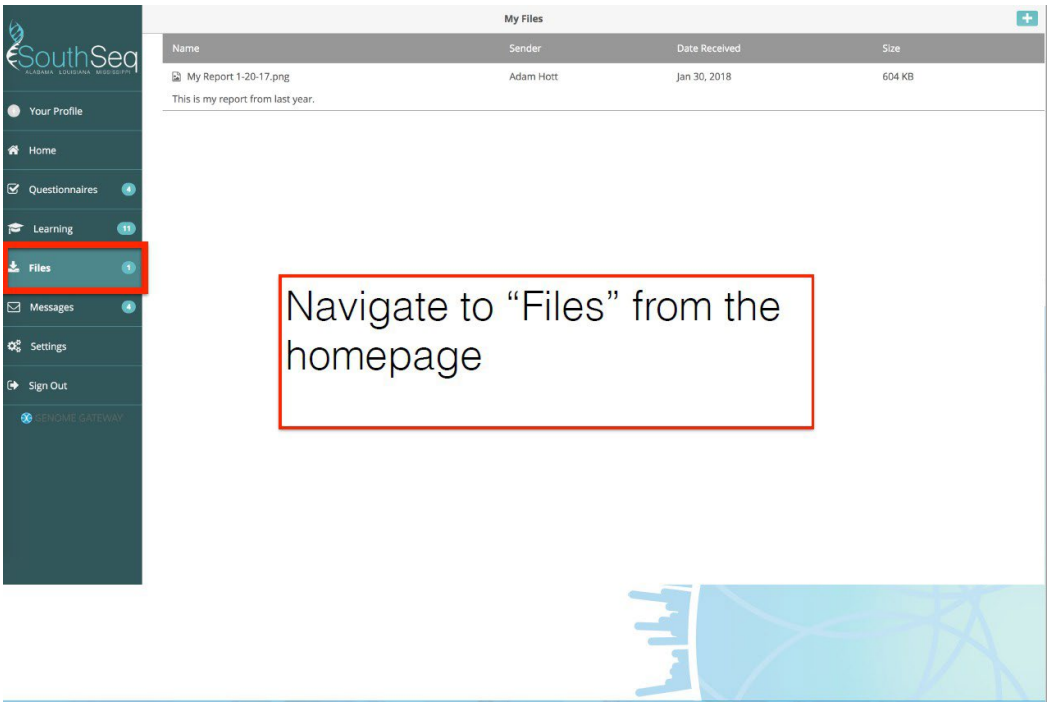


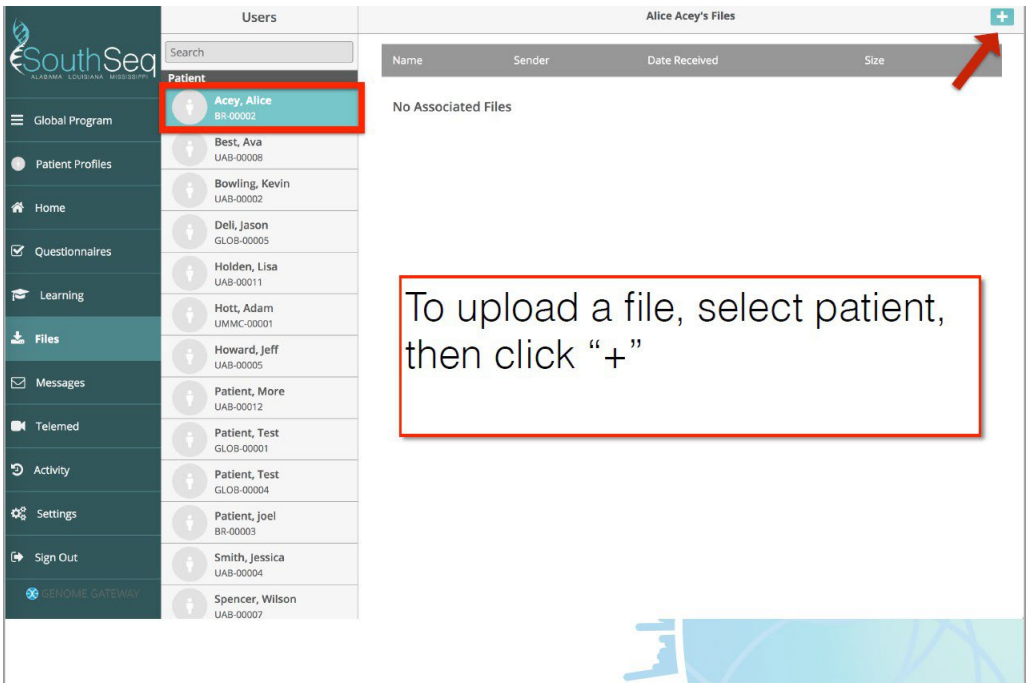


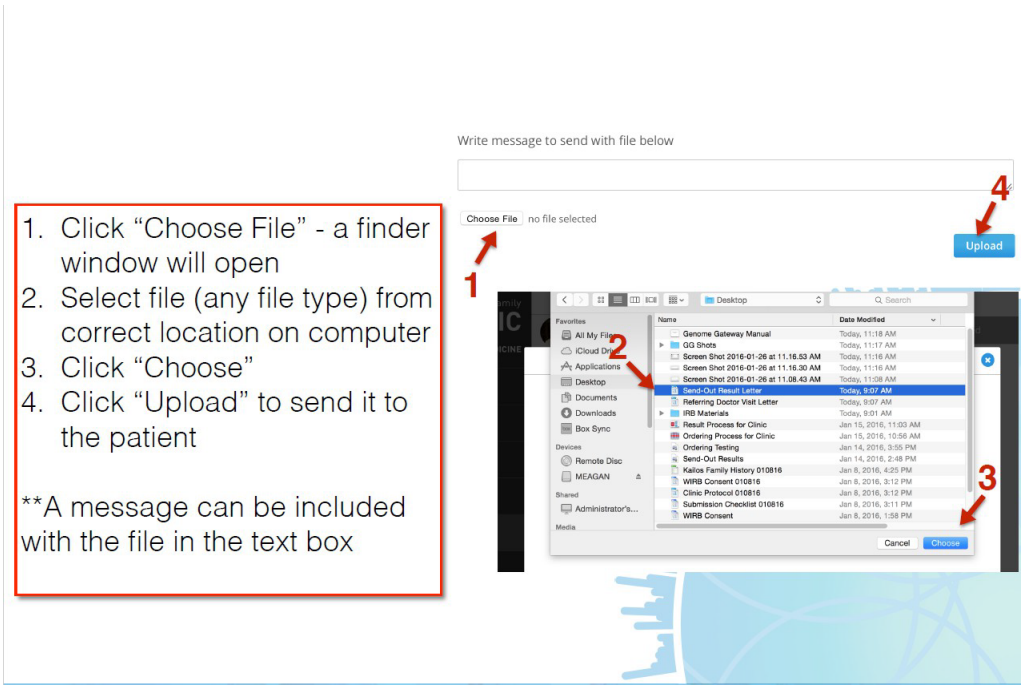
- The due date should be up to ROR (roughly 2 ½ months for baseline). All subsequent surveys will be set 1-month from the day you assign the survey.
- The due date reminders will be automatically preselected for you (2-day before, 7-days before, and 14-days before)

- Research nurse will ship samples to the Clinical Services Laboratory at HudsonAlpha and submit them for sequencing via online portal.
- The research nurse will upload the W9 (needed for payment) and the informed consent form to GG.
  - Screenshots highlighting how to upload documents are below.

Uploading Documents to Genome Gateway







- Forms/survey measures completed at enrollment
    - Informed Consent Form (ICF)- (paper form uploaded to Genome Gateway; hard copy kept in study binder)
    - W9 form (paper form uploaded to GG; hard copy kept in study binder until clinical trial team informs the coordinator to destroy- 7 years)
    - Participant Enrollment Survey
    - Sociodemographic in GG
    - Genetic Counseling Outcome Scale (GCOS)
    - Genetic Knowledge Assessment (GKA)
    - Visual Analog Scale (VAS)- Child’s Health
    - Parental Perceptions of Uncertainties in Genomic Sequencing (PUGS)
    - Health Literacy
    - Subjective Numeracy Scale (SNS)
    - 12-item Short Form Survey (SF-12)
    - Medical Outcomes Survey (MOS)
    - Research Nurse/Coordinator Surveys (phenotype, other genetic testing, enrollment notes, etc.)

If a parent/caretaker participant doesn’t respond to the baseline measures, the clinical trial team will contact the study coordinator, to remind the participant to complete surveys via GG and/or over the phone, after a biweekly data pull is completed to generate a list of non-completers. All data collected pre-ROR, will still be valid as baseline data.

(2) Return of Results (ROR) Visit

- After samples are sequenced, analyzed, and variants of interest have been Sanger validated (by HudsonAlpha, PerkinElmer, EGL, etc.), the HudsonAlpha analysis team will contact the clinical team and hold a variant review meeting (VRC) to discuss any findings.

- After VRC, the enrolled families will be scheduled for a return of results (ROR) appointment by the site research nurse/coordinator (preferably in-person) where a GC/healthcare provider will return the finding(s)
    - The ROR can be completed over the phone if necessary, as a last resort. Reasons for offering a phone ROR include families who are unwilling to return to clinic because of distance or psychosocial distress. Caution should be made to not let the type of result dictate the ROR setting (i.e. do not preferentially offer negative results phone disclosures and positive results in-person consultations).
    - If a phone ROR is to be completed, the same provider should do the disclosure who would have been expected to do an in-person meeting. The phone experience should be made to feel as similar to the in-person experience as possible (length, content, staff, flow).
    - **It is important that the parent/caregiver who completes the enrollment surveys continue to be the person attending and completing the ROR visit and surveys (In-clinic survey and At-home survey).**
- The research nurse will place the clinical Sanger report along with the family-friendly genetic counseling letter in the child's medical record so that clinicians will have access to the finding(s).
- The (GCOS/FACToR) ROR questionnaire is administered by the research nurse immediately following the ROR visit. After completion of the ROR visit, the 1-month post ROR, and 4-month post ROR post-enrollment can be programmed for automatic administration.
    - If completed over the phone, the answers need to be recorded on paper, and uploaded to Genome Gateway
- Forms/survey measures completed at ROR visit
    - Sociodemographic
    - Genetic Counseling Outcome Scale (GCOS)
        - **This survey needs to be administered by the research nurse/coordinator after ROR. This is the primary outcome and needs to be completed directly after ROR.**
    - The Feelings About genomic Testing Results (FACToR)
        - **This survey needs to be administered by the research nurse/coordinator after ROR. This needs to be completed directly after ROR because it is an important covariate.**
    - Patient Assessment of Communication (Adapted from PACE) (Mazor *et. al*., 2016)
    - Visual Analog Scale (VAS)- Child's Health
    - Parental Perceptions of Uncertainties in Genomic Sequencing (PUGS)
    - Parental Personal Utility Scale (PrU)
    - 12-item Short Form Survey (SF-12)
    - Medical Outcomes Survey (MOS)
    - Understanding (Novel Measure)
- The research nurse/coordinator in partnership with HudsonAlpha will determine who the most appropriate clinical provider at each site is to receive the harmonized "provider survey." This provider should be the physician likely to make a clinical decision based on the WGS results at the time of ROR. If the neonate is inpatient this physician will likely be a neonatologist providing medical care for the neonate, if already discharged it could be pediatrician or another specialist depending on the neonate's symptoms. The site coordinator will determine the status of the proband (inpatient/outpatient) at the time of ROR (consulting with the family about this issue if already discharged) and will send the provider's name and contact information to Kyle Brothers, MD, PhD (kyle.brothers@louisville.edu) within a week of

ROR appointment. Information can be sent via the Genome Gateway messaging tool. Information to be sent includes:

- Study ID
- Result type (positive/inconclusive/no finding)
- ROR date
- Clinical provider's name
- Clinical provider's contact information (email (required), phone, address)

(3) 1-month post-ROR Visit

- Forms/survey measures completed at 1-month post-ROR visit
  - Sociodemographic (if status has changed)
  - The Feelings About Genomic Testing Results (FACToR)
  - Patient Assessment of Communication (Adapted from PACE)
  - Visual Analog Scale (VAS)-Child's Health
  - 12-item Short Form Survey (SF-12)
  - Medical Outcomes Survey (MOS)
  - Understanding (Novel Measure)
  - Information Seeking

(4) 4-month post-ROR Visit

- Forms/survey measures completed at 4-month post-ROR visit
  - Sociodemographic (if status has changed)
  - The Feelings About Genomic Testing Results (FACToR)
  - Patient Assessment of Communication (Adapted from PACE)
  - Visual Analog Scale (VAS)- Child's Health
  - Parental Personal Utility Scale (PrU)
  - 12-item Short Form Survey (SF-12)
  - Medical Outcomes Survey (MOS)
  - Understanding (Novel Measure)
  - Information Seeking

(5) 4-month plus 2 weeks post-ROR Visit

- Forms/survey measures to be completed at 4-month plus 2 weeks post-ROR visit
  - Family Communication
  - Medical Actions and non-Med/Patient-Initiated Actions Attributable to Genomic Testing

3.f.3 Follow-Up of Participants during the Study

Participants will be actively followed through all study visits until completion of the study. This includes, but is not limited to:

- Genome Gateway can provide email and text reminders (if participant provided a cell phone number and consented to text reminders) to users for the purpose of notifications of due dates, new messages, new file uploads, new learning assignments, and new questionnaires.
- Research Nurses/coordinators will confirm contact information and remind the participants that they will be paid for follow-up surveys
- A generic mailing will be sent to participants to keep them engaged and informed of their participation ** pending IRB approval**

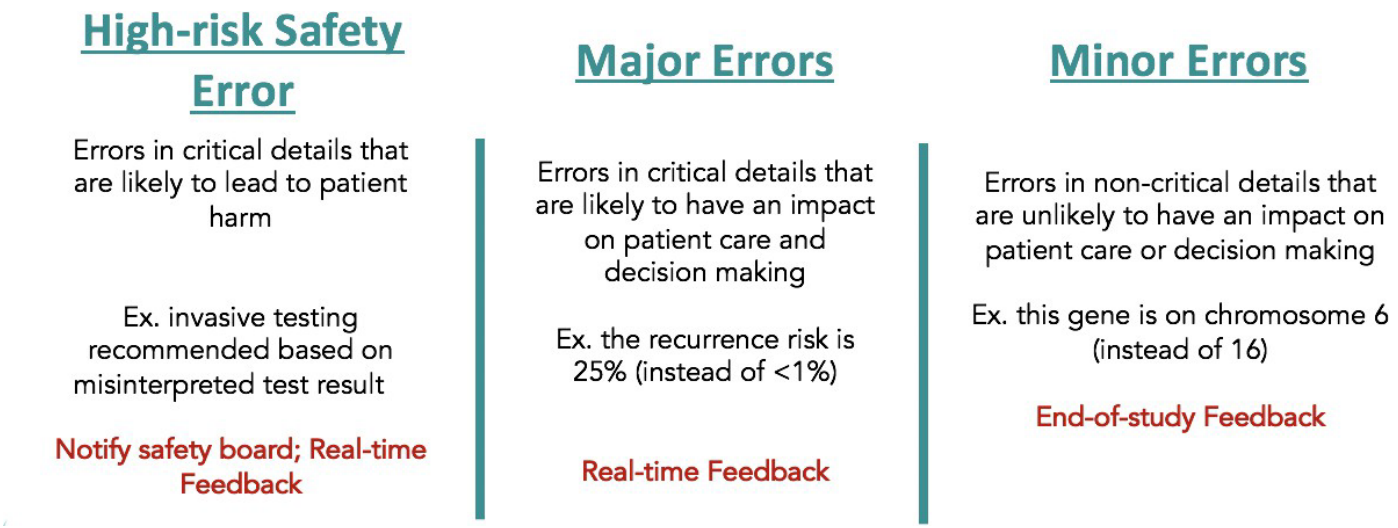
Upon onboarding of Genome Gateway, by default, all participants will receive text and email notifications from GG when any new assignment, questionnaire, files, or message is sent. The participants will have the option to decline email/text notifications during the onboarding process. They may also decline email/text notifications during the course of the trial, if the alerts become burdensome. When a provider or administrator assigns learning articles and questionnaires, a due date for those items must be set (the deadline for questionnaires is 1 month). If a due date is set for the completion of those, a set of reminders can be added which will cause an automatic email/text notification to be sent at a designated number of days before the due date. For example, it is possible to set a due date of January 12 with reminders to be sent 2, 7, and 14 days prior to the due date. This is done at the time of assignment.

3.g Safety Reporting

3.g.1 Errors in Reporting of Results

Errors will be tracked within GG utilizing a participant-specific questionnaire that is assigned to the GC completing the review. This questionnaire will ask about the length of the recording, the name of the clinician doing the disclosure, and whether any errors were noted as well as the contents of the error. The questionnaire will ask separately about each error type (safety error, major error, minor error). See Figure 2 for a breakdown of error types.

Figure 2. Types of Genetic Test Reporting Errors



Minor Errors

In the case of a minor error, these errors will be tracked internally but no intervention will be made.

Definition: Errors in the non-critical details that have little expected impact on participant understanding, decision-making and management.

Examples:

- Saying the participant "has the gene" instead of saying the participant "has a gene mutation"
- Saying the gene is on the incorrect chromosome
- Terminology misuse - heterozygous versus homozygous

Major Errors

In the case of a major error, the disclosing healthcare provider will receive a message from the reviewing GC clarifying the error and recommending he/she follow-up with the participant to convey corrected/additional information. The clinician is expected to correct the misconception both with the patient and any documentation they did clinically at their site. If the clinician asks for assistance or does not feel comfortable addressing the error, the genetic counselor will be responsive to those requests. If a participant reaches out to HA with questions, Kelly East will address concerns, but the disclosing healthcare provider is expected to be the one to have direct patient contact and a patient relationship.

Definition: Errors in the critical content that have a significant expected impact on participant understanding, decision-making, and/or management.

Examples:

- Wrong recurrence risk (i.e. stating recurrence risk is 25% when it is actually <1%)
- Confusion regarding etiology (*de novo*, parental carrier status)
- False reassurance (i.e. counseling that WGS will provide a concrete answer as to participant's life expectancy)
    - Negative results and the misconception that it rules out genetic etiology (explicit statements)
- Misunderstanding of pathogenicity/penetrance
    - Likelihood of actual development of features/severity
- Incorrect understanding of a VUS (saying it is highly unlikely to be the cause/is nothing to worry about; or saying it is definitely the cause)

High-risk Safety Errors

In the case of a high-risk safety error, this will be brought to the attention of the clinical trial leadership team and the Data Safety Monitoring Board (DSMB) for recommendations on how to manage the situation.

Definition: Errors that have a high risk of immediate and detrimental impact on participant safety; should be reported to DSMB.

Examples:

- Recommendation of invasive testing or procedure based on a misinterpreted test result
- Giving back wrong result; counseling the wrong family
- Failure to report a high impact incidental finding

3.h Data and Safety Monitoring Board (DSMB) Activities

We will convene a DSMB for additional monitoring of study procedures. The safety of the study participants is the highest priority for this project. The ability to make appropriate, sound scientific decisions regarding the outcome of each participant, as early as possible, is the top priority. The DSMB will be comprised of three scientists/clinicians who are independent of the study. All safety monitoring body member(s) will complete and sign the Conflict of Interest (COI) Statement. Elizabeth Rahn, PhD (Clinical Trial/Scientist) will provide and track the COI statements prior to providing DSMB members study materials and then track this on an annual basis. See appendix 8 for additional information.

3.h.1 DSMB Responsibilities

- Review the outcome instruments, informed consent documents and plans for data safety and monitoring
- Evaluate the progress of the clinical trial, including periodic assessments of data quality and timeliness, recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect study outcome
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial
- Review study performance, make recommendations and assist in the resolution of problems reported by the Principal Investigator(s) (Clinical Trial PIs)
- Protect the safety of the study participants and monitor the rate and scope of errors reported in the experimental arm of the clinical trial.
- Report on the safety and progress of the trial
- Make recommendations to the PIs concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the intervention under study
- The PIs will report findings of the DSMB to NGHRI in accordance with reporting guidelines
- Ensure the confidentiality of the study data and the results of monitoring
- Assist in commenting on any problems with study conduct, enrollment, sample size, and/or data collection.

The DSMB will discharge itself from its duties when the last participant completes the clinical trial.

3.h.2 DSMB Board Process

At the initial meeting the DSMB will discuss the protocol, suggest modifications, and establish guidelines to study monitoring by the Board. The DSMB Chairperson, in consultation with the Principal Investigator and the study team, will prepare the agenda to address the review of provider education materials, modifications to the study protocol and informed consent document, initiation of the trial, reporting of return of results errors, and statistical analysis plan. Meetings of the DSMB will be held annually or more frequently at the discretion of the DSMB, if necessary. The study investigators or their designees will attend the meetings. An emergency meeting of the DSMB may be called at any time by the Chairperson or by the PIs should safety questions or other unanticipated problems arise. The meetings are closed to the public because discussions may address confidential participant data. The meetings are attended by the Principal Investigators and members of their staff. Meetings may be convened as conference calls, as well as in-person.

3.h.3 DSMB Meeting Format

DSMB meetings will consist of open and closed sessions. Discussion held in all sessions is confidential. The PI and key members of the study team attend the open sessions. Discussion will focus on the conduct and progress of the study, including participant accrual, protocol compliance, and problems encountered.

Each meeting must include a recommendation to continue or to terminate the study and whether the DSMB has any concerns about participant safety made by a formal DSMB majority or unanimous vote. Should the DSMB decide to issue a termination recommendation, the full vote of the DSMB is required. In the event of a split vote, majority vote will rule and a minority report will be appended. The DSMB Chair provides the tiebreaking vote in the event of a 50-50 split vote. A recommendation to terminate the study may be made by the DSMB at any time by majority vote. The Chair should provide such a recommendation to the PIs immediately by telephone and email.

3.h.4 Meeting Materials

A DSMB interim report template will be prepared by the study staff, typically by the study statistician, and will be reviewed by the DSMB members at the first meeting. The format and the content of the reports for, and the plans for, interim analyses will be finalized and approved at the initial DSMB meeting, although changes throughout the trial may be requested by the Board. The reports will list and summarize safety data and describe the status of the study. All meeting materials will be sent to PIs who will forward the materials to the DSMB between 7 to 14 days prior to the meeting. The reports will be numbered and provided in sealed envelopes and can be returned within an express mailing package or by secure email, as the DSMB prefers. In select cases, PIs may approve direct mailing of the reports from the study to the DSMB.

3.h.5 DSMB Reports

Reports generally include administrative reports by site that describe participants screened, enrolled, completed, and discontinued, as well as baseline characteristics of the study population, and interim error statistics from HudsonAlpha obtained through review of the ROR sessions (i.e. errors tracking). Other general information on study status may also be presented. The DSMB may direct additions and other modifications to the reports on a one-time or continuing basis. The reports may also contain data on study outcomes, including safety data, and perhaps efficacy data.

A formal report containing the recommendations for continuation of, or modification to the study will be prepared by the DSMB Chairperson, PIs, or designee. The draft report will be sent to the DSMB members for review and approval. It is the responsibility of the PIs to distribute the DSMB recommendation to all co-investigators and to ensure that copies are submitted to the IRBs. As previously stated, the formal DSMB report must include a recommendation to continue or to terminate the study. This recommendation should be made by formal majority vote. A termination recommendation may be made by the DSMB at any time by majority vote. In the event of a split vote in favor of continuation, a minority report will be contained within the regular DSMB report. See Data Safety Monitoring Plan appendix 9 for additional information.

3.h.6 DSMB Confidentiality

All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.

3.i Study Compliance

Investigators will conduct the study in an efficient and diligent manner and in conformity with this protocol; generally accepted standards of GCP; and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study. The clinical trial PI also will allow audits, IRB/Independent Ethics Committee review and regulatory

agency inspection (if required) of trial-related documents and procedures and provide for direct access to all study-related source data and documents. The investigators will prepare and maintain complete and accurate study documentation in compliance with GCP standards and applicable federal, state, and local laws, rules and regulations. Study documentation will be promptly and fully disclosed by the clinical trial PI upon request for inspection, copying, review, and audit at reasonable times by any regulatory agencies. The investigators will promptly take any reasonable steps that are requested by designated representatives as a result of an audit to cure deficiencies in the study documentation and GG surveys. Persons debarred from conducting or working on clinical studies by any court or regulatory agency will NOT be allowed to conduct or work on this study.

3.j Data Collection and Outcome Instruments

All data for this study will be collected by study staff in accordance with 21 CFR Part 11 rules and will meet all regulatory requirements. All data entry will use the Genome Gateway platform, with which our team has extensive experience. All outcome instruments will be completed electronically in the Genome Gateway platform by the participants or research nurse/study coordinator(s). Beyond the informed consent, participants will complete no paper surveys, unless there is a technical issue with the Genome Gateway platform, or a family cannot complete the survey measures online (paper copies will be used and scanned into Genome Gateway). All Genome Gateway forms filled out by participants or study personnel will be considered source documents and must be maintained in a study binder.

3.j.1 Source Documentation

All Genome Gateway forms filled out by participants or study personnel will be considered source documents and kept electronically. All electronic forms and logs in Genome Gateway platform are encrypted and password protected and hard copies can be printed if required. A detailed listing of all current study forms is below in Table 3.

Table 3. Study Forms

Form	Visit Administered	Instructions	Location
Informed Consent	Enrollment Visit	Participant/s reads consent. Study staff obtaining consent should sign, date, and time stamp	Paper, uploaded to Genome Gateway
Screening/Decliner Survey	Enrollment Visit	Completed by research nurse or study coordinator	Electronic Copy
Enrollment Survey	Enrollment Visit	Completed by parent or caregiver after study enrollment	Genome Gateway
Return of Results (ROR) Survey (In-clinic and At-home surveys)	**GCOS and FACToR at ROR Visit**; Additional measures after visit	Complete primary outcome measure (GCOS) and FACToR measure immediately after ROR, additional measures can be completed at participant's convenience	Genome Gateway
1-month post-ROR Survey	Complete 1-month post ROR	Complete survey online using GG	Genome Gateway
4-month post-ROR Survey	Complete 4-months post ROR	Complete survey online using GG	Genome Gateway
4-month plus 2 weeks post-ROR Survey	Complete 4-months plus 2 weeks post-ROR	Complete survey online using GG	Genome Gateway

User roles (researchers, providers, patients/participants and administrators) with secure log-in will be defined. The following information will be tracked: current user, database accessed, date, and time and the application will be stopped automatically after 15 minutes of user inactivity requiring a fresh log-in. All data will be collected via the questionnaires in Genome Gateway. The clinical trial study coordinator, clinical trial project manager and statistician will review all data collected weekly. This will help ensure all electronic forms are being completed correctly, are intact, and have been entered into system correctly.

3.j.2 General Instructions for Completing Forms

All data recorded in Genome Gateway will be maintained according to the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines. Instructions for completing the questionnaires to ensure quality and consistency in data collection are below.

3.j.3 Retention of Study Documentation

Investigators will adhere to rigorous requirements and will retain copies of all paper (e.g. informed consent), electronic forms, and all other study documents for a period of no less than 7 years. Each site will maintain all documents, and at the close of the study UAB will retain all site documents.

3.j.4 Administrative Forms

Table 4. Administrative Forms

Form	Description	Location
Study Roster	Complete study personnel roster and signature of all members of the study team. It is the responsibility of the Principal Investigators and/or Clinical Project Manager to: designate individuals approved to make form entries and changes, and note the date when any study team member is removed from the team for any reason.	Study Binder; Table 1, section 3.b
Schedule of Visits and Evaluations	Listing of all schedule study visits and evaluations	Study Binder; Table 2, section 3.f.1
Training Log	Record of trained study personnel	Study Binder Appendix 10
Screening Log	Log of individuals screened and enrolled	Study Binder Appendix 11
Project Team Communication Log	Record of official study calls/emails between study staff	Study Binder Appendix 12

3.k <u>Data Management</u>

HudsonAlpha has extensive experience in data management, currently managing several studies. HudsonAlpha has developed the Genome Gateway platform that serves as a shared platform to seamlessly support data management

needs across the spectrum of this project. Genome Gateway is hosted on and data in is stored on a secure, HIPAA cloud-based platform offered through Datica, Inc. Data from SouthSeq participants used by researchers and genome analysts is coded and de-identified prior to being made available to those individuals. De-identified data is stored on a secure File Transfer Protocol (FTP) server hosted by HudsonAlpha and can be tracked via a unique study ID number generated for each participant. Genome Gateway is the center of data management for SouthSeq across all sites involved in the study.

3.l Reports

Reports will be prepared by the project manager, Dr. Finnila to keep the study staff up to date and engaged, as well as help to check quality control. These reports will take the form of:

- Bi-weekly status emails to the PI
  - Number of enrollees
  - Status of any non-compliance (Number of participants who haven't completed the required surveys)
  - Rate of WGS results (how long it takes for WGS results to be generated)
  - Any site-identified problems or concerns
- Bi-weekly emails to Clinical Trials Team
  - Number of enrollees
  - Status of any non-compliance (Number of participants who haven't completed the required surveys)
  - Rate of WGS results (how long it takes for WGS results to be generated)
  - List of completers for payment
  - Any site-identified problems or concerns
- Enrollment and data and safety monitoring reports prepared by study personnel to be reported to the DSMB, NGHRI, and the IRB as requested.
- Bi-weekly reports that will be compiled by the program manager in presentation form for the clinical trial meetings will include
  - Target and actual enrollment,
  - Enrollment status (screened, declined, active, completed, and lost to follow-up).
    - Individuals who have a Provider Genome Gateway account type can see if a participant has completed a survey
  - Electronic forms completed and entered

Reports will start at month 2 of the clinical trial.

3.m Study Completion and Closeout Procedures

At the conclusion of the study, the following procedures will be done to verify all study-related obligations have been met. Verification that all study procedures have been completed include, but are not limited to the following procedures include:

- All data has been collected
- All data queries have been completed
- All electronic source materials have been properly documented and archived
- Assurance that correspondence and study files are accessible for audits
- Reminder to investigators of their ongoing responsibility to maintain study records and to report any relevant study information to NGHRI.
- IRB notification of the study completion and stored copy of the notification.

- Preparation of a report summarizing the study's conduct and results.
- Participant notification of the study completion.

3.n Policies

All staff will be instructed in their study-specific responsibilities regarding data safety and confidentiality. Additionally all staff will be cautioned against the release of data to any unauthorized individuals and no data will be released to any individual without first obtaining approval from NGHRI and/or the IRBs.

This section of the MOOP will discuss the safeguards that have been put in place by the PIs to ensure participant confidentiality and data security.

The following is a list of study participant confidentiality safeguards:

- Data flow procedures – HudsonAlpha will provide thorough data entry and confidentiality training to all staff involved in data collection and data entry.
- Electronic files – All data identifying participants is kept as part of Genome Gateway and is hosted on a HIPAA-compliant server that uses both physical security as well as data encryption to secure data.
- Data listings – No personally identifying data will be included in any published item (paper, database, etc.). The only place personally identifiable data is stored is within Genome Gateway. That data is only accessible to provider and administrator level users at the study sites.
- Data distribution – Data listings containing names and other PHI are never distributed. Data access is controlled through Genome Gateway accounts. Only providers and administrators have access to PHI through Genome Gateway. Every assurance to keep those accounts to a minimum is being made.
- Data disposal – Computer listings that contain participant-identifying information will be disposed of in an appropriate manner.
- Access – Access to participant records in Genome Gateway is tightly controlled. Each research site has its own 'program' within Genome Gateway allowing it to operate semi-autonomously from the other sites with regards to participant data. Provider accounts can be associated with a program providing that user with participant data that is limited only to those participants enrolled at that site. Any individual requesting a Genome Gateway account outside of a participant being enrolled in the study must have an administrator level user create the account. The limited number of administrator accounts associated with SouthSeq keep this capability limited to 5 individuals at HudsonAlpha involved in the study that are all certified to access PHI.
- Storage – All data will be stored on either HudsonAlpha servers or by Datica, Inc., the HIPAA compliant hosting platform used by Genome Gateway.
- Passwords – Accessing Genome Gateway requires both a unique username and password that must be at least 8 characters in length, contain at least one capital letter, one number and one special character. There is no general access to Genome Gateway allowed for the SouthSeq instance of the platform. Additionally, all users can have specific permissions added or removed based on need.
- User Training – All staff at sites using Genome Gateway will have training on using the Genome Gateway platform that includes an emphasis on system security and on how participant data stored in Genome Gateway should be accessed, used and shared.
- System Testing – All changes, updates, and new programs within Genome Gateway undergo multiple rounds of testing prior to deployment. A separate staging instance that mirrors the functionality of, but contains no data related to, the SouthSeq instance has been created for this purpose. Once testing has been conducted and verified on the staging instance, the deployment to the SouthSeq instance is also tested to ensure that functionality and performance is operational as expected. This includes an assurance that the username and password access still functions as expected.

- System Backups – Data is automatically backed up by Datica, Inc. as part of the hosting and storage service. Genome Gateway is hosted by Datica, Inc. and uses a cloud-based computer strategy to have multiple, redundant backup systems in place. Non-PHI data is backed up and stored each night on a separate, secure FTP site hosted by HudsonAlpha Institute for Biotechnology.

3.n.1 Confidentiality Procedures

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in the UAB Department of Biostatistics in the School of Public Health, directed by Dr. David Redden (Co-Investigator). This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by research staff will be secured and password protected. At the end of the study, all survey data will be de-identified and archived at UAB.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or NGHRI requirements.

3.n.2 Publications

National Institutes of Health (NIH) Public Access Policy ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

Publication will be based on data from HudsonAlpha, UAB, UMMC, Children's Hospital of New Orleans and Woman's Hospital (Baton Rouge) that has been analyzed as stipulated in the statistical analysis plan. Investigators will not present data gathered from one site before the full publication, unless formally agreed to by all Investigators. Upon completion of the study we will publish our findings in peer-reviewed journals. Authors must participate in the writing of the paper in accordance with the International Committee of Medical Journal Editors guidelines (*N Engl J Med* 1991). First authors are expected to delete names from the final list of authors if those individuals have not satisfied criteria for authorship in accordance with those guidelines. In general, the researcher who first conceived of the project and submitted a plan for the manuscript should have the option of serving as first author. Conflicts in first authorship will be resolved by the study team PIs. In addition to SouthSeq publications, study team members will be involved in Phase II of the Clinical Sequencing Evidence-Generating Research (CSER2)-wide consortium projects and publications.

The SouthSeq study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, dbGap, and results information from this trial will be submitted to ClinicalTrials.gov.

3.o <u>MOOP Maintenance</u>

The MOOP will be maintained and updated throughout the study by the clinical trial study staff at UAB, as necessary. The most current copies of the MOOP will be kept on Freedcamp platform (www.freedcamp.com), and a hard copy, in loose-leaf form, will be kept in staff issued binders along with other study files for staff reference. Each page of the MOOP is numbered, dated, and contains the version number to eliminate any confusion. As a living document the MOOP will be continuously reviewed by study staff to ensure the operating procedures described are accurate. If any procedures are

changed or modified, the MOOP will be updated and the new version will be emailed and printed (by each site) for study binders for all study staff members.

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Appendix 1: WGS Results Report (Family-Friendly)

Participant Name:
Participant ID#:
Participant DOB:
Report Date:

This letter describes genetic test results from the SouthSeq research study (research protocol No. 300000328).

Your child was enrolled because he or she was in the neonatal intensive care unit (NICU) and had symptoms that may be due to a genetic problem.

Reason for testing: Based on information provided to the research lab, the child has a history of ***[symptoms].***

Results related to the reason for testing (also called primary results):

No genetic changes reported (also called a negative result)

Result

- The whole genome sequencing test was not able to find a genetic cause for your child's symptoms.
- It is still possible that your child's symptoms have a genetic cause. Current tests cannot find or understand all of the genetic changes that may cause health problems.

Future care

- No test is perfect. Genetic testing will continue to change and improve over time, as will the knowledge of how genetic changes can cause health problems.
- Other genetic tests may be needed for your child based on ***[his/her]*** personal and family medical histories. Please continue follow-up with your child's healthcare providers to learn about new information, testing options, or research studies.

Results NOT related to the reason for testing (also called secondary results):

No other genetic changes reported (also called a negative result).

Keep in mind:

- In addition to looking for the reason for your child's symptoms, this test looked at 59 other genes* that can cause disease in the future.
- The whole genome sequencing test did not find any specific genetic changes associated with risk of developing a disease in the future.
- This does not mean your child will not develop a genetic disease in the future. Humans have more than 20,000 genes. There are many gene changes that may cause disease that the lab cannot find or understand.

If you have questions, please contact your child's healthcare team at the NICU where **[he/she]** was enrolled.

You may also contact a study genetic counselor at the information below.

Kelly East, MS, CGC
Certified Genetic Counselor
HudsonAlpha Institute for Biotechnology
256-327-0461

Participant Name:
Participant ID#:
Participant DOB:
Report Date:

Information about the test
Keep this information for future use

Whole genome sequencing was done on a research basis at the HudsonAlpha Institute for Biotechnology (not in a CAP/CLIA environment). Sequencing was done on an Illumina HiSeq X sequencer at an approximate depth of 30X. Variant pathogenicity was determined using ACMG criteria.

*Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2017. https://www.nature.com/articles/gim2016190

Participant Name:
Participant ID#:
Participant DOB:
Report Date:

This letter describes genetic test results from the SouthSeq research study (research protocol No. 300000328).

Your child was enrolled because he or she was in the neonatal intensive care unit (NICU) and had symptoms that may be due to a genetic problem.

Reason for testing: Based on information provided to the research lab, the child has a history of ***[symptoms].***

Results related to the reason for testing (also called primary results):

No genetic changes report (also called a negative result)

Result

- The whole genome sequencing test was not able to find a genetic cause for your child's symptoms.
- It is still possible that your child's symptoms have a genetic cause. Current tests cannot find or understand all of the genetic changes that may cause health problems.

Future care

- No test is perfect. Genetic testing will continue to change and improve over time, as will the knowledge of how genetic changes can cause health problems.
- Other genetic tests may be needed for your child based on ***[his/her]*** personal and family medical histories. Please continue follow-up with your child's healthcare providers to learn about new information, testing options, or research studies.

Results NOT related to the reason for testing (also called secondary results):

Disease-causing genetic change found (also called a positive result)

Result

- **A change was found in one copy of your child's *APOB* gene.**
- Changes in the *APOB* gene have been seen in people with high cholesterol. Based on this result your child may have an increased chance to have high cholesterol.

Chance family members could have the same genetic change (recurrence risk)

- This *APOB* gene change was inherited from your child's mother. Other relatives on your child's mother's side of the family, including your child's brothers and sisters, may also have this change and want to discuss this with their doctors.

Future care

- Your child's doctors and nurses may talk with you about changes to your child's care based on this result.
- Please see the attached lab report for more specific information about this genetic change.

Participant Name:
Participant ID#:
Participant DOB:
Report Date:

- This test looked at 59 genes* that can cause disease in the future. Humans have more than 20,000 genes. There are many gene changes that may cause disease that the lab cannot find or understand.

For More Information:

- About *[insert gene/condition]*:
  - [Insert Source]: [insert link]
- For support related to *[insert gene/condition]*: [insert link]

If you have questions, please contact your child's healthcare team at the NICU where **[he/she]** was enrolled.

You may also contact a study genetic counselor at the information below.

Kelly East, MS, CGC
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HudsonAlpha Institute for Biotechnology
256-327-0461

Information about the test
Keep this information for future use

Whole genome sequencing was done on a research basis at the HudsonAlpha Institute for Biotechnology (not in a CAP/CLIA environment). Sequencing was done on an Illumina HiSeq X sequencer at an approximate depth of 30X. Variant pathogenicity was determined using ACMG criteria.

In addition to the affected child, laboratory reports may be available for parent samples. The last digit of the "ID2" section of the laboratory report header indicates whether a report is for the child/proband (P), mom (M), or dad (D).

*Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2017. https://www.nature.com/articles/gim2016190

Participant Name:
Participant ID#:
Participant DOB:
Report Date:

This letter describes genetic test results from the SouthSeq research study (research protocol No. 300000328).

Your child was enrolled because he or she was in the neonatal intensive care unit (NICU) and had symptoms that may be due to a genetic problem.

Reason for testing: Based on information provided to the research lab, the child has a history of ***[symptoms].***

Results related to the reason for testing (also called primary results):

Genetic change was found (also called a positive result)

Result

- The whole genome sequencing test found a change in the *SATB2* gene that is likely the reason for most or all of your child's symptoms.
- Changes in this gene have been seen in people with Glass syndrome.
- People with glass syndrome can have difficulty learning, speech delay, and certain physical differences.

Chance that family members could have the same genetic change (recurrence risk)

- This genetic change was new in your child and not found in the blood of either parent. The chance that these two parents have another child together with the same genetic change is less than 1% (less than 1 in 100).
- For your child, the chance of having a child with the same *SATB2* change is 50% (1 in 2).

Future care

- Your child's doctors and nurses may talk with you about changes to your child's care based on this result.
- Other genetic tests may be needed for your child based on ***[his/her]*** personal and family medical histories.
- Please continue follow-up with your child's healthcare providers to learn about new information, testing options, or research studies.
- Please see the attached lab report for more specific information about this genetic change.

Results NOT related to the reason for testing (also called secondary results):

No other genetic changes found (also called a negative result)

Keep in mind:

- In addition to looking for the reason for your child's symptoms, this test looked at 59 other genes* that can cause disease in the future.
- The whole genome sequencing test did not find any specific genetic changes associated with risk of developing a disease in the future.

- This does not mean your child will not develop a genetic disease in the future. Humans have more than 20,000 genes. There are many gene changes that may cause disease that the lab cannot find or understand.

For More Information:

- About *[insert gene/condition]*:
  - [Insert Source]: [insert link]
- For support related to *[insert gene/condition]*: [insert link]

If you have questions, please contact your child's healthcare team at the NICU where **[he/she]** was enrolled.

You may also contact a study genetic counselor at the information below.

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In addition to the affected child, laboratory reports may be available for parent samples. The last digit of the "ID2" section of the laboratory report header indicates whether a report is for the child/proband (P), mom (M), or dad (D).

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Participant Name:
Participant ID:
Participant DOB:
Report Date:

This letter describes genetic test results from the SouthSeq research study (research protocol No. 300000328).

Your child was enrolled because he or she was in the neonatal intensive care unit (NICU) and had symptoms that may be due to a genetic problem.

Reason for testing: Based on information provided to the research lab, the child has a history of ***[symptoms].***

Results related to the reason for testing (also called primary results):

Genetic change was found (also called a positive result)

Result

- The whole genome sequencing test found two changes in the *DHCR7* gene that together are likely the reason for most or all of your child's symptoms.
- Changes in this gene have been seen in people with Smith-Lemli-Optiz syndrome (SLOS).
- People with SLOS can have learning difficulties and certain facial and physical differences.

Chance that family members could have the same genetic changes (recurrence risk)

- One of the genetic changes was found in her mother's blood. The other genetic change was found in her father's blood.
- Having one genetic change in *DHCR7* does not cause SLOS. One change means someone is a carrier for SLOS.
- When two carriers of SLOS have a child together, there is a 25% (1 in 4) chance with each pregnancy to have a child with SLOS.

Future care

- Your child's doctors and nurses may talk with you about changes to your child's care based on this result.
- Other genetic tests may be needed for your child based on ***[his/her]*** personal and family medical histories.
- Please continue to follow-up with your child's healthcare providers to learn about new information, testing options, or research studies.
- Please see the attached lab report for more specific information about these genetic changes.

Results NOT related to the reason for testing (also called secondary results):

No other genetic changes found (also called a negative result)

Keep in mind:

- In addition to looking for the reason for your child's symptoms, this test looked at 59 other genes* that can cause disease in the future.

Participant Name:
Participant ID:
Participant DOB:
Report Date:

- The whole genome sequencing test did not find any specific genetic changes associated with risk of developing a disease in the future.
- This does not mean your child will not develop a genetic disease in the future. Humans have more than 20,000 genes. There are many gene changes that may cause disease that the lab cannot find or understand.

For More Information:

- About *[insert gene/condition]:* [insert linik]
  - Genetics Home Reference
  - GeneReviews
- For support related to *[insert gene/condition]*: [insert link]

If you have questions, please contact your child's healthcare team at the NICU where **[he/she]** was enrolled.

You may also contact a study genetic counselor at the information below.

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Information about the test
Keep this information for future use

Whole genome sequencing was done on a research basis at the HudsonAlpha Institute for Biotechnology (not in a CAP/CLIA environment). Sequencing was done on an Illumina HiSeq X sequencer at an approximate depth of 30X. Variant pathogenicity was determined using ACMG criteria.

In addition to the affected child, laboratory reports may be available for parent samples. The last digit of the "ID2" section of the laboratory report header indicates whether a report is for the child/proband (P), mom (M), or dad (D).

*Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2017. https://www.nature.com/articles/gim2016190

Participant Name:
Participant ID#:
Participant DOB:
Report Date:

This letter describes genetic test results from the SouthSeq research study (research protocol No. 300000328).

Your child was enrolled because he or she was in the neonatal intensive care unit (NICU) and had symptoms that may be due to a genetic problem.

Reason for testing: Based on information provided to the research lab, the participant has a history of ***[symptoms].***

Results related to the reason for testing (also called primary results):

Uncertain genetic change found (also called an uncertain result)

Result

- The whole genome sequencing test found a change in the *TPM3* gene. Some changes in the *TPM3* gene have been seen in people with several forms of myopathy, or muscle weakness.
- The specific *TPM3* gene change found in your child has not been seen before. The lab is not sure whether it can cause symptoms or is just a harmless (benign) gene change.

Chance that family members could have the same genetic change (recurrence risk)

- This genetic change was inherited from your child's mother who has not reported symptoms. The child's mother may need to have further testing to look for any signs or symptoms of the condition.
- The chance that your child's mother will have another child with the same genetic change is 50% (1 in 2).
- For your child, the chance of having a child with the same *TPM3* change is also 50% (1 in 2).
- Because the meaning of this change is unknown, future children with the same *TPM3* gene change may not necessarily have health problems. This result should not be used to predict symptoms in other children or family members until it is better understood.

Future care

- Your child's doctors and nurses offer your child more tests or exams that would help them learn whether this change is the cause of your child's symptoms. However, most of the time an uncertain genetic result will not change your child's care.
- If the lab gets more information about this change during the course of the research study, your child's doctor will get an updated report.
- Other genetic tests may be needed for your child based on ***[his/her]*** personal and family medical histories. Please continue to follow-up with your child's healthcare providers to learn about new information, testing options, or research studies.
- Please see the attached lab report for more specific information about this genetic change.

Participant Name:
Participant ID#:
Participant DOB:
Report Date:

Results NOT related to the reason for testing (also called secondary results):

No other genetic changes reported (also called a negative result)

Keep in mind:

- In addition to looking for the reason for your child's symptoms, this test looked at 59 other genes* that can cause disease in the future.
- The whole genome sequencing test did not find any specific genetic changes associated with risk of developing a disease in the future.
- This does not mean your child will not develop a genetic disease in the future. Humans have more than 20,000 genes. There are many gene changes that may cause disease that the lab cannot find or understand.

For More Information:

- About *[insert gene/condition]*:
  - [Insert Source]: [insert link]
- For support related to *[insert gene/condition]*: [insert link]

If you have questions, please contact your child's healthcare team at the NICU where **[he/she]** was enrolled.

You may also contact a study genetic counselor at the information below.

Kelly East, MS, CGC
Certified Genetic Counselor
HudsonAlpha Institute for Biotechnology
256-327-0461

Information about the test
Keep this information for future use

Whole genome sequencing was done on a research basis at the HudsonAlpha Institute for Biotechnology (not in a CAP/CLIA environment). Sequencing was done on an Illumina HiSeq X sequencer at an approximate depth of 30X. Variant pathogenicity was determined using ACMG criteria.

In addition to the affected child, laboratory reports may be available for parent samples. The last digit of the "ID2" section of the laboratory report header indicates whether a report is for the child/proband (P), mom (M), or dad (D).

*Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2017. https://www.nature.com/articles/gim2016190

Appendix 2: Decliner Survey

1. **Please identify the individual completing this survey.**
   - ☐ Mother
   - ☐ Father
   - ☐ Other (please specify): _____

2. **What is your date of birth?** --/--/----

3. **What category or categories best describe you?** Check all that apply.
   - ☐ American Indian, Native American, or Alaskan Native
   - ☐ Asian
   - ☐ Black or African American
   - ☐ Native Hawaiian/Pacific Islander
   - ☐ White or European American
   - ☐ Middle Eastern or North African/Mediterranean
   - ☐ Hispanic/Latino(a)
   - ☐ Prefer not to answer
   - ☐ Unknown/None of these fully describe me

4. **What category or categories best describe your child?** Check all that apply.
   - ☐ American Indian, Native American, or Alaska Native
   - ☐ Asian
   - ☐ Black or African American
   - ☐ Native Hawaiian/Pacific Islander
   - ☐ White or European American
   - ☐ Middle Eastern or North African/Mediterranean
   - ☐ Hispanic/Latino(a)
   - ☐ Prefer not to answer
   - ☐ Unknown/None of these fully describe my child

5. **What is the highest grade or level of school you completed or the highest degree you received?** (Check one)
   - ☐ No schooling completed
   - ☐ Elementary school (kindergarten through 5th grade)
   - ☐ Middle school (6th, 7th, or 8th grade)
   - ☐ Some high school (9th, 10th, or 11th grade)
   - ☐ 12th grade, no diploma
   - ☐ High school graduate (diploma or GED or equivalent)
   - ☐ Some post-high school training (college or occupational, technical, or vocational training), no degree or certificate
   - ☐ Completed occupational, technical, or vocational program, received degree or certificate
   - ☐ Associate (2-year) college degree
   - ☐ Bachelor's degree (for example: BA, AB, BS)
   - ☐ Master's degree (for example: MA, MS, MEng, MEd, MSW, MBA)
   - ☐ Professional degree (for example: MD, DDS, DVM, LLB, JD)
   - ☐ Doctoral degree (for example: PhD, EdD)

6. Please tell us why you decided not to join this study: [open response]

Instructions for investigator: please select every box that corresponds to the reasons given for non-participation in the free text above.

Study

- ❑ The study will take too much of my time/too busy/no time
- ❑ The study does not give me enough money for the amount of time it requires from me
- ❑ The study location or visits are not convenient for me/too far/unable to travel/no transportation
- ❑ I do not wish to give the study samples (blood, saliva, etc.)

Privacy

- ❑ Results are stored in my/my child's electronic health record
- ❑ My/my child's genetic results could be seen by:
  - ❑ The government
  - ❑ My employer
  - ❑ My insurance company
- ❑ My/my child's genetic results could be used to discriminate against me/my child by my:
  - ❑ Health Insurance
  - ❑ Life Insurance
  - ❑ Long-Term Care Insurance
  - ❑ Disability Insurance
  - ❑ Other [Free Text]

Health

- ❑ I am overwhelmed by my own/my child's health problems right now
- ❑ I do not want more testing than my own/my child's doctor recommends
- ❑ I am too ill

Do not want certain types of genetic results

- ❑ Results that aren't related to my own/my child's health problems right now
- ❑ Results that only cause health problems in adults
- ❑ Results that don't affect my health but could be important for my children or other family members
- ❑ Results that are uncertain
- ❑ Results about conditions with no treatment

Other

- ❑ Religious/spiritual reasons
- ❑ Genetic test results may affect my family relationships
- ❑ I want my child to choose for him/herself when he/she is an adult
- ❑ Not interested in [my child] participating in research (general)/Not interested in [my child]participating in genetics research
- ❑ Too many other competing demands (caring for others, long work hours)
- ❑ Other [Free Text]

- ❑ **REFUSED TO ANSWER/NO REASON PROVIDED**

7. [OPTIONAL] This list is from other patients/parents who decided not to join studies like this one. Did any of these reasons affect your decision not to join this study? Please choose up to three reasons.

- ❑ The things I/my child need to do to be in the study didn't work well for me
- ❑ I have concerns about my privacy
- ❑ I am not interested in participating in research
- ❑ My/my child's current health condition is all I want to focus on right now
- ❑ I don't want genetic research results from this study
- ❑ I'm worried about how I will cope with the genetic information I might receive

Appendix 3: Informed Consent Forms (Site-Specific)

CONSENT FORM

Title of Research:	South-seq: DNA sequencing for newborn nurseries in the South (NIH Grant Number 2U01HG007301-05)
UAB IRB Protocol #:	IRB-300000328
Principal Investigators:	Bruce Korf MD, PhD
Sponsor:	NIH National Human Genome Research Institute (Contact: Lucia Hindorff PhD, MPH)

For Children (persons under 18 years of age) participating in this study, the term "You" addresses both the participant ("you") and the parent or legally authorized representative ("your child").

Purpose of the Research

We are asking you to take part in a research study. The purpose of this research study is to use whole genome sequencing (WGS), looking at your DNA, to identify the genetic cause of conditions like those observed in your child. For individuals with rare, undiagnosed diseases and their families, this experimental genetic test may provide information about what is causing the disease or condition. This information may be beneficial to your family in directing your child's health care, medical treatments, and your family planning decisions. Educational tools about your child's condition may also become available with a confirmed genetic diagnosis.

In addition, due to the limited number of genetic counselors available to support patients that may benefit from WGS, we will be comparing two results delivery methods: genetic counselors (standard of care), and healthcare providers (e.g. neonatologists and neonatology nurse practitioners) who undergo specific genetics results delivery training. In this clinical trial, we aim to demonstrate that both delivery methods are equivalent (i.e. there is no difference between the two methods). In order to so this, we plan to record the return of results conversations that you will have as part of this study.

Due to the experimental nature of this research study, data generated is based upon the knowledge currently accepted in the field. As more genomes are sequenced and as sequencing techniques improve, we will be better at identifying and understanding extremely rare variants (rare changes in DNA). In doing this, we will learn more about how certain variants may cause disease. For this reason, we plan to store samples for future research.

There will be approx. 1500 newborn participants enrolled for WGS, and 800 parents and caregivers enrolled for the clinical trial across 6 NICU sites: UAB/Children's of Alabama, University of Mississippi Medical Center (UMMC), Woman's Hospital, University of Louisville and Norton Healthcare (UofL). Samples will also be collected from biological mothers and fathers (up to 2,250 individuals), when available, so that we can use their samples to determine inheritance of any variants we find in their child. We also hope to include a diverse group of participants so we are planning to offer this test to

all populations, especially those underrepresented in science and genomic research such as African Americans and those from rural areas.

Explanation of Procedures

If you agree to join the study, you are agreeing to:

- Give us permission to collect a blood sample for DNA analysis
    - Adults will give approximately 8mL (approx. 1.6 tsp) of blood that will be drawn from the arm.
    - Newborns will give no more than the maximum amount allowed for their body weight according to the Children's Of Alabama guidelines.
- Give us permission to fully analyze your DNA (or other related material, like RNA or protein) and determine the health significance of your genetic results.
- Allow us to return health information to you that we feel may be important to your child's health or other biological relatives.
- Allow key study personnel to access your child's personal medical records to aid in analysis. Study personnel may collect information about the child's symptoms, health history, medications/treatments, etc.
- Provide key study personnel with information about your child's health history, pregnancy and birth history, information about your health and that of other family members, if you know it, etc. Study personnel will not access your medical record. They will only have access to the information that you choose to share with them.
- Allow us, if you so choose, to return genetic results that are not related to your child's condition but are medically important for other reasons.
- Answer survey questions at 5 time points: the time of consent, return of results (ROR) appointment, 1-month post-ROR, 4-months post-ROR, and 4.5-months post-ROR. Each survey will take approximately 20-35 minutes to complete.

You will be asked to take part in two clinic visits here in the nursery or at the outpatient clinic. During the first visit, you will be asked to enroll in the study and give a blood sample (1.5hrs) and during the second visit you will receive the results of your child's DNA test either by a genetic counselor or a trained healthcare provider (1.5-2hrs). The return of results visit can either take place in-person or over the phone. A certified letter with results will be sent to those who do not participate in either in the in-person or phone ROR appointment.

More than one parent/guardian/caregiver of a child receiving WGS can participate in the study. It is important that anyone participating in the survey portion of the study be present at ROR and complete every survey.

Collecting samples from both biological parents increases the chances of identifying genetic variation in your child that might be causing his or her symptoms. However if both parents are not available, we can still analyze eligible patients and potentially find valuable information. In cases where we enroll family members, our DNA test can identify whether a person is the biological parent or not. We will not tell you or your family members if we find out that one or both parents

are not biologically related to the child, however we are less likely to discover diagnostic information about your condition without both biological parents.

Your blood samples will be labeled with a unique code (coded) and sent to researchers at the HudsonAlpha Institute for Biotechnology, a non-profit genetics research center located in Huntsville, AL. Some relevant, health information will also be given to the research staff, and coded with a unique study identifier, to aid in their analysis.

We will use state-of-the-art technologies to generate large amounts of information about the DNA from you and your child. A group of experts, including medical doctors and researchers, will use scientific findings and genetic databases to help decide what genetic information may be important to the health of your child. The sequence of all results believed to be medically relevant or important to your child's or your own health will be validated at HudsonAlpha Clinical Services Laboratory in Huntsville, AL or another independent clinical laboratory. We expect the entire DNA analysis process to take 2-4 months.

We do intend to perform analysis of each sample within our budgetary and technical means. If we are unable to analyze your samples you will be notified within 6 months of enrollment and sample collection. There is no cause for concern if you are told that we could not complete the analysis and provide you with results.

Return of results is at the discretion of the clinicians and researchers involved with this study. If they identify results that may impact your child's health, they may return those results to you. You will be scheduled for an appointment to discuss these findings with a genetic counselor or a trained healthcare provider. Only a subset of results believed to be important to your child's medical care or those in line with the goals of this study will be reported to you. We will not provide you with all of the genetic information that we generate. At your results appointment, you may be provided with information regarding:

- Primary findings - These findings will include information about a variant(s) (DNA change) that may potentially be the reason for your child's symptoms or condition.
    - Most children will not receive a primary finding (or diagnosis). If no diagnosis is found, we will tell you. Even if we do not find a genetic diagnosis, your condition may still be the result of a change in your DNA that we are currently unable to identify.
    - If you receive a genetic diagnosis, this may not change your child's prognosis or medical treatment. However it may help you and your doctor to better understand the cause of your child's condition and the risks of similar conditions affecting your biological children.
- Secondary findings – These findings may be reported to any study participant and may include any genetic changes that might impact your health or the health of your current or future children. These may include:
    - Whether there are any changes in your DNA that could put you at a higher risk for developing a disease unrelated to your child's condition in the future, such as cancer or heart disease.

1. Some of these diseases may be medically useful and some may not be medically useful. We will not return results that are not medically useful.
2. Some of these diseases will appear in childhood and others will appear when you are an adult.

- Carrier status – In the event that we discover that your child's symptoms are caused by a recessive genetic condition where he or she inherited one variant (DNA change) from each parent, we may provide information about whether or not you are a "carrier" for a genetic change that may be passed on to your biological children.

We will arrange for a genetic counselor or a trained healthcare provider to discuss the results of the test with you. Educational materials will also be made available to you to help you better understand any results that you may or may not receive as part of this study.

You will be actively enrolled in this study for up to one year however, we may continue to access your medical record for up to 5 years. We plan to use coded information from our medical record to determine the impact of whole genome sequencing and genetic diagnosis on medical care. After you receive the results of the genetic test, you may be contacted by your physician or key study personnel to check on you or to ask follow-up questions. Your DNA samples may be stored indefinitely for future research unless you choose to withdraw from the study. Please note that participation in this study is voluntary and you may withdraw from this study at any time.

You will also be presented with a baseline survey at the time of enrollment that you can complete online using Genome Gateway. The survey will ask you questions about basic demographics, how you feel about your child's health and your experience in the hospital, how well you understand medical terms, math and genetics. After you receive results, you will be asked some of these same questions and some additional ones related to your health, your understanding of the genetics results returned, and how the results influence future planning at 1-month post-ROR, 4-months post-ROR, and 4.5-months post-ROR.

Risks and Discomforts

The risks of drawing blood include pain, bruising, lightheadedness, and fainting. Infection at the site of the needle stick is a rare side effect. These are the same risks you face any time you have a blood test.

The main concerns associated with genetic testing are anxiety, depression, or other forms of emotional distress that may result from receiving genetic information about the suspected cause of your child's condition. This is especially true for those diseases that are not treatable or preventable. Though some treatments have been shown to help individuals with certain genetic conditions, there is no "cure" for most.

When performing genetic testing, it may be discovered that family relationships are not as predicted. For example, a child might not be biologically related to his/her father, or two people who are married might turn out to be biologically related. These findings will not be disclosed as part of this study.

In some cases, you may receive information about your carrier status and/or changes in your DNA that may impact your health. These findings will only be returned if they were inherited by your child who is enrolled in this study and suspected to contribute to their condition. Genetic changes in children that affect development may be inherited from one or both parents, even if the parents appear to be healthy. This information may affect the way you view or evaluate yourself or your family. It may also influence, or generate anxiety about, future family planning decisions.

It is also important to keep in mind that you and your biological relatives have similar DNA sequences. This means that genetic information about your child may also have implications for your relatives if the variation was inherited.

You may be referred to an additional physician or clinic for further testing or advice depending on the type of genetic information we generate from your sample. If you experience psychological distress or other difficulties, we can also refer you to an appropriate resource for care and/or support.

There may be unforeseeable risks associated with receiving genetic information and the potential decisions, actions, or inactions that may be required in response to that information. Please consider this carefully and ask any questions that you may have before deciding whether or not to participate in this study.

It is important that you consider the risks and uncertainties of this research study that make it different from traditional medical testing.

We will make sure that the information that you are given is as accurate as possible to the best of our ability. We will use the best standards, practices, and technologies available to researchers. However, the technologies available to analyze DNA and our knowledge of how DNA affects health are changing rapidly. They are also subject to much uncertainty. Some DNA changes that are important to health may be missed, and other DNA changes that are not important may be incorrectly identified as if they are important. There are also moral and ethical questions about using genetic information on which scientific and medical communities have not yet reached a consensus. Therefore, we do NOT guarantee that our test will have the same levels of completeness, accuracy, or standardization associated with more traditional medical tests.

Before offering your consent to participate in this research study, please consider all of the risks associated with:

- The return or possible lack of return of results;
- Whether our interpretation of those results is accurate;
- How you and/or your family will choose to act upon or not act upon the information or lack of information.

Benefits

You may not benefit directly from taking part in this study. However, your participation may lead to new discoveries that help to advance medical research and improve patient care, especially, but not only, newborn patient care in the future. Your participation in this study may help to make health care and access to health care broader and more representative.

You may find out if there is a change in your child's DNA that has altered their development. You might also find out if this change could affect future biological children.

A genetic diagnosis may help you connect with other families in the community who face similar medical problems. While unlikely, it is possible that a genetic diagnosis may point your doctor to a better medical and/or educational treatment.

You may discover that you or your child are at an increased risk for developing other diseases and that information may be of medical benefit.

None of the above benefits are guaranteed, and it is expected that many participants will not receive specific information that is relevant to their health.

Alternatives

This is not a treatment study. Your alternative is not to participate in this research study.

Confidentiality

Information obtained about you for this study will be kept confidential to the extent allowed by law. However, research information that identifies you may be shared with people or organizations for quality assurance or data analysis, or with those responsible for ensuring compliance with laws and regulations related to research. They include:

- the UAB Institutional Review Board (IRB). An IRB is a group that reviews the study to protect the rights and welfare of research participants.
- the NIH National Human Genome Research Institute (NHGRI)
- the Office for Human Research Protections (OHRP)

The information from the research including your child's clinical information, family history, and genetic variants may be published for scientific purposes; however, your identity will not be given out to anyone outside of the clinical team involved with the study.

Your consent form will be placed in your child's medical record at UAB Health System or UMMC. This may include either a paper medical record or electronic medical record (EMR). An EMR is an electronic version of a paper medical record of your care within this health system. Your child's EMR may indicate that you and your child are enrolled in this study and provide the name and contact information for the principal investigator.

Results of research tests or procedures that have been clinically validated (i.e. Sanger reports) may be placed in your child's medical record. All information within your medical record can be viewed by individuals authorized to access the record.

Information relating to this study, including your name, medical record number, date of birth and social security number, may be shared with the billing offices of UAB and UAB Health System affiliated entities or UMMC so costs for clinical services can be appropriately paid for by either the study account or by your insurance.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and some employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware this federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance, nor does it protect you against genetic discrimination by some employers.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Voluntary Participation and Withdrawal

Whether or not you take part in this study is your choice. There will be no penalty if you decide not to be in the study. If you decide not to be in the study, you will not lose any benefits you are otherwise

owed. You are free to withdraw from this research study at any time. Your choice to leave the study will not affect your relationship with any institution participating in this study.

In the event that you chose to withdraw from the study:

- No further genetic information from the study will be reported to you.
- Your blood samples will be destroyed.
- You will not be contacted to provide new information, additional samples, or participate in additional studies related to this project.
- If the analysis of your DNA has been completed, this information will be retained for the study.

If you would like to withdraw from the study, please contact Dr. Bruce Korf at 205-934-9411.

Cost of Participation

There will be no cost to you for taking part in this study. The blood draw, genomic sequencing and analysis, and genetic counseling related to this study will be provided to you at no cost during the study period.

After you receive your research results, you may decide with your doctor or your child's doctor to get more testing. The costs of your standard medical care or any services rendered in response to a genetic finding identified by this research project will be billed to you and/or your insurance company in the usual manner. This type of follow-up medical testing will be considered part of your clinical care, and will not be paid for by the research study.

Payment for Participation in Research

Participation in this study is voluntary and $25 will be provided for each survey completed for a total of $125 for your completion of all 5 study-related surveys. Ask the study staff about the method of payment that will be used for this study (e.g., check, cash, gift card, direct deposit); payment may take up to 4 weeks to process.

Payment for Research-Related Injuries

UAB, UMMC, HudsonAlpha and NIH/NHGRI/sponsors of this research project have not provided for any payment if you are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge.

Significant New Findings

The study doctor or study staff will tell you if new information becomes available that might affect your choice to stay in the study. Please note that HudsonAlpha may, but is not required to, reanalyze your sample or report any new findings after results have been returned.

Storage of Specimens for Future Use

As part of this study, we would like to store some of the blood and DNA specimens collected from you and your child for validation of variants (to determine if a variant was inherited from a parent, etc.) identified by this project and for future research relevant to rare disease or other genetic

disorders. The future research may be conducted by the study doctor or by other researchers that obtain IRB approval for their research. The specimens will be labeled with a code that only the study doctor can link back to you. Results of any future research will not be given to you or your doctor. The specimens obtained from you in this research may help in the development of a future commercial product. There are no plans to provide financial compensation to you should this occur. You do not have to agree to allow your specimens to be stored in order to be part of this study.

You may at any time withdraw from the study and request that your specimens be removed from storage and not be used for future research. If you decide you want your specimens removed, you may contact Dr. Bruce Korf at 205-934-9411. Once the request is received, and if your samples have not already been used for other research, they will be destroyed. If you do not make such a request, your specimens will be stored indefinitely or until used.

Initial next to your choice below:

____I agree to allow my specimens to be kept in the HudsonAlpha CSL and used for future genetics research.

____I do NOT agree to allow my specimens to be kept and used for future research.

Genomic Data Sharing (GDS)

We consider the privacy of your information to be of high priority and will take a variety of steps to ensure that privacy. However it is important for researchers to share some of the information that they learn from studying human samples. We will never share personally identifiable information, like names and addresses, with anyone outside of the research study. However, parts of your information may be shared.

Some of your genetic information, limited to a very small subset that will not cause privacy loss risks to you, may be published in scientific journals or other unrestricted-access public venues to encourage sharing of the knowledge that may be learned by analyzing your DNA and DNA from other individuals. This could include information about your child's symptoms, their age, and any genetic findings that we discover.

We may share coded lists of the DNA differences that we identify in public genetic databases. These databases gather genetic information from large groups of people and are pooled together such that no specific participant can be identified.

There is a very small chance that some commercial value may result from the use of your donated samples or genetic information. If that happens, you will not receive a share in any profits.

Unless you opt out, we may submit your complete genomic data along with some of your coded health information to an NIH-designated Data Repository such as dbGAP (http://www.ncbi.nlm.nih.gov/gap), AnVIL (https://anvilproject.org/), or another controlled access database. Access to dbGAP and AnVIL is only available to qualified researchers at qualified

institutions who have agreed to abide by certain privacy safeguards, obligating them, both legally and ethically, to protect your privacy and to maintain information confidentiality. However, since your genetic information is unique to you, there is a small chance that someone could trace your information back to you. This risk is very small, but may grow in the future. Some risks and benefits are listed below:

Risks: The risk of sharing your genomic data is that someone could link the information stored in the databases back to you. If your information suggests something about your health such as increased risk for disease, it could be misused. For example, it could be used to make it harder for you to get or keep a job or insurance or be used to discriminate against you or your family. There may also be other unknown risks. As stated above (confidentiality section of this form), there are federal protections against the misuse of your data (i.e. the Genetic Information Nondiscrimination Act, GINA).

Benefits: There is no direct benefit to you from sharing your genomic data with NIH-designated data repositories, however allowing researchers to use your data may lead to a better understanding of how genes affect health which may help other people in the future.

Initial next to your choice below:

____ I agree for my genetic and other relevant study data, such as health information, to be shared with NIH-designated repositories such as dbGAP and AnVIL in a coded form for future research or analysis

____ I do NOT agree for my genetic and other relevant study data, such as health information, to be shared with NIH-designated repositories such as dbGAP and AnVIL in a coded form for future research or analysis

Contact For Future Research

As new research opportunities are identified, the researchers may wish to perform additional tests on fresh samples or invite eligible participants to enroll in new studies. We would like permission to contact you in the future, however this is not a requirement to participate in this study. A separate consent form will be obtained if you wish to participate in future research.

Initial next to your choice below:

____ You have permission to contact me about new research opportunities that may interest me.

____ You do NOT have permission to contact me about new research opportunities.

Secondary Findings

One unanimous decision to receive or not to receive secondary findings must be made by each participant family. Because parental samples are only used for confirmation of variation identified in the child's whole genome sequence for this project, only those secondary findings identified in the child will be confirmed in the parental samples. Participant families may opt to receive this information, if available. If a family chooses to do so, information about an identified secondary finding will be included in the child's medical record. Nothing will be placed in the parent's medical record.

Initial next to your choice below:

____ We (child and parent(s), if enrolled) would like to receive information about secondary findings.

____ We (child and parent(s), if enrolled) would NOT like to receive information about secondary findings.

Questions

If you have any questions, concerns, or complaints about the research or a research-related injury including available treatments, please contact Dr. Bruce Korf at 205-934-9411.

If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact the UAB Office of the IRB (OIRB) at (205) 934-3789 or toll free at 1-855-860-3789. Regular hours for the OIRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday.

Legal Rights

You are not waiving any of your legal rights by signing this consent form.

Signatures

Your signature below indicates that you have read (or been read) the information provided above and agree to have your child participate in this study. You will receive a copy of this signed consent form.

Your signature below indicates that you have read (or been read) the information provided above and agree to participate in this study. You will receive a copy of this signed consent form.

_____

Name of Proband Child (printed)

_____

Signature of Parent or Legally Authorized Representative Date

_____ Mother/Father/Caregiver

Name of Parent Participant (printed) Relationship

_____

Signature of Parent Participant Date

_____ Mother/Father/Caregiver

Name of Parent Participant (printed) Relationship

_____

Signature of Parent Participant Date

_____

Signature of Person Obtaining Consent Date

In this research study, one consent form may be used to waive consent for the infant and capture informed consent of both parents; however, a separate HIPPA Authorization form will be completed for each participant.

Waiver of Assent

The assent of _____(name of child/minor) was waived because of:
Age _____ Maturity _____ Psychological state of the child _____

University of Alabama at Birmingham

AUTHORIZATION FOR USE/DISCLOSURE OF PROTECTED HEALTH INFORMATION (PHI) FOR RESEARCH

Participant Name: _____ **UAB IRB Protocol Number:** IRB-300000328

Research Protocol: South-seq: DNA sequencing for newborn nurseries in the South **Principal Investigator:** Bruce Korf MD, PhD

Sponsor: NIH/NHGRI

What is the purpose of this form? You are being asked to sign this form so that UAB may use and release your protected health information for research. Participation in research is voluntary. If you choose to participate in the research, you must sign this form so that your protected health information may be used for the research.

Why do the researchers want my protected health information? The researchers want to use your protected health information as part of the research protocol listed above and as described to you in the informed consent.

What protected health information do the researchers want to use? All medical information, including but not limited to information and/or records of any diagnosis or treatment of disease or condition, which may include sexually transmitted diseases (e.g., HIV, etc.) or communicable diseases, drug/alcohol dependency, etc.; all personal identifiers, including but not limited to your name, social security number, medical record number, date of birth, dates of service, etc.; any past, present, and future history, examinations, laboratory results, imaging studies and reports and treatments of whatever kind, including but not limited to drug/alcohol treatment, psychiatric/psychological treatment; financial/billing information, including but not limited to copies of your medical bills, and any other information related to or collected for use in the research protocol, regardless of whether the information was collected for research or non-research (e.g., treatment) purposes.

Who will disclose, use and/or receive my protected health information? All Individuals/entities listed in the informed consent documents, including but not limited to, the physicians, nurses and staff and others performing services related to the research (whether at UAB or elsewhere); other operating units of UAB, HSF, UAB Highlands, Children's of Alabama, Eye Foundation Hospital, and the Jefferson County Department of Health, as necessary for their operations; the IRB and its staff; the sponsor of the research and its employees and agents, including any CRO; and any outside regulatory agencies, such as the Food and Drug Administration, providing oversight or performing other legal and/or regulatory functions for which access to participant information is required.

How will my protected health information be protected once it is given to others? Your protected health information that is given to the study sponsor will remain private to the extent possible, even though the study sponsor is not required to follow the federal privacy laws. However, once your information is given to other organizations that are not required to follow federal privacy laws, we cannot assure that the information will remain protected.

How long will this Authorization last? Your authorization for the uses and disclosures described in this Authorization does not have an expiration date.

Can I cancel this Authorization? You may cancel this Authorization at any time by notifying the Principal Investigator, in writing, referencing the research protocol and IRB Protocol Number. If you cancel this Authorization, the study doctor and staff will not use any new health information for research. However, researchers may continue to use the protected health information that was provided before you cancelled your authorization.

Can I see my protected health information? You have a right to request to see your protected health information. However, to ensure the scientific integrity of the research, you will not be able to review the research information until after the research protocol has been completed.

Signature of participant: _____ Date: _____

or participant's legally authorized representative: _____ Date: _____

Printed Name of participant's representative: _____

Relationship to the participant: _____

University of Alabama at Birmingham

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or participant's legally authorized representative: _____ Date: _____

Printed Name of participant's representative: _____

Relationship to the participant: _____

University of Alabama at Birmingham

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Participant Name: _____ **UAB IRB Protocol Number:** IRB-300000328

Research Protocol: South-seq: DNA sequencing for newborn nurseries in the South **Principal Investigator:** Bruce Korf MD, PhD

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Who will disclose, use and/or receive my protected health information? All Individuals/entities listed in the informed consent documents, including but not limited to, the physicians, nurses and staff and others performing services related to the research (whether at UAB or elsewhere); other operating units of UAB, HSF, UAB Highlands, Children's of Alabama, Eye Foundation Hospital, and the Jefferson County Department of Health, as necessary for their operations; the IRB and its staff; the sponsor of the research and its employees and agents, including any CRO; and any outside regulatory agencies, such as the Food and Drug Administration, providing oversight or performing other legal and/or regulatory functions for which access to participant information is required.

How will my protected health information be protected once it is given to others? Your protected health information that is given to the study sponsor will remain private to the extent possible, even though the study sponsor is not required to follow the federal privacy laws. However, once your information is given to other organizations that are not required to follow federal privacy laws, we cannot assure that the information will remain protected.

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Can I cancel this Authorization? You may cancel this Authorization at any time by notifying the Principal Investigator, in writing, referencing the research protocol and IRB Protocol Number. If you cancel this Authorization, the study doctor and staff will not use any new health information for research. However, researchers may continue to use the protected health information that was provided before you cancelled your authorization.

Can I see my protected health information? You have a right to request to see your protected health information. However, to ensure the scientific integrity of the research, you will not be able to review the research information until after the research protocol has been completed.

Signature of participant: _____ Date: _____

or participant's legally authorized representative: _____ Date: _____

Printed Name of participant's representative: _____

Relationship to the participant: _____

CONSENT FORM

Title of Research:	South-seq: DNA sequencing for newborn nurseries in the South (NIH Grant Number 2U01HG007301-05)
Site:	University of Mississippi Medical Center
UAB IRB Protocol #:	IRB-300000328
Principal Investigators:	Renate Savich, MD and Brian Kirmse, MD
Sponsor:	NIH National Human Genome Research Institute (Contact: Lucia Hindorff PhD, MPH)

For Children (persons under 18 years of age) participating in this study, the term "You" addresses both the participant ("you") and the parent or legally authorized representative ("your child").

Purpose of the Research

We are asking you to take part in a research study. The purpose of this research study is to use whole genome sequencing (WGS), looking at your DNA, to identify the genetic cause of conditions like those observed in your child. For individuals with rare, undiagnosed diseases and their families, this experimental genetic test may provide information about what is causing the disease or condition. This information may be beneficial to your family in directing your child's health care, medical treatments, and your family planning decisions. Educational tools about your child's condition may also become available with a confirmed genetic diagnosis.

In addition, due to the limited number of genetic counselors available to support patients that may benefit from WGS, we will be comparing two results delivery methods: genetic counselors (standard of care), and healthcare providers (e.g. neonatologists and neonatology nurse practitioners) who undergo specific genetics results delivery training. In this clinical trial, we aim to demonstrate that both delivery methods are equivalent (i.e. there is no difference between the two methods). In order to so this, we plan to record the return of results conversations that you will have as part of this study.

Due to the experimental nature of this research study, data generated is based upon the knowledge currently accepted in the field. As more genomes are sequenced and as sequencing techniques improve, we will be better at identifying and understanding extremely rare variants (rare changes in DNA). In doing this, we will also improve and we will learn more about how certain variants may cause disease. For this reason, we plan to store samples for future research.

There will be approx. 1500 newborn participants enrolled for WGS, and 800 parents and caregivers enrolled for the clinical trial across 6 NICU sites: UAB, Children's of Alabama, University of Mississippi Medical Center (UMMC), Woman's Hospital, University of Louisville and Norton Healthcare (UofL). Samples will also be collected from biological mothers and fathers (up to 2,250 individuals), when

available, so that we can use their samples to determine inheritance of any variants we find in their child. We also hope to include a diverse group of participants so we are planning to offer this test to all populations, especially those underrepresented in science and genomic research such as African Americans and those from rural areas.

Explanation of Procedures

If you agree to join the study, you are agreeing to:

- Give us permission to collect a blood sample for DNA analysis
    - Adults will give approximately 8mL (approx. 1.6 tsp) of blood that will be drawn from the arm.
    - Newborns will give no more than the maximum amount allowed for their body weight according to the Children's of Alabama guidelines.
- Give us permission to fully analyze your DNA (or other related material, like RNA or protein) and determine the health significance of your genetic results.
- Allow us to return health information to you that we feel may be important to your child's health or other biological relatives.
- Allow key study personnel to access your child's personal medical records to aid in analysis. Study personnel may collect information about the child's symptoms, health history, medications/treatments, etc.
- Provide key study personnel with information about your child's health history, pregnancy and birth history, information about your health and that of other family members, if you know it, etc. Study personnel will not access your medical record. They will only have access to the information that you choose to share with them.
- Allow us, if you so choose, to return genetic results that are not related to your child's condition but are medically important for other reasons.
- Answer survey questions at 5 time points: the time of consent, return of results (ROR) appointment, 1-month post-ROR, 4-months post-ROR, and 4.5-months post-ROR. Each survey will take approximately 20-35 minutes to complete.

You will be asked to take part in two clinic visits here in the nursery or at the outpatient clinic. During the first visit, you will be asked to enroll in the study and give a blood sample (1.5hrs) and during the second visit you will receive the results of your child's DNA test either by a genetic counselor or a trained healthcare provider (1.5-2hrs). The return of results visit can either take place in-person or over the phone. A certified letter with results will be sent to those who do not participate in either in the in-person or phone ROR appointment.

More than one parent/guardian/caregiver of a child receiving WGS can participate in the study. It is important that anyone participating in the survey portion of the study be present at ROR and complete every survey.

Collecting samples from both biological parents increases the chances of identifying genetic variation in your child that might be causing his or her symptoms. However, if both parents are not available, we can still analyze eligible patients and potentially find valuable information. In cases where we enroll family members, our DNA test can identify whether a person is the

biological parent or not. We will not tell you or your family members if we find out that one or both parents are not biologically related to the child, however we are less likely to discover diagnostic information about your condition without both biological parents.

Your blood samples will be labeled with a unique code (coded) and sent to researchers at the HudsonAlpha Institute for Biotechnology, a non-profit genetics research center located in Huntsville, AL. Some relevant, health information will also be given to the research staff, and coded with a unique study identifier, to aid in their analysis.

We will use state-of-the-art technologies to generate large amounts of information about the DNA from you and your child. A group of experts, including medical doctors and researchers, will use scientific findings and genetic databases to help decide what genetic information may be important to the health of your child. The sequence of all results believed to be medically relevant or important to your child's or your own health will be validated at HudsonAlpha Clinical Services Laboratory in Huntsville, AL or another independent clinical laboratory. We expect the entire DNA analysis process to take 2-4 months.

We do intend to perform analysis of each sample within our budgetary and technical means. If we are unable to analyze your samples you will be notified within 6 months of enrollment and sample collection. There is no cause for concern if you are told that we could not complete the analysis and provide you with results.

Return of results is at the discretion of the clinicians and researchers involved with this study. If they identify results that may impact your child's health, they may return those results to you. You will be scheduled for an appointment to discuss these findings with a genetic counselor or a trained healthcare provider. Only a subset of results believed to be important to your child's medical care or those in line with the goals of this study will be reported to you. We will not provide you with all of the genetic information that we generate. At your results appointment, you may be provided with information regarding:

- Primary findings - These findings will include information about a variant(s) (DNA change) that may potentially be the reason for your child's phenotype (symptoms) or condition.
    - Most children will not receive a primary finding (or diagnosis). If no diagnosis is found, we will tell you. Even if we do not find a genetic diagnosis, your condition may still be the result of a change in your DNA that we are currently unable to identify.
    - If you receive a genetic diagnosis, this may not change your child's prognosis or medical treatment. However, it may help you and your doctor to better understand the cause of your child's condition and the risks of similar conditions affecting your biological children.
- Secondary findings – These findings may be reported to any study participant and may include any genetic changes that might impact your health or the health of your current or future children. These may include:

- Whether there are any changes in your DNA that could put you at a higher risk for developing a disease unrelated to your child's condition in the future, such as cancer or heart disease.
    1. Some of these diseases may be medically useful and some may not be medically useful. We will not return results that are not medically useful.
    2. Some of these diseases will appear in childhood and others will appear when you are an adult.
- Carrier status – In the event that we discover that your child's symptoms are caused by a recessive genetic condition where he or she inherited one variant (DNA change) from each parent, we may provide information about whether or not you are a "carrier" for a genetic change that may be passed on to your biological children.

We will arrange for a genetic counselor or a trained healthcare provider to discuss the results of the test with you. Educational materials will also be made available to you to help you better understand any results that you may or may not receive as part of this study.

You will be actively enrolled in this study for up to one year however we may continue to access your medical record for up to 5 years. We plan to use coded information from our medical record to determine the impact of whole genome sequencing and genetic diagnosis on medical care. After you receive the results of the genetic test, you may be contacted by your physician or key study personnel to check on you or to ask follow-up questions. Your DNA samples may be stored indefinitely for future research unless you choose to withdraw from the study. Please note that participation in this study is voluntary and you may withdraw from this study at any time.

You will also be presented with a baseline survey at the time of enrollment that you can complete online using Genome Gateway. The survey will ask you questions about basic demographics, how you feel about your child's health and your experience in the hospital, how well you understand medical terms, math and genetics. After you receive results, you will be asked some of these same questions and some additional ones related to your health, your understanding of the genetics results returned, and how the results influence future planning at 1-month post-ROR, 4-months post-ROR, and 4.5-months post-ROR.

Risks and Discomforts

The risks of drawing blood include pain, bruising, lightheadedness, and fainting. Infection at the site of the needle stick is a rare side effect. These are the same risks you face any time you have a blood test.

The main concerns associated with genetic testing are anxiety, depression, or other forms of emotional distress that may result from receiving genetic information about the suspected cause of your child's condition. This is especially true for those diseases that are not treatable or preventable. Though some treatments have been shown to help individuals with certain genetic conditions, there is no "cure" for most.

When performing genetic testing, it may be discovered that family relationships are not as predicted. For example, a child might not be biologically related to his/her father, or two people who are married might turn out to be biologically related. These findings will not be disclosed as part of this study.

In some cases, you may receive information about your carrier status and/or changes in your DNA that may impact your health. These findings will only be returned if they were inherited by your child who is enrolled in this study and suspected to contribute to their condition. Genetic changes in children that affect development may be inherited from one or both parents, even if the parents appear to be healthy. This information may affect the way you view or evaluate yourself or your family. It may also influence, or generate anxiety about, future family planning decisions.

It is also important to keep in mind that you and your biological relatives have similar DNA sequences. This means that genetic information about your child may also have implications for your relatives if the variation was inherited.

You may be referred to an additional physician or clinic for further testing or advice depending on the type of genetic information we generate from your sample. If you experience psychological distress or other difficulties, we can also refer you to an appropriate resource for care and/or support.

There may be unforeseeable risks associated with receiving genetic information and the potential decisions, actions, or inactions that may be required in response to that information. Please consider this carefully and ask any questions that you may have before deciding whether or not to participate in this study.

It is important that you consider the risks and uncertainties of this research study that make it different from traditional medical testing.

We will make sure that the information that you are given is as accurate as possible to the best of our ability. We will use the best standards, practices, and technologies available to researchers. However, the technologies available to analyze DNA and our knowledge of how DNA affects health are changing rapidly. They are also subject to much uncertainty. Some DNA changes that are important to health may be missed, and other DNA changes that are not important may be incorrectly identified as if they are important. There are also moral and ethical questions about using genetic information on which scientific and medical communities have not yet reached a consensus. Therefore, we do NOT guarantee that our test will have the same levels of completeness, accuracy, or standardization associated with more traditional medical tests.

Before offering your consent to participate in this research study, please consider all of the risks associated with:

- The return or possible lack of return of results;
- Whether our interpretation of those results is accurate;
- How you and/or your family will choose to act upon or not act upon the information or lack of information.

Benefits

You may not benefit directly from taking part in this study. However, your participation may lead to new discoveries that help to advance medical research and improve patient care, especially, but not only, newborn patient care in the future. Your participation in this study may help to make health care and access to health care broader and more representative.

You may find out if there is a change in your child's DNA that has altered their development. You might also find out if this change could affect future biological children.

A genetic diagnosis may help you connect with other families in the community who face similar medical problems. While unlikely, it is possible that a genetic diagnosis may point your doctor to a better medical and/or educational treatment.

You may discover that you or your child are at an increased risk for developing other diseases and that information may be of medical benefit.

None of the above benefits are guaranteed, and it is expected that many participants will not receive specific information that is relevant to their health.

Alternatives

This is not a treatment study. Your alternative is not to participate in this research study.

Confidentiality

Every effort will be made to keep the information we learn about you private. Study personnel, the Food and Drug Administration (FDA), the NIH National Human Genome Research Institute (NHGRI), the Office for Human Research Protections (OHRP), and the University of Mississippi Medical Center's Institutional Review Board (IRB) and Office of Integrity and Compliance, Grants and Contracts and the UAB (University of Alabama at Birmingham) Institutional Review Board (IRB) may review the study records. If study results are published your name will not be used.

The information from the research including your child's clinical information, family history, and genetic variants may be published for scientific purposes; however, your identity will not be given out to anyone outside of the clinical team involved with the study.

Although every effort will be made to keep your information confidential, hospital staff and health professionals are required to report suspected abuse or neglect of children, elderly and disabled

persons, reportable communicable diseases and/or possible threat of harm to self or others to appropriate state agencies.

If this research involves your child's care, diagnosis, or treatment a copy of this research Informed Consent Document will be included in your child's health record. Individuals involved in your child's treatment; who obtain information for payment of services; or who access information for health care operations may have access to your child's research records.
This may include either a paper medical record or electronic medical record (EMR). An EMR is an electronic version of a paper medical record of your care within this health system. Your child's EMR may indicate that you and your child are enrolled in this study and provide the name and contact information for the principal investigator.

This study has a Certificate of Confidentiality from the National Institutes of Health which will help us protect the privacy of our research participants. The Certificate is intended to protect against the involuntary release of participant information collected during this study.

The Certificate does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, medical care provider or other person gets your written authorization to receive research information UMMC will not use the Certificate to withhold that information.

The Certificate will not protect against mandatory reporting by the researchers to local, state or federal agencies of information on suspected child abuse, reportable communicable diseases and/or possible threat of harm to self or others.

Results of research tests or procedures that have been clinically validated (i.e. Sanger reports) may be placed in your child's medical record. All information within your child's medical record can be viewed by individuals authorized to access the record.

Information relating to this study, including your name, your child's medical record number, date of birth and social security number, may be shared with the billing offices of UMMC so costs for clinical services can be appropriately paid for by either the study account or by your insurance.

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and some employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware this federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance, nor does it protect you against genetic discrimination by some employers.

Protected Health Information

Protected health information is any personal health information through which your child can be identified. The data collected in this study includes: your child's name; date of birth; zip code; the history and diagnosis of your child's disease; current and previous treatments your child has received; other medical conditions that may affect your child's treatment; laboratory, radiology and pathology test results; and follow-up information about your child's general health, the status of your child's disease and late effects from treatment.

By signing this permission document, you authorize the study doctors at the University of Mississippi Medical Center and their study staff to collect this information and use your child's records as necessary for this study.

The HudsonAlpha, the University of Alabama at Birmingham, Woman's Hospital and the University of Mississippi Medical Center will use your information to determine the effectiveness of this study. Your child's medical information and records, once disclosed, may be re-disclosed by any of the recipients identified above and may no longer be protected by the Privacy Standards of the Health Insurance Portability and Accountability Act (HIPAA), which is a federal regulation designed to protect medical information, including medical information and records created through research.

You have the right to cancel this authorization at any time by providing one of the study doctors with a written request to cancel the authorization. If you cancel this authorization medical information and records about your child that were created before the authorization was cancelled will still be used and disclosed as needed to preserve the integrity of the study.

This authorization has no expiration date. If you do not sign this consent document, you and your child will not be allowed to participate in this study.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Voluntary Participation and Withdrawal

Whether or not you take part in this study is your choice. There will be no penalty if you decide not to be in the study. If you decide not to be in the study, you will not lose any benefits you are otherwise owed. You are free to withdraw from this research study at any time. Your choice to leave the study will not affect your relationship with any institution participating in this study.

In the event that you chose to withdraw from the study:

- No further genetic information from the study will be reported to you.
- Your blood samples will be destroyed.

- You will not be contacted to provide new information, additional samples, or
- participate in additional studies related to this project.
- If the analysis of your DNA has been completed, this information will be retained for the study.

If you would like to withdraw from the study, please contact Dr. Renate Savich at 601-815-7158 or Dr. Brian Kirmse at 601-984-1900.

Cost of Participation

There will be no cost to you for taking part in this study. The blood draw, genomic sequencing and analysis, and genetic counseling related to this study will be provided to you at no cost during the study period.

After you receive your research results, you may decide with your doctor or your child's doctor to get more testing. The costs of your standard medical care or any services rendered in response to a genetic finding identified by this research project will be billed to you and/or your insurance company in the usual manner. This type of follow-up medical testing will be considered part of your clinical care and will not be paid for by the research study.

Payment for Participation in Research

Participation in this study is voluntary and $25 will be provided for each survey completed for a total of $125 for your completion of all 5 study-related surveys. Ask the study staff about the method of payment that will be used for this study (e.g., check, cash, gift card, direct deposit); payment may take up to 4 weeks to process.

Payment for Research-Related Injuries

In the case of injury or illness resulting from your direct participation in this study, medical treatment is available to you at the University of Mississippi Medical Center. You will be charged the usual and customary charges for any such treatment you receive.

UAB, UMMC, HudsonAlpha, and NIH/NHGRI/sponsors of this research project have not provided for any payment if you are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge.

Significant New Findings

The study doctor or study staff will tell you if new information becomes available that might affect your choice to stay in the study. Please note that HudsonAlpha may, but is not required to, reanalyze your sample or report any new findings after results have been returned.

Storage of Specimens for Future Use

As part of this study, we would like to store some of the blood and DNA specimens collected from you and your child for validation of variants (to determine if a variant was inherited from a parent, etc.) identified by this project and for future research relevant to rare disease or other genetic

disorders. The future research may be conducted by the study doctor or by other researchers that obtain IRB approval for their research. The specimens will be labeled with a code that only the study doctor can link back to you. Results of any future research will not be given to you or your doctor. The specimens obtained from you in this research may help in the development of a future commercial product. There are no plans to provide financial compensation to you should this occur. You do not have to agree to allow your specimens to be stored in order to be part of this study.

You may at any time withdraw from the study and request that your specimens be removed from storage and not be used for future research. If you decide you want your specimens removed, you may contact Dr. Bruce Korf at 205-934-9411. Once the request is received, and if your samples have not already been used for other research, they will be destroyed. If you do not make such a request, your specimens will be stored indefinitely or until used.

Initial next to your choice below:

____I agree to allow my specimens to be kept in the HudsonAlpha CSL and used for future genetics research.

____I do NOT agree to allow my specimens to be kept and used for future research.

Genomic Data Sharing (GDS)

We consider the privacy of you and your child's information to be of high priority and will take a variety of steps to ensure that privacy. However, it is important for researchers to share some of the information that they learn from studying human samples. We will never share personally identifiable information, like names and addresses, with anyone outside of the research study. However, parts of you and your child's information may be shared.

Some of you and your child's genetic information, limited to a very small subset that will not cause privacy loss risks to you, may be published in scientific journals or other unrestricted-access public venues to encourage sharing of the knowledge that may be learned by analyzing your DNA and DNA from other individuals. This could include information about your child's symptoms, their age, and any genetic findings that we discover.

We may share coded lists of the DNA differences that we identify in public genetic databases. These databases gather genetic information from large groups of people and are pooled together such that no specific participant can be identified.

There is a very small chance that some commercial value may result from the use of you and your child's donated samples or genetic information. If that happens, you will not receive a share in any profits.

Unless you opt out, we may submit you and your child's complete genomic data along with some of your child's coded health information to an NIH-designated Data Repository such as dbGAP (http://www.ncbi.nlm.nih.gov/gap), AnVIL (https://anvilproject.org/), or another controlled access

database. Access to dbGAP and AnVIL is only available to qualified researchers at qualified institutions who have agreed to abide by certain privacy safeguards, obligating them, both legally and ethically, to protect you and your child's privacy and to maintain information confidentiality. However, since your genetic information is unique to you, there is a small chance that someone could trace your information back to you and your child. This risk is very small, but may grow in the future. Some risks and benefits are listed below:

Risks: The risk of sharing your genomic data is that someone could link the information stored in the databases back to you and your child. If your information suggests something about your health such as increased risk for disease, it could be misused. For example, it could be used to make it harder for you to get or keep a job or insurance or be used to discriminate against you or your family. There may also be other unknown risks. As stated above (confidentiality section of this form), there are federal protections against the misuse of your data (i.e. the Genetic Information Nondiscrimination Act, GINA).

Benefits: There is no direct benefit to you and your child from sharing your genomic data with NIH-designated repositories, however allowing researchers to use your data may lead to a better understanding of how genes affect health which may help other people in the future.

Initial next to your choice below:

____ I agree for my and my child's genetic and other relevant study data, such as health information, to be shared with NIH-designated repositories such as dbGAP and AnVIL in a coded form for future research or analysis

____ I do NOT agree for my and my child's genetic and other relevant study data, such as health information, to be shared with NIH-designated repositories such as dbGAP and AnVIL in a coded form for future research or analysis

Contact for Future Research

As new research opportunities are identified, the researchers may wish to perform additional tests on fresh samples or invite eligible participants to enroll in new studies. We would like permission to contact you in the future, however this is not a requirement to participate in this study. A separate consent form will be obtained if you wish to participate in future research.

Initial next to your choice below:

____ You have permission to contact me about new research opportunities that may interest me.

____ You do NOT have permission to contact me about new research opportunities.

Secondary Findings

One unanimous decision to receive or not to receive secondary findings must be made by each participant family. Because parental samples are only used for confirmation of variation identified in

the child's whole genome sequence for this project, only those secondary findings identified in the child will be confirmed in the parental samples. Participant families may opt to receive this information, if available. If a family chooses to do so, information about an identified secondary finding will be included in the child's medical record. Nothing will be placed in the parent's medical record.

Initial next to your choice below:

____ We (child and parent(s), if enrolled) would like to receive information about secondary findings.

____ We (child and parent(s), if enrolled) would NOT like to receive information about secondary findings.

Questions

If you have any questions, concerns, or complaints about the research or a research-related injury including available treatments, please contact Dr. Renate Savich at 601-815-7158or Dr. Brian Kirmse at 601-984-1900 or Dr. Bruce Korf (205-934-9411) at UAB.

If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact the UAB Office of the IRB (OIRB) at (205) 934-3789 or toll free at 1-855-860-3789. Regular hours for the OIRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday.

You may also discuss your rights as a research participant with the Chairman of the University of Mississippi Medical Center's Institutional Review Board, 2500 North State Street, Jackson, Mississippi 39216; telephone 601 984-2815; facsimile 601 984-2961 or via email, UMCIRB@umc.edu

Statement of Participation

I have been told about this study and the possible risks and benefits. I agree for my child to participate in this study, to follow instructions, and to report any side effects to my child's study doctor. My child's participation is voluntary and my child may withdraw at any time without any penalty or loss of benefits to which he/she is entitled, including medical care at the University of Mississippi Medical Center.

By signing this form, I am not giving up any legal rights I or my child may have.

Signatures

Your signature below indicates that you have read (or been read) the information provided above and agree to have your child participate in this study. You will receive a copy of this signed consent form.

Your signature below indicates that you have read (or been read) the information provided above and agree to participate in this study. You will receive a copy of this signed consent form.

Name of Proband Child (printed)

Signature of Parent or Legally Authorized Representative — Date

Name of Parent Participant (printed) — Mother/Father/Caregiver Relationship

Signature of Parent Participant — Date

Name of Parent Participant (printed) — Mother/Father/Caregiver Relationship

Signature of Parent Participant — Date

Printed Name of Person Obtaining Consent — Date

Signature of Person Obtaining Consent — Date

Signature of Minor Mother — Date

Name of Minor Mother (printed)

Signature of Minor Mother's Parent/Guardian — Date

Name of Minor Mother's Parent/Guardian (printed) — Mother/Father/Caregiver Relationship

I acknowledge that the participant identified above has been entered into this study, with properly obtained informed consent.

Signature of Investigator — Date

In this research study, one consent form may be used to waive consent for the infant and capture informed consent of both parents; however, a separate HIPAA Authorization form will be completed for each participant.

CONSENT FORM

Title of Research:	South-seq: DNA sequencing for newborn nurseries in the South (NIH Grant Number 2U01HG007301-05)
Site:	Woman's Hospital, Baton Rouge, Louisiana
UAB IRB Protocol #:	IRB-300000328
Principal Investigators:	Steven Spedale, MD
Sponsor:	NIH National Human Genome Research Institute (Contact: Lucia Hindorff PhD, MPH)

For Children (persons under 18 years of age) participating in this study, the term "You" addresses both the participant ("you") and the parent or legally authorized representative ("your child").

Purpose of the Research

We are asking you to take part in a research study. The purpose of this research study is to use whole genome sequencing (WGS), looking at your DNA, to identify the genetic cause of conditions like those observed in your child. For individuals with rare, undiagnosed diseases and their families, this experimental genetic test may provide information about what is causing the disease or condition. This information may be beneficial to your family in directing your child's health care, medical treatments, and your family planning decisions. Educational tools about your child's condition may also become available with a confirmed genetic diagnosis.

In addition, due to the limited number of genetic counselors available to support patients that may benefit from WGS, we will be comparing two results delivery methods: genetic counselors (standard of care), and healthcare providers (e.g. neonatologists and neonatology nurse practitioners) who undergo specific genetics results delivery training. In this clinical trial, we aim to demonstrate that both delivery methods are equivalent (i.e. there is no difference between the two methods). In order to so this, we plan to record the return of results conversations that you will have as part of this study.

Due to the experimental nature of this research study, data generated is based upon the knowledge currently accepted in the field. As more genomes are sequenced and as sequencing techniques improve, we will be better at identifying and understanding extremely rare variants (rare changes in DNA). In doing this, we will also improve and we will learn more about how certain variants may cause disease. For this reason, we plan to store samples for future research.

There will be approx. 1500 newborn participants enrolled for WGS, and 800 parents and caregivers enrolled for the clinical trial across 6 NICU sites: UAB, Children's of Alabama, University of Mississippi Medical Center (UMMC), Woman's Hospital, University of Louisville and Norton Healthcare (UofL). Samples will also be collected from biological mothers and fathers (up to 2,250 individuals), when

available, so that we can use their samples to determine inheritance of any variants we find in their child. We also hope to include a diverse group of participants so we are planning to offer this test to all populations, especially those underrepresented in science and genomic research such as African Americans and those from rural areas.

Explanation of Procedures

If you agree to join the study, you are agreeing to:

- Give us permission to collect a blood sample for DNA analysis
    - Adults will give approximately 8mL (approx. 1.6 tsp) of blood that will be drawn from the arm.
    - Newborns will give no more than the maximum amount allowed for their body weight according to the Children's Of Alabama guidelines.
- Give us permission to fully analyze your DNA (or other related material, like RNA or protein) and determine the health significance of your genetic results.
- Allow us to return health information to you that we feel may be important to your child's health or other biological relatives.
- Allow key study personnel to access your child's personal medical records to aid in analysis. Study personnel may collect information about the child's symptoms, health history, medications/treatments, etc.
- Provide key study personnel with information about your child's health history, pregnancy and birth history, information about your health and that of other family members, if you know it, etc. Study personnel will not access your medical record. They will only have access to the information that you choose to share with them.
- Allow us, if you so choose, to return genetic results that are not related to your child's condition but are medically important for other reasons.
- Answer survey questions at 5 time points: the time of consent, return of results (ROR) appointment, 1-month post-ROR, 4-months post-ROR, and 4.5-months post-ROR. Each survey will take approximately 20-35 minutes to complete.

You will be asked to take part in two clinic visits here in the nursery or at the outpatient clinic. During the first visit, you will be asked to enroll in the study and give a blood sample (1.5hrs) and during the second visit you will receive the results of your child's DNA test either by a genetic counselor or a trained healthcare provider (1.5-2hrs). The return of results visit can either take place in-person or over the phone. A certified letter with results will be sent to those who do not participate in either in the in-person or phone ROR appointment.

More than one parent/guardian/caregiver of a child receiving WGS can participate in the study. It is important that anyone participating in the survey portion of the study be present at ROR and complete every survey.

Collecting samples from both biological parents increases the chances of identifying genetic variation in your child that might be causing his or her symptoms. However if both parents are not available, we can still analyze eligible patients and potentially find valuable information. In cases where we enroll family members, our DNA test can identify whether a person is the biological

parent or not. We will not tell you or your family members if we find out that one or both parents are not biologically related to the child, however we are less likely to discover diagnostic information about your condition without both biological parents.

Your blood samples will be labeled with a unique code (coded) and sent to researchers at the HudsonAlpha Institute for Biotechnology, a non-profit genetics research center located in Huntsville, AL. Some relevant, health information will also be given to the research staff, and coded with a unique study identifier, to aid in their analysis.

We will use state-of-the-art technologies to generate large amounts of information about the DNA from you and your child. A group of experts, including medical doctors and researchers, will use scientific findings and genetic databases to help decide what genetic information may be important to the health of your child. The sequence of all results believed to be medically relevant or important to your child's or your own health will be validated at HudsonAlpha Clinical Services Laboratory in Huntsville, AL or another independent clinical laboratory. We expect the entire DNA analysis process to take 2-4 months.

We do intend to perform analysis of each sample within our budgetary and technical means. If we are unable to analyze your samples you will be notified within 6 months of enrollment and sample collection. There is no cause for concern if you are told that we could not complete the analysis and provide you with results.

Return of results is at the discretion of the clinicians and researchers involved with this study. If they identify results that may impact your child's health, they may return those results to you. You will be scheduled for an appointment to discuss these findings with a genetic counselor or a trained healthcare provider. Only a subset of results believed to be important to your child's medical care or those in line with the goals of this study will be reported to you. We will not provide you with all of the genetic information that we generate. At your results appointment, you may be provided with information regarding:

- Primary findings - These findings will include information about a variant(s) (DNA change) that may potentially be the reason for your child's phenotype (symptoms) or condition.
    - Most children will not receive a primary finding (or diagnosis). If no diagnosis is found, we will tell you. Even if we do not find a genetic diagnosis, your condition may still be the result of a change in your DNA that we are currently unable to identify.
    - If you receive a genetic diagnosis, this may not change your child's prognosis or medical treatment. However it may help you and your doctor to better understand the cause of your child's condition and the risks of similar conditions affecting your biological children.
- Secondary findings – These findings may be reported to any study participant and may include any genetic changes that might impact your health or the health of your current or future children. These may include:

- Whether there are any changes in your DNA that could put you at a higher risk for developing a disease unrelated to your child's condition in the future, such as cancer or heart disease.
    1. Some of these diseases may be medically useful and some may not be medically useful. We will not return results that are not medically useful.
    2. Some of these diseases will appear in childhood and others will appear when you are an adult.
- Carrier status – In the event that we discover that your child's symptoms are caused by a recessive genetic condition where he or she inherited one variant (DNA change) from each parent, we may provide information about whether or not you are a "carrier" for a genetic change that may be passed on to your biological children.

We will arrange for a genetic counselor or a trained healthcare provider to discuss the results of the test with you. Educational materials will also be made available to you to help you better understand any results that you may or may no receive as part of this study.

You will be actively enrolled in this study for up to one year however we may continue to access your medical record for up to 5 years. We plan to use coded information from our medical record to determine the impact of whole genome sequencing and genetic diagnosis on medical care. After you receive the results of the genetic test, you may be contacted by your physician or key study personnel to check on you or to ask follow-up questions. Your DNA samples may be stored indefinitely for future research unless you choose to withdraw from the study. Please note that participation in this study is voluntary and you may withdraw from this study at any time.

You will also be presented with a baseline survey at the time of enrollment that you can complete online using Genome Gateway. The survey will ask you questions about basic demographics, how you feel about your child's health and your experience in the hospital, how well you understand medical terms, math and genetics. After you receive results, you will be asked some of these same questions and some additional ones related to your health, your understanding of the genetics results returned, and how the results influence future planning at 1-month post-ROR, 4-months post-ROR, and 4.5-months post-ROR.

Risks and Discomforts

The risks of drawing blood include pain, bruising, lightheadedness, and fainting. Infection at the site of the needle stick is a rare side effect. These are the same risks you face any time you have a blood test.

The main concerns associated with genetic testing are anxiety, depression, or other forms of emotional distress that may result from receiving genetic information about the suspected cause of your child's condition. This is especially true for those diseases that are not treatable or preventable. Though some treatments have been shown to help individuals with certain genetic conditions, there is no "cure" for most.

When performing genetic testing, it may be discovered that family relationships are not as predicted. For example, a child might not be biologically related to his/her father, or two people who are married might turn out to be biologically related. These findings will not be disclosed as part of this study.

In some cases, you may receive information about your carrier status and/or changes in your DNA that may impact your health. These findings will only be returned if they were inherited by your child who is enrolled in this study and suspected to contribute to their condition. Genetic changes in children that affect development may be inherited from one or both parents, even if the parents appear to be healthy. This information may affect the way you view or evaluate yourself or your family. It may also influence, or generate anxiety about, future family planning decisions.

It is also important to keep in mind that you and your biological relatives have similar DNA sequences. This means that genetic information about your child may also have implications for your relatives if the variation was inherited.

You may be referred to an additional physician or clinic for further testing or advice depending on the type of genetic information we generate from your sample. If you experience psychological distress or other difficulties, we can also refer you to an appropriate resource for care and/or support.

There may be unforeseeable risks associated with receiving genetic information and the potential decisions, actions, or inactions that may be required in response to that information. Please consider this carefully and ask any questions that you may have before deciding whether or not to participate in this study.

It is important that you consider the risks and uncertainties of this research study that make it different from traditional medical testing.

We will make sure that the information that you are given is as accurate as possible to the best of our ability. We will use the best standards, practices, and technologies available to researchers. However, the technologies available to analyze DNA and our knowledge of how DNA affects health are changing rapidly. They are also subject to much uncertainty. Some DNA changes that are important to health may be missed, and other DNA changes that are not important may be incorrectly identified as if they are important. There are also moral and ethical questions about using genetic information on which scientific and medical communities have not yet reached a consensus. Therefore, we do NOT guarantee that our test will have the same levels of completeness, accuracy, or standardization associated with more traditional medical tests.

Before offering your consent to participate in this research study, please consider all of the risks associated with:

- The return or possible lack of return of results;
- Whether our interpretation of those results is accurate;
- How you and/or your family will choose to act upon or not act upon the information or lack of information.

Benefits

You may not benefit directly from taking part in this study. However, your participation may lead to new discoveries that help to advance medical research and improve patient care, especially, but not only, newborn patient care in the future. Your participation in this study may help to make health care and access to health care broader and more representative.

You may find out if there is a change in your child's DNA that has altered their development. You might also find out if this change could affect future biological children.

A genetic diagnosis may help you connect with other families in the community who face similar medical problems. While unlikely, it is possible that a genetic diagnosis may point your doctor to a better medical and/or educational treatment.

You may discover that you or your child are at an increased risk for developing other diseases and that information may be of medical benefit.

None of the above benefits are guaranteed, and it is expected that many participants will not receive specific information that is relevant to their health.

Alternatives

This is not a treatment study. Your alternative is not to participate in this research study.

Confidentiality

Information obtained about you for this study will be kept confidential to the extent allowed by law. However, research information that identifies you may be shared with people or organizations for quality assurance or data analysis, or with those responsible for ensuring compliance with laws and regulations related to research. They include:

- the UAB Institutional Review Board (IRB). An IRB is a group that reviews the study to protect the rights and welfare of research participants.
- Woman's IRB, Woman's Research and Development Committee, and Woman's Health Research Department
- the NIH National Human Genome Research Institute (NHGRI)
- the Office for Human Research Protections (OHRP)

The information from the research including your child's clinical information, family history, and genetic variants may be published for scientific purposes; however, your identity will not be given out to anyone outside of the clinical team involved with the study.

Your consent form will be placed in your child's medical record at Woman's Hospital. This may include either a paper medical record or electronic medical record (EMR). An EMR is an electronic version of a paper medical record of your care within this health system. Your child's EMR may indicate that you and your child are enrolled in this study and provide the name and contact information for the principal investigator.

Results of research tests or procedures that have been clinically validated (i.e. Sanger reports) may be placed in your child's medical record. All information within your medical record can be viewed by individuals authorized to access the record.

Information relating to this study, including your name, medical record number, date of birth and social security number, may be shared with the billing offices of Woman's Hospital so costs for clinical services can be appropriately paid for by either the study account or by your insurance.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and some employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware this federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance, nor does it protect you against genetic discrimination by some employers.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Voluntary Participation and Withdrawal

Whether or not you take part in this study is your choice. There will be no penalty if you decide not to be in the study. If you decide not to be in the study, you will not lose any benefits you are otherwise owed. You are free to withdraw from this research study at any time. Your choice to leave the study will not affect your relationship with any institution participating in this study.

In the event that you chose to withdraw from the study:

- No further genetic information from the study will be reported to you.
- Your blood samples will be destroyed.
- You will not be contacted to provide new information, additional samples, or participate in additional studies related to this project.
- If the analysis of your DNA has been completed, this information will be retained for the study.

If you would like to withdraw from the study, please contact Steven Spedale, MD, at 225-928-2555.

Cost of Participation

There will be no cost to you for taking part in this study. The blood draw, genomic sequencing and analysis, and genetic counseling related to this study will be provided to you at no cost during the study period.

After you receive your research results, you may decide with your doctor or your child's doctor to get more testing. The costs of your standard medical care or any services rendered in response to a genetic finding identified by this research project will be billed to you and/or your insurance company in the usual manner. This type of follow-up medical testing will be considered part of your clinical care, and will not be paid for by the research study.

Payment for Participation in Research

Participation in this study is voluntary and $25 will be provided for each survey completed for a total of $125 for your completion of all 5 study-related surveys. Ask the study staff about the method of payment that will be used for this study (e.g., check, cash, gift card, direct deposit); payment may take up to 4 weeks to process.

Payment for Research-Related Injuries

UAB, UMMC, HudsonAlpha, Woman's Hospital, and NIH/NHGRI/sponsors of this research project have not provided for any payment if you are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge.

Significant New Findings

The study doctor or study staff will tell you if new information becomes available that might affect your choice to stay in the study. Please note that HudsonAlpha may, but is not required to, reanalyze your sample or report any new findings after results have been returned.

Storage of Specimens for Future Use

As part of this study, we would like to store some of the blood and DNA specimens collected from you and your child for validation of variants (to determine if a variant was inherited from a parent, etc.) identified by this project and for future research relevant to rare disease or other genetic disorders. The future research may be conducted by the study doctor or by other researchers that obtain IRB approval for their research. The specimens will be labeled with a code that only the study doctor can link back to you. Results of any future research will not be given to you or your doctor. The specimens obtained from you in this research may help in the development of a future commercial product. There are no plans to provide financial compensation to you should this occur. You do not have to agree to allow your specimens to be stored in order to be part of this study.

You may at any time withdraw from the study and request that your specimens be removed from storage and not be used for future research. If you decide you want your specimens removed, you may contact Dr. Bruce Korf at 205-934-9411. Once the request is received, and if your samples have not already been used for other research, they will be destroyed. If you do not make such a request, your specimens will be stored indefinitely or until used.

Initial next to your choice below:

___I agree to allow my specimens to be kept in the HudsonAlpha CSL and used for future genetics research.

___I do NOT agree to allow my specimens to be kept and used for future research.

Genomic Data Sharing (GDS)

We consider the privacy of your information to be of high priority and will take a variety of steps to ensure that privacy. However it is important for researchers to share some of the information that they learn from studying human samples. We will never share personally identifiable information, like names and addresses, with anyone outside of the research study. However, parts of your information may be shared.

Some of your genetic information, limited to a very small subset that will not cause privacy loss risks to you, may be published in scientific journals or other unrestricted-access public venues to encourage sharing of the knowledge that may be learned by analyzing your DNA and DNA from other individuals. This could include information about your child's symptoms, their age, and any genetic findings that we discover.

We may share coded lists of the DNA differences that we identify in public genetic databases. These databases gather genetic information from large groups of people and are pooled together such that no specific participant can be identified.

There is a very small chance that some commercial value may result from the use of your donated samples or genetic information. If that happens, you will not receive a share in any profits.

Unless you opt out, we may submit your complete genomic data along with some of your coded health information to an NIH-designated Data Repository such as dbGAP (http://www.ncbi.nlm.nih.gov/gap), AnVIL (https://anvilproject.org/), or another controlled access database. Access to dbGAP and AnVIL is only available to qualified researchers at qualified institutions who have agreed to abide by certain privacy safeguards, obligating them, both legally and ethically, to protect your privacy and to maintain information confidentiality. However, since your genetic information is unique to you, there is a small chance that someone could trace your information back to you. This risk is very small, but may grow in the future. Some risks and benefits are listed below:

Risks: The risk of sharing your genomic data is that someone could link the information stored in the databases back to you. If your information suggests something about your health such as increased risk for disease, it could be misused. For example, it could be used to make it harder for you to get or keep a job or insurance or be used to discriminate against you or your family. There may also be other unknown risks. As stated above (confidentiality section of this form), there are federal protections against the misuse of your data (i.e. the Genetic Information Nondiscrimination Act, GINA).

Benefits: There is no direct benefit to you from sharing your genomic data with NIH-designated repositories, however allowing researchers to use your data may lead to a better understanding of how genes affect health which may help other people in the future.

Initial next to your choice below:

____ I agree for my genetic and other relevant study data, such as health information, to be shared with NIH-designated repositories such as dbGAP and AnVIL in a coded form for future research or analysis

____ I do NOT agree for my genetic and other relevant study data, such as health information, to be shared with NIH-designated repositories such as dbGAP and AnVIL in a coded form for future research or analysis

Contact For Future Research

As new research opportunities are identified, the researchers may wish to perform additional tests on fresh samples or invite eligible participants to enroll in new studies. We would like permission to contact you in the future, however this is not a requirement to participate in this study. A separate consent form will be obtained if you wish to participate in future research.

Initial next to your choice below:

____ You have permission to contact me about new research opportunities that may interest me.

____ You do NOT have permission to contact me about new research opportunities.

Secondary Findings

One unanimous decision to receive or not to receive secondary findings must be made by each participant family. Because parental samples are only used for confirmation of variation identified in the child's whole genome sequence for this project, only those secondary findings identified in the child will be confirmed in the parental samples. Participant families may opt to receive this information, if available. If a family chooses to do so, information about an identified secondary finding will be included in the child's medical record. Nothing will be placed in the parent's medical record.

Initial next to your choice below:

____ We (child and parent(s), if enrolled) would like to receive information about secondary findings.

____ We (child and parent(s), if enrolled) would NOT like to receive information about secondary findings.

Questions

If you have any questions, concerns, or complaints about the research or a research-related injury including available treatments, please contact Dr. Bruce Korf at 205-934-9411 or Dr. Steven Spedale at 225-928-2555.

If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact, Ericka Seidemann, Human Protections Administrator at Woman's Hospital, at 225-231-5296 or ericka.seidemann@womans.org.

Legal Rights

You are not waiving any of your legal rights by signing this consent form.

Signatures

Your signature below indicates that you have read (or been read) the information provided above and agree to have your child participate in this study. You will receive a copy of this signed consent form.

Your signature below indicates that you have read (or been read) the information provided above and agree to participate in this study. You will receive a copy of this signed consent form.

_____

Name of Proband Child (printed)

_____

Signature of Parent or Legally Authorized Representative Date

_____ Mother/Father/Caregiver

Name of Parent Participant (printed) Relationship

_____

Signature of Parent Participant Date

_____ Mother/Father/Caregiver

Name of Parent Participant (printed) Relationship

_____

Signature of Parent Participant Date

_____

Signature of Person Obtaining Consent Date

In this research study, one consent form may be used to waive consent for the infant and capture informed consent of both parents; however, a separate HIPPA Authorization form will be completed for each participant.

Waiver of Assent

The assent of _____(name of child/minor) was waived because of:
Age _____ Maturity _____ Psychological state of the child _____

WOMAN'S HOSPITAL *Medical Record Number:* _____

Authorization to Release Health Information from Woman's Hospital

Patient's Name_____
Patient's Date of Birth_____

I hereby authorize appropriate personnel at **WOMANS HOSPITAL** to release my health information to, and/or allow my records to be reviewed by:

Recipient(s)	Study doctors, nurses, and personnel; public health agencies and government agencies as required by law; Woman's Institutional Review Board; UAB Institutional Review Board; Woman's Research and Development Committee; Woman's Health Research Department; NIH National Human Genome Research Institute (NHGRI)
Recipient's Address	
Attention:	

Purpose of Release

☐ for Treatment at Another Facility
☐ for Treatment by a Physician
☐ for Processing of my Insurance Claim
☐ for an Interview
☐ for Publication, Broadcast, or Other Dissemination by the hospital or media
☐ Other Reasons; Specify: _____
☐ for Application for Insurance
x for Research
☐ Personal (at my request)

Specify information to be released by placing a check mark in the appropriate box(es):	
Dates of Services	

x Entire Record
☐ Diagnosis
☐ History & Physical Examination Reports
☐ Physician's Progress Notes
☐ Physician's Orders
☐ Nurse's Notes
☐ Discharge Summary
☐ Operative Report
☐ Consultation Reports; Specify by Doctor _____
☐ Other Records; Specify_____
☐ Information Concerning Illness, surgery, or events surrounding the birth of my child
☐ Treatment Room Record
☐ Clinic Record
  ☐ Entire Billing Record
  ☐ Itemized Bill
  ☐ Demographic Information
☐ X-Ray Reports
  ☐ Lab Results
  ☐ Photograph/Video

Special consent is required to release the following information. Indicate

Your Authorization by placing a checkmark in the appropriate box(es). NO INFORMATION WILL BE RELEASED IF BOX IS NOT CHECKED

x Alcohol abuse records/test results/diagnosis
x HIV or AIDS test results
x Drug Abuse records/tests results/diagnosis
x Mental Disorder records/test results/diagnosis ***GENETIC TEST RESULTS – You must specify the test results to be released by checking or writing below:***

Chromosome Analysis (specify below):

☐ Factor V Leiden ☐ Methylenetetrahydrofolate Reductase ☐ Blood ☐ Bone Marrow
☐ CVS ☐ Prothrombin DNA ☐ Her2/neu Fish for breast cancer ☐ Amniotic Fluid
☐ Tissue ☐ Cystic Fibrosis x Other _ANY GENETIC TESTING RESULTS

MARKETING

If I am providing authorization for marketing purposes, I understand that

☐ Woman's Hospital will not receive a monetary benefit from a third party for the use of my patient information.

☐ Woman's Hospital will receive a monetary benefit (directly or indirectly) from a third party for the use of my patient information.

Authorization Expiration Date or Event

Unless otherwise revoked, this authorization will expire on the indicated date, event or condition. If an expiration date, event or condition is not specified below, this authorization will expire six (6) months from date of signature. For genetic information, the expiration date must be sixty days or less from date of signature. If no expiration date is specified, the authorization will expire sixty days from date of signature. The statement "end of research," "none," or similar language is sufficient if disclosure is for research, (except for research on genetic information) including the creation and maintenance of a research database or repository.

Expiration (Month,Day,Year / Event / Condition) _____60 days from signature_____

REQUIRED STATEMENTS

I understand that:

1. Authorizing the release of this health information is voluntary and I can refuse to sign this authorization.
2. I have the right to revoke this authorization at any time (upon written notification to the Health Information Management Department at Woman's Hospital) except to the extent that Woman's Hospital has already released the health information before receipt of the revocation. For genetic information, I have the right to revoke the authorization at any time before the disclosure is actually made or when I am made aware of the details of the genetic information.

3. If the authorization is for research, the researcher may continue to use and disclose the health information collected prior to the receipt of the written revocation.
4. Woman's Hospital cannot condition treatment, payment, enrollment, or eligibility for benefits on the patient providing this authorization.
5. If the authorization is for research-related treatment, Woman's Hospital may condition the provision of research-related treatment on provision of an authorization for the use or disclosure of protected health information for such research.
6. Any release of information carries with it the potential for an unauthorized redisclosure by the Recipient and the information may not be protected by federal law.
7. The authorization shall be invalid if used for any other purpose other than the described purpose for which the disclosure is made.
8. A photocopy of this authorization may serve as an original.

_____ _____

Patient's Signature Date

_____ _____

Personal Representative's Signature (if necessary) Date

PERSONAL REPRESENTATIVE

If it is necessary for a personal representative to sign and date this authorization due to lack of capacity of the patient, including minority, interdiction or any other legal reason, indicate below how the person signing as representative has authority to do so:

- ☐ The court appointed person acting for the patient, if one has been appointed.
- ☐ An agent acting pursuant to a valid mandate, specifically authorizing the agent to make health care decisions.
- ☐ The patient's spouse not judicially separated.
- ☐ An adult child of the patient.
- ☐ Any parent, whether adult or minor, for his minor child.
- ☐ The patient's sibling.
- ☐ The patient's other ascendants or descendants.
- ☐ Any person temporarily standing in for the parents, whether formally serving or not, for a minor under his care and any guardian for his ward.
- ☐ Other (Please specify): _____

For Office Use Only: Date copy of authorization given to patient _____

Date copy of authorization mailed to patient _____

Date records sent _____

Revised: 11/04

WOMAN'S HOSPITAL *Medical Record Number:* _____

Authorization to Release Health Information from Woman's Hospital

Patient's Name_____
Patient's Date of Birth_____

I hereby authorize appropriate personnel at **WOMANS HOSPITAL** to release my health information to, and/or allow my records to be reviewed by:

Recipient(s)	Study doctors, nurses, and personnel; public health agencies and government agencies as required by law; Woman's Institutional Review Board; UAB Institutional Review Board; Woman's Research and Development Committee; Woman's Health Research Department; NIH National Human Genome Research Institute (NHGRI)
Recipient's Address	
Attention:	

Purpose of Release

☐ for Treatment at Another Facility
☐ for Treatment by a Physician
☐ for Processing of my Insurance Claim
☐ for an Interview
☐ for Publication, Broadcast, or Other Dissemination by the hospital or media
☐ Other Reasons; Specify: _____
☐ for Application for Insurance
x for Research
☐ Personal (at my request)

Specify information to be released by placing a check mark in the appropriate box(es):	
Dates of Services	

☐ Entire Record
☐ Diagnosis
☐ History & Physical Examination Reports
☐ Physician's Progress Notes
☐ Physician's Orders
☐ Nurse's Notes
☐ Discharge Summary
☐ Operative Report
☐ Consultation Reports; Specify by Doctor _____
☐ Other Records; Specify_____
☐ Information Concerning Illness, surgery, or events surrounding the birth of my child
☐ Treatment Room Record
☐ Clinic Record
  ☐ Entire Billing Record
  ☐ Itemized Bill
  ☐ Demographic Information
☐ X-Ray Reports
  ☐ Lab Results
  ☐ Photograph/Video

Special consent is required to release the following information. Indicate

Your Authorization by placing a checkmark in the appropriate box(es). NO INFORMATION WILL BE RELEASED IF BOX IS NOT CHECKED

x Alcohol abuse records/test results/diagnosis
x HIV or AIDS test results
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x Mental Disorder records/test results/diagnosis ***GENETIC TEST RESULTS – You must specify the test results to be released by checking or writing below:***

Chromosome Analysis (specify below):

☐ Factor V Leiden ☐ Methylenetetrahydrofolate Reductase ☐ Blood ☐ Bone Marrow
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☐ Tissue ☐ Cystic Fibrosis x Other _ANY GENETIC TESTING RESULTS

MARKETING

If I am providing authorization for marketing purposes, I understand that

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Expiration (Month,Day,Year / Event / Condition) _____60 days from signature_____

REQUIRED STATEMENTS

I understand that:

9. Authorizing the release of this health information is voluntary and I can refuse to sign this authorization.
10. I have the right to revoke this authorization at any time (upon written notification to the Health Information Management Department at Woman's Hospital) except to the extent that Woman's Hospital has already released the health information before receipt of the revocation. For genetic information, I have the right to revoke the authorization at any time before the disclosure is actually made or when I am made aware of the details of the genetic information.

11. If the authorization is for research, the researcher may continue to use and disclose the health information collected prior to the receipt of the written revocation.
12. Woman's Hospital cannot condition treatment, payment, enrollment, or eligibility for benefits on the patient providing this authorization.
13. If the authorization is for research-related treatment, Woman's Hospital may condition the provision of research-related treatment on provision of an authorization for the use or disclosure of protected health information for such research.
14. Any release of information carries with it the potential for an unauthorized redisclosure by the Recipient and the information may not be protected by federal law.
15. The authorization shall be invalid if used for any other purpose other than the described purpose for which the disclosure is made.
16. A photocopy of this authorization may serve as an original.

_____ _____

Patient's Signature Date

_____ _____

Personal Representative's Signature (if necessary) Date

PERSONAL REPRESENTATIVE

If it is necessary for a personal representative to sign and date this authorization due to lack of capacity of the patient, including minority, interdiction or any other legal reason, indicate below how the person signing as representative has authority to do so:

- ☐ The court appointed person acting for the patient, if one has been appointed.
- ☐ An agent acting pursuant to a valid mandate, specifically authorizing the agent to make health care decisions.
- ☐ The patient's spouse not judicially separated.
- ☐ An adult child of the patient.
- ☐ Any parent, whether adult or minor, for his minor child.
- ☐ The patient's sibling.
- ☐ The patient's other ascendants or descendants.
- ☐ Any person temporarily standing in for the parents, whether formally serving or not, for a minor under his care and any guardian for his ward.
- ☐ Other (Please specify): _____

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Date records sent _____

Revised: 11/04

WOMAN'S HOSPITAL *Medical Record Number:* _____

Authorization to Release Health Information from Woman's Hospital

Patient's Name_____
Patient's Date of Birth_____

I hereby authorize appropriate personnel at **WOMANS HOSPITAL** to release my health information to, and/or allow my records to be reviewed by:

Recipient(s)	Study doctors, nurses, and personnel; public health agencies and government agencies as required by law; Woman's Institutional Review Board; UAB Institutional Review Board; Woman's Research and Development Committee; Woman's Health Research Department; NIH National Human Genome Research Institute (NHGRI)
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Attention:	

Purpose of Release

☐ for Treatment at Another Facility
☐ for Treatment by a Physician
☐ for Processing of my Insurance Claim
☐ for an Interview
☐ for Publication, Broadcast, or Other Dissemination by the hospital or media
☐ Other Reasons; Specify: _____
☐ for Application for Insurance
x for Research
☐ Personal (at my request)

Specify information to be released by placing a check mark in the appropriate box(es):	
Dates of Services	

☐ Entire Record
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☐ History & Physical Examination Reports
☐ Physician's Progress Notes
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☐ Operative Report
☐ Consultation Reports; Specify by Doctor _____
☐ Other Records; Specify_____
☐ Information Concerning Illness, surgery, or events surrounding the birth of my child
☐ Treatment Room Record
☐ Clinic Record
  ☐ Entire Billing Record
  ☐ Itemized Bill
  ☐ Demographic Information
☐ X-Ray Reports
  ☐ Lab Results
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Special consent is required to release the following information. Indicate

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Expiration (Month,Day,Year / Event / Condition) _____60 days from signature_____

REQUIRED STATEMENTS

I understand that:

17. Authorizing the release of this health information is voluntary and I can refuse to sign this authorization.
18. I have the right to revoke this authorization at any time (upon written notification to the Health Information Management Department at Woman's Hospital) except to the extent that Woman's Hospital has already released the health information before receipt of the revocation. For genetic information, I have the right to revoke the authorization at any time before the disclosure is actually made or when I am made aware of the details of the genetic information.

19. If the authorization is for research, the researcher may continue to use and disclose the health information collected prior to the receipt of the written revocation.
20. Woman's Hospital cannot condition treatment, payment, enrollment, or eligibility for benefits on the patient providing this authorization.
21. If the authorization is for research-related treatment, Woman's Hospital may condition the provision of research-related treatment on provision of an authorization for the use or disclosure of protected health information for such research.
22. Any release of information carries with it the potential for an unauthorized redisclosure by the Recipient and the information may not be protected by federal law.
23. The authorization shall be invalid if used for any other purpose other than the described purpose for which the disclosure is made.
24. A photocopy of this authorization may serve as an original.

_____ _____

Patient's Signature Date

_____ _____

Personal Representative's Signature (if necessary) Date

PERSONAL REPRESENTATIVE

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- ☐ An agent acting pursuant to a valid mandate, specifically authorizing the agent to make health care decisions.
- ☐ The patient's spouse not judicially separated.
- ☐ An adult child of the patient.
- ☐ Any parent, whether adult or minor, for his minor child.
- ☐ The patient's sibling.
- ☐ The patient's other ascendants or descendants.
- ☐ Any person temporarily standing in for the parents, whether formally serving or not, for a minor under his care and any guardian for his ward.
- ☐ Other (Please specify): _____

For Office Use Only: Date copy of authorization given to patient _____

Date copy of authorization mailed to patient _____

Date records sent _____

Revised: 11/04

CONSENT FORM

Title of Research:	South-seq: DNA sequencing for newborn nurseries in the South (NIH Grant Number 2U01HG007301-05)
Site:	Children's Hospital 200 Henry Clay Ave., New Orleans, LA 70118
UAB IRB Protocol #:	IRB-300000328
Principal Investigators:	Jessica Patrick-Esteve, MD
Sponsor:	NIH National Human Genome Research Institute (Contact: Lucia Hindorff PhD, MPH)

For Children (persons under 18 years of age) participating in this study, the term "You" addresses both the participant ("you") and the parent or legally authorized representative ("your child").

Purpose of the Research

We are asking you to take part in a research study. The purpose of this research study is to use whole genome sequencing (WGS), looking at your DNA, to identify the genetic cause of conditions like those observed in your child. For individuals with rare, undiagnosed diseases and their families, this experimental genetic test may provide information about what is causing the disease or condition. This information may be beneficial to your family in directing your child's health care, medical treatments, and your family planning decisions. Educational tools about your child's condition may also become available with a confirmed genetic diagnosis.

In addition, due to the limited number of genetic counselors available to support patients that may benefit from WGS, we will be comparing two results delivery methods: genetic counselors (standard of care), and healthcare providers (e.g. neonatologists and neonatology nurse practitioners) who undergo specific genetics results delivery training. In this clinical trial, we aim to demonstrate that both delivery methods are equivalent (i.e. there is no difference between the two methods).

Due to the experimental nature of this research study, data generated is based upon the knowledge currently accepted in the field. As more genomes are sequenced and as sequencing techniques improve, we will be better at identifying and understanding extremely rare variants (rare changes in DNA). In doing this, we will also improve and we will learn more about how certain variants may cause disease. For this reason, we plan to store samples for future research.

There will be approx. 1500 newborn participants enrolled for WGS and 800 parents and/or caregivers enrolled for the clinical trial across 5 NICU sites: UAB/Children's of Alabama, University of Mississippi Medical Center (UMMC), Woman's Hospital, University of Louisville and Norton Health (UofL) and Children's Hospital New Orleans. Samples will also be collected from biological mothers and fathers (up to 2,250 individuals), when available, so that we can use their samples to determine inheritance of any variants we find in their child. We also hope to include a diverse group of participants so we

are planning to offer this test to all populations, especially those underrepresented in science and genomic research such as African Americans and those from rural areas.

Explanation of Procedures

If you agree to join the study, you are agreeing to:

- Give us permission to collect a blood sample for DNA analysis
    - Adults will give approximately 8mL (approx. 1.6 tsp) of blood that will be drawn from the arm.
    - Newborns will give no more than the maximum amount allowed for their body weight according to the Children's Of Alabama guidelines.
- Give us permission to fully analyze your DNA (or other related material, like RNA or protein) and determine the health significance of your genetic results.
- Allow us to return health information to you that we feel may be important to your child's health or other biological relatives.
- Allow key study personnel to access your child's personal medical records to aid in analysis. Study personnel may collect information about the child's symptoms, health history, medications/treatments, etc.
- Provide key study personnel with information about your child's health history, pregnancy and birth history, information about your health and that of other family members, if you know it, etc. Study personnel will not access your medical record. They will only have access to the information that you choose to share with them.
- Allow us, if you so choose, to return genetic results that are not related to your child's condition but are medically important for other reasons.
- Answer survey questions at the time of consent, return of results (ROR), 1-month post ROR, 4-months post ROR, and 4.5-months post ROR that will take approximately 20-35 minutes to complete.

You will be asked to take part in two clinic visits here in the nursery or at the outpatient clinic. During the first visit, you will be asked to enroll in the study and give a blood sample (1.5hrs) and during the second visit you will receive the results of your child's DNA test either by a genetic counselor or a trained healthcare provider (1.5-2hrs). The return of results visit can either take place in-person or over the phone. A certified letter with results will be sent to those who do not participate in either in the in-person or phone ROR appointment.

More than one parent/guardian/caregiver of a child receiving WGS can participate in the study. It is important that anyone participating in the survey portion of the study be present at ROR and complete every survey.

Collecting samples from both biological parents increases the chances of identifying genetic variation in your child that might be causing his or her symptoms. However if both parents are not available, we can still analyze eligible patients and potentially find valuable information. In cases where we enroll family members, our DNA test can identify whether a person is the biological parent or not. We will not tell you or your family members if we find out that one or both parents

are not biologically related to the child, however we are less likely to discover diagnostic information about your condition without both biological parents.

Your blood samples will be labeled with a unique code (coded) and sent to researchers at the HudsonAlpha Institute for Biotechnology, a non-profit genetics research center located in Huntsville, AL. Some relevant, health information will also be given to the research staff, and coded with a unique study identifier, to aid in their analysis.

We will use state-of-the-art technologies to generate large amounts of information about the DNA from you and your child. A group of experts, including medical doctors and researchers, will use scientific findings and genetic databases to help decide what genetic information may be important to the health of your child. The sequence of all results believed to be medically relevant or important to your child's or your own health will be validated at HudsonAlpha Clinical Services Laboratory in Huntsville, AL or another independent clinical laboratory. We expect the entire DNA analysis process to take 2-4 months.

We do intend to perform analysis of each sample within our budgetary and technical means. If we are unable to analyze your samples you will be notified within 6 months of enrollment and sample collection. There is no cause for concern if you are told that we could not complete the analysis and provide you with results.

Return of results is at the discretion of the clinicians and researchers involved with this study. If they identify results that may impact your child's health, they may return those results to you. You will be scheduled for an appointment to discuss these findings with a genetic counselor or trained healthcare provider. Only a subset of results believed to be important to your child's medical care or those in line with the goals of this study will be reported to you. We will not provide you with all of the genetic information that we generate. At your results appointment, you may be provided with information regarding:

- Primary findings - These findings will include information about a variant(s) (DNA change) that may potentially be the reason for your child's phenotype (symptoms) or condition.
    - Most children will not receive a primary finding (or diagnosis). If no diagnosis is found, we will tell you. Even if we do not find a genetic diagnosis, your condition may still be the result of a change in your DNA that we are currently unable to identify.
    - If you receive a genetic diagnosis, this may not change your child's prognosis or medical treatment. However it may help you and your doctor to better understand the cause of your child's condition and the risks of similar conditions affecting your biological children.
- Secondary findings – These findings may be reported to any study participant and may include any genetic changes that might impact your health or the health of your current or future children. These may include:
    - Whether there are any changes in your DNA that could put you at a higher risk for developing a disease unrelated to your child's condition in the future, such as cancer or heart disease.

1. Some of these diseases may be medically useful and some may not be medically useful. We will not return results that are not medically useful.
2. Some of these diseases will appear in childhood and others will appear when you are an adult.

- Carrier status – In the event that we discover that your child's symptoms are caused by a recessive genetic condition where he or she inherited one variant (DNA change) from each parent, we may provide information about whether or not you are a "carrier" for a genetic change that may be passed on to your biological children.

We will arrange for a genetic counselor or a trained healthcare provider to discuss the results of the test with you. Educational materials will also be made available to you to help you better understand any results that you may or may not receive as part of this study.

You will be actively enrolled in this study for up to one year however we may continue to access your medical record for up to 5 years. We plan to use coded information from our medical record to determine the impact of whole genome sequencing and genetic diagnosis on medical care. After you receive the results of the genetic test, you may be contacted by your physician or key study personnel to check on you or to ask follow-up questions. Your DNA samples may be stored indefinitely for future research unless you choose to withdraw from the study. Please note that participation in this study is voluntary and you may withdraw from this study at any time.

You will also be presented with a baseline survey at the time of enrollment that you can complete online using Genome Gateway. The survey will ask you questions about basic demographics, how you feel about your child's health and your experience in the hospital, how well you understand medical terms, math and genetics. After you receive results from this testing, you will be asked some of these same questions and some additional ones related to your health, your understanding of the genetic results returned, and how the results influence future life planning at 1-month post ROR, 4-months post ROR, and 4.5 months post ROR.

Risks and Discomforts

The risks of drawing blood include pain, bruising, lightheadedness, and fainting. Infection at the site of the needle stick is a rare side effect. These are the same risks you face any time you have a blood test.

The main concerns associated with genetic testing are anxiety, depression, or other forms of emotional distress that may result from receiving genetic information about the suspected cause of your child's condition. This is especially true for those diseases that are not treatable or preventable. Though some treatments have been shown to help individuals with certain genetic conditions, there is no "cure" for most.

When performing genetic testing, it may be discovered that family relationships are not as predicted. For example, a child might not be biologically related to his/her father, or two people who are married might turn out to be biologically related. These findings will not be disclosed as part of this study.

In some cases, you may receive information about your carrier status and/or changes in your DNA that may impact your health. These findings will only be returned if they were inherited by your child who is enrolled in this study and suspected to contribute to their condition. Genetic changes in children that affect development may be inherited from one or both parents, even if the parents appear to be healthy. This information may affect the way you view or evaluate yourself or your family. It may also influence, or generate anxiety about, future family planning decisions.

It is also important to keep in mind that you and your biological relatives have similar DNA sequences. This means that genetic information about your child may also have implications for your relatives if the variation was inherited.

You may be referred to an additional physician or clinic for further testing or advice depending on the type of genetic information we generate from your sample. If you experience psychological distress or other difficulties, we can also refer you to an appropriate resource for care and/or support.

There may be unforeseeable risks associated with receiving genetic information and the potential decisions, actions, or inactions that may be required in response to that information. Please consider this carefully and ask any questions that you may have before deciding whether or not to participate in this study.

It is important that you consider the risks and uncertainties of this research study that make it different from traditional medical testing.

We will make sure that the information that you are given is as accurate as possible to the best of our ability. We will use the best standards, practices, and technologies available to researchers. However, the technologies available to analyze DNA and our knowledge of how DNA affects health are changing rapidly. They are also subject to much uncertainty. Some DNA changes that are important to health may be missed, and other DNA changes that are not important may be incorrectly identified as if they are important. There are also moral and ethical questions about using genetic information on which scientific and medical communities have not yet reached a consensus. Therefore, we do NOT guarantee that our test will have the same levels of completeness, accuracy, or standardization associated with more traditional medical tests.

Before offering your consent to participate in this research study, please consider all of the risks associated with:

- The return or possible lack of return of results;
- Whether our interpretation of those results is accurate;
- How you and/or your family will choose to act upon or not act upon the information or lack of information.

Benefits

You may not benefit directly from taking part in this study. However, your participation may lead to new discoveries that help to advance medical research and improve patient care, especially, but not only, newborn patient care in the future. Your participation in this study may help to make health care and access to health care broader and more representative.

You may find out if there is a change in your child's DNA that has altered their development. You might also find out if this change could affect future biological children.

A genetic diagnosis may help you connect with other families in the community who face similar medical problems. While unlikely, it is possible that a genetic diagnosis may point your doctor to a better medical and/or educational treatment.

You may discover that you or your child are at an increased risk for developing other diseases and that information may be of medical benefit.

None of the above benefits are guaranteed, and it is expected that many participants will not receive specific information that is relevant to their health.

Alternatives

This is not a treatment study. Your alternative is not to participate in this research study.

Confidentiality

Information obtained about you for this study will be kept confidential to the extent allowed by law. However, research information that identifies you may be shared with people or organizations for quality assurance or data analysis, or with those responsible for ensuring compliance with laws and regulations related to research. They include:

- the UAB Institutional Review Board (IRB). An IRB is a group that reviews the study to protect the rights and welfare of research participants.
- Louisiana State University Health Sciences Center-New Orleans IRB
- Children's Hospital New Orleans IRB
- the NIH National Human Genome Research Institute (NHGRI)
- the Office for Human Research Protections (OHRP)

The information from the research including your child's clinical information, family history, and genetic variants may be published for scientific purposes; however, your identity will not be given out to anyone outside of the clinical team involved with the study.

Your consent form will be placed in your child's medical record at Children's Hospital New Orleans. This may include either a paper medical record or electronic medical record (EMR). An EMR is an electronic version of a paper medical record of your care within this health system. Your child's EMR may indicate that you and your child are enrolled in this study and provide the name and contact information for the principal investigator.

Results of research tests or procedures that have been clinically validated (i.e. Sanger reports) may be placed in your child's medical record. All information within your medical record can be viewed by individuals authorized to access the record.

Information relating to this study, including your name, medical record number, date of birth and social security number, may be shared with the billing offices of Children's Hospital New Orleans so costs for clinical services can be appropriately paid for by either the study account or by your insurance.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and some employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware this federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance, nor does it protect you against genetic discrimination by some employers.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Louisiana law prohibits discrimination in employment or insurability based on your genetic information. Your genetic information is considered your property and no insurer or employer may obtain genetic information or a DNA sample without first obtaining your written consent. (LA Statute RS22:1023 and RS23:368).

Voluntary Participation and Withdrawal

Whether or not you take part in this study is your choice. There will be no penalty if you decide not to be in the study. If you decide not to be in the study, you will not lose any benefits you are otherwise owed. You are free to withdraw from this research study at any time. Your choice to leave the study will not affect your relationship with any institution participating in this study.

In the event that you chose to withdraw from the study:

- No further genetic information from the study will be reported to you.
- Your blood samples will be destroyed.
- You will not be contacted to provide new information, additional samples, or participate in additional studies related to this project.
- If the analysis of your DNA has been completed, this information will be retained for the study.

If you would like to withdraw from the study, please contact Dr. Patrick-Esteve at 504-896-9418.

Cost of Participation

There will be no cost to you for taking part in this study. The blood draw, genomic sequencing and analysis, and genetic counseling related to this study will be provided to you at no cost during the study period.

After you receive your research results, you may decide with your doctor or your child's doctor to get more testing. The costs of your standard medical care or any services rendered in response to a genetic finding identified by this research project will be billed to you and/or your insurance company in the usual manner. This type of follow-up medical testing will be considered part of your clinical care, and will not be paid for by the research study.

Payment for Participation in Research

Participation in this study is voluntary and $25 will be provided for each survey completed for a total of $125 for your completion of all 5 study-related surveys. Ask the study staff about the method of payment that will be used for this study (e.g., check, cash, gift card, direct deposit); payment may take up to 4 weeks to process.

Payment for Research-Related Injuries

UAB, UMMC, HudsonAlpha, UofL, Children's Hospital New Orleans/LSUHSC-NO, and NIH/NHGRI/sponsors of this research project have not provided for any payment if you are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge.

Significant New Findings

The study doctor or study staff will tell you if new information becomes available that might affect your choice to stay in the study. Please note that HudsonAlpha may, but is not required to, reanalyze your sample or report any new findings after results have been returned.

Storage of Specimens for Future Use

As part of this study, we would like to store some of the blood and DNA specimens collected from you and your child for validation of variants (to determine if a variant was inherited from a parent, etc.) identified by this project and for future research relevant to rare disease or other genetic disorders. The future research may be conducted by the study doctor or by other researchers that obtain IRB approval for their research. The specimens will be labeled with a code that only the study doctor can link back to you. Results of any future research will not be given to you or your doctor. The specimens obtained from you in this research may help in the development of a future commercial product. There are no plans to provide financial compensation to you should this occur. You do not have to agree to allow your specimens to be stored in order to be part of this study.

You may at any time withdraw from the study and request that your specimens be removed from storage and not be used for future research. If you decide you want your specimens removed, you may contact Dr. Bruce Korf at 205-934-9411. Once the request is received, and if your samples have not already been used for other research, they will be destroyed. If you do not make such a request, your specimens will be stored indefinitely or until used.

Initial next to your choice below:

____I agree to allow my specimens to be kept in the HudsonAlpha CSL and used for future genetics research.

____I do NOT agree to allow my specimens to be kept and used for future research.

Genomic Data Sharing (GDS)

We consider the privacy of your information to be of high priority and will take a variety of steps to ensure that privacy. However, it is important for researchers to share some of the information that they learn from studying human samples. We will never share personally identifiable information, like names and addresses, with anyone outside of the research study. However, parts of your information may be shared.

Some of your genetic information, limited to a very small subset that will not cause privacy loss risks to you, may be published in scientific journals or other unrestricted-access public venues to encourage sharing of the knowledge that may be learned by analyzing your DNA and DNA from other individuals. This could include information about your child's symptoms, their age, and any genetic findings that we discover.

We may share coded lists of the DNA differences that we identify in public genetic databases. These databases gather genetic information from large groups of people and are pooled together such that no specific participant can be identified.

There is a very small chance that some commercial value may result from the use of your donated samples or genetic information. If that happens, you will not receive a share in any profits.

Unless you opt out, we may submit your complete genomic data along with some of your coded health information to an NIH-designated Data Repository such as dbGAP (http://www.ncbi.nlm.nih.gov/gap) , AnVIL (https://anvilproject.org/), or another controlled access database. Access to dbGAP is only available to qualified researchers at qualified institutions who have agreed to abide by certain privacy safeguards, obligating them, both legally and ethically, to protect your privacy and to maintain information confidentiality. However, since your genetic information is unique to you, there is a small chance that someone could trace your information back to you. This risk is very small, but may grow in the future. Some risks and benefits are listed below:

Risks: The risk of sharing your genomic data is that someone could link the information stored in the databases back to you. If your information suggests something about your health such as increased risk for disease, it could be misused. For example, it could be used to make it harder for you to get or keep a job or insurance or be used to discriminate against you or your family. There may also be other unknown risks. As stated above (confidentiality section of this form), there are federal protections against the misuse of your data (i.e. the Genetic Information Nondiscrimination Act, GINA).

Benefits: There is no direct benefit to you from sharing your genomic data with NIH-designated repositories, however allowing researchers to use your data may lead to a better understanding of how genes affect health which may help other people in the future.

Initial next to your choice below:

____ I agree for my genetic and other relevant study data, such as health information, to be shared with NIH-designated repositories such as dbGAP and AnVIL in a coded form for future research or analysis

____ I do NOT agree for my genetic and other relevant study data, such as health information, to be shared with NIH-designated repositories such as dbGAP and AnVIL in a coded form for future research or analysis

Contact For Future Research

As new research opportunities are identified, the researchers may wish to perform additional tests on fresh samples or invite eligible participants to enroll in new studies. We would like permission to contact you in the future, however this is not a requirement to participate in this study. A separate consent form will be obtained if you wish to participate in future research.

Initial next to your choice below:

____ You have permission to contact me about new research opportunities that may interest me.

____ You do NOT have permission to contact me about new research opportunities.

Secondary Findings

One unanimous decision to receive or not to receive secondary findings must be made by each participant family. Because parental samples are only used for confirmation of variation identified in the child's whole genome sequence for this project, only those secondary findings identified in the child will be confirmed in the parental samples. Participant families may opt to receive this information, if available. If a family chooses to do so, information about an identified secondary finding will be included in the child's medical record. Nothing will be placed in the parent's medical record.

Initial next to your choice below:

____ We (child and parent(s), if enrolled) would like to receive information about secondary findings.

____ We (child and parent(s), if enrolled) would NOT like to receive information about secondary findings.

Questions

If you have any questions, concerns, or complaints about the research or a research-related injury including available treatments, please contact Dr. Bruce Korf at 205-934-9411 or Dr. Patrick-Esteve at 504-896-9418.

If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact, Dr. Patrick-Esteve, at Children's Hospital, 200 Henry Clay Ave., New Orleans, LA 70118, jpatri@lsuhsc.edu, 504-896-9418. You may also contact the Chancellor of the LSU Health Sciences Center of New Orleans at (504) 568-4801 and Dr. Druby Hebert, Chairman of the Children's Hospital New Orleans IRB, at 504-899-9511.

Legal Rights

You are not waiving any of your legal rights by signing this consent form.

Signatures

Your signature below indicates that you have read (or been read) the information provided above and agree to have your child participate in this study. You will receive a copy of this signed consent form.

Your signature below indicates that you have read (or been read) the information provided above and agree to participate in this study. You will receive a copy of this signed consent form.

_____

Name of Proband Child (printed)

_____

Signature of Parent or Legally Authorized Representative Date

_____ Mother/Father/Caregiver

Name of Parent Participant (printed) Relationship

_____

Signature of Parent Participant Date

_____ Mother/Father/Caregiver

Name of Parent Participant (printed) Relationship

_____

Signature of Parent Participant Date

_____

Signature of Person Obtaining Consent Date

In this research study, one consent form may be used to waive consent for the infant and capture informed consent of both parents; however, a separate HIPPA Authorization form will be completed for each participant.

Waiver of Assent

The assent of _____(name of child/minor) was waived because of:
Age _____ Maturity _____ Psychological state of the child _____

LOUISIANA STATE UNIVERSITY HEALTH SCIENCES CENTER

At New Orleans (LSUHSC-NO) and CHILDREN'S HOSPITAL

INSTITUTIONAL REVIEW BOARD/ADMINISTRATIVE REVIEW COMMITTEE

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AUTHORIZATION FOR USE AND DISCLOSURE OF PROTECTED HEALTH INFORMATION FOR RESEARCH PURPOSES – Proband

Title of Research Project: **South-seq: DNA sequencing for newborn nurseries in the South**

Name of Sponsor: National Institutes of Health (NIH) National Human Genome Research Institute
If applicable IRB Number: N/A

Principal Investigator: Jessica Patrick-Esteve, MD IRB or Protocol Number: new / ARC #new

I hereby request and authorize the LSUHSC-NO and/or Children's Hospital to use and disclose protected health information from the record(s) of:

Patient's Name/Address:

_____

Birth Date: ____/____/____

Specifically, I request and authorize any part of my health information relevant to the research project, identified above and in the Informed Consent document, to be used and/or disclosed to the Principal Investigator identified above or his/her designee, in connection with the research project. (NOTE: The following sentence may be deleted if not appropriate): I understand that this may include information relating to: Human Immunodeficiency Virus ("HIV") infection or Acquired Immunodeficiency Syndrome ("AIDS"); treatment for or history of drug or alcohol abuse; and/or mental or behavioral health or psychiatric care.

I specifically authorize the use and disclosure of the following PHI:
(Please provide a detailed description of the particular data and period of time you are requesting)

_X__Complete health record(s) for date(s) of service from date of birth to 5 years after study enrollment, which may contain all of the documents listed below, as well as other notes or documents relating to my treatment or hospitalization.
_____History and physical exam _____
_____Hospital Inpatient Records _____

_____Clinic/Outpatient Records_____
_____ Consultation reports _____
_____Laboratory test results_____
_____Radiology Reports_____
_____Pathology Reports_____
_____Discharge Summary_____
_____Progress Notes_____
_____Photographs, videotapes_____
_____X-Ray films/images, digital or other images_____
_____Diagnosis and Treatment Codes_____
_____Complete billing record_____
_____Other: _____

I understand that copies of the records indicated above will be:

- Used by employees of LSUHSC-NO and/or Children's Hospital including treatment providers, and/or other members of its workforce.

- Disclosed to LSUHSC-NO and/or Children's Hospital, government officials or government agencies, such as the Food and Drug Administration study sponsors, study monitors, or others responsible for oversight of the research project.

- Sent to collaborating researchers outside LSUHSC-NO and/or Children's Hospital if and to the extent indicated in the attached Informed Consent document(s).

I understand that by signing this form, I am allowing LSUHSC-NO and/or Children's Hospital and their researchers to use or disclose my health information in connection with the attached Informed Consent and for the purpose of the research that is described in the Informed Consent. For example, the researchers may need the information to verify that I am eligible to participate in the study, or to monitor the results, including expected or unexpected side effects or outcomes. Other University/Hospital and government officials, safety monitors, and study sponsors may need the information to ensure that the study is conducted properly. Also, I understand that my health information may be disclosed to insurance companies or others responsible for my medical bills in order to secure payment.

I understand that any privacy rights not specifically mentioned in this Authorization are contained in the Notice of Privacy Practices that I received or will receive from the Principal Investigator or at the facility that I attend.

I understand that I may revoke this authorization at any time, except to the extent that LSUHSC-NO and/or Children's Hospital has already relied on the authorization, by sending or transmitting of a facsimile, a written notice to the contact person listed in the attached Informed Consent document(s).

I understand that if my information already has been included in a research database or registry as described in the attached Informed Consent document(s), LSUHSC-NO and/or Children's Hospital considers itself to have relied on it, and therefore my information will not be removed from those repositories. Unless otherwise revoked, I understand that this authorization (_X_) will not expire or (__) will expire upon {date or event}_____. I understand that if I do not sign this form, I will not be able to participate in the above research study or receive the study-related interventions, but that LSUHSC-NO and/or Children's Hospital cannot otherwise condition treatment on my signing this form.

While the research study is in progress, my right to access any research records or results that are maintained by the facility may be suspended until the research study is over. If my access is denied, I understand that it will be reinstated at the end of the research study.

I understand the information disclosed by this authorization may be subject to re-disclosure by the recipient and no longer be protected by the Health Insurance Portability and Accountability Act. The LSUHSC and/or Children's Hospital facilities, their employees, officers, and physicians are hereby released from any legal responsibility or liability for disclosure of the above information to the extent indicated and authorized herein.

I UNDERSTAND THAT THIS AUTHORIZATION SUPERSEDES ANY CONTRARY INFORMATION IN ANY OTHER DOCUMENTS I HAVE SIGNED RELATED TO THE ATTACHED STUDY.

Signature of Patient or Patient's Legal Representative:_____
Date:___/___/____

Printed Name of Legal Representative (if any):
_____

Representative's Authority to Act for Patient (e.g., relationship to patient):
_____

Verification of Representative's Authority: ( ) viewed driver's license ( ) viewed Power of Attorney
( ) viewed other_____(specify)

LOUISIANA STATE UNIVERSITY HEALTH SCIENCES CENTER

At New Orleans (LSUHSC-NO) and CHILDREN'S HOSPITAL

INSTITUTIONAL REVIEW BOARD/ADMINISTRATIVE REVIEW COMMITTEE

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AUTHORIZATION FOR USE AND DISCLOSURE OF PROTECTED HEALTH INFORMATION FOR RESEARCH PURPOSES – Biological Mother

Title of Research Project: **South-seq: DNA sequencing for newborn nurseries in the South**

Name of Sponsor: National Institutes of Health (NIH) National Human Genome Research Institute
If applicable IRB Number: N/A

Principal Investigator: Jessica Patrick-Esteve, MD IRB or Protocol Number: new / ARC #new

I hereby request and authorize the LSUHSC-NO and/or Children's Hospital to use and disclose protected health information from the record(s) of:

Patient's Name/Address:

_____

Birth Date: ____/____/____

Specifically, I request and authorize any part of my health information relevant to the research project, identified above and in the Informed Consent document, to be used and/or disclosed to the Principal Investigator identified above or his/her designee, in connection with the research project. (NOTE: The following sentence may be deleted if not appropriate): I understand that this may include information relating to: Human Immunodeficiency Virus ("HIV") infection or Acquired Immunodeficiency Syndrome ("AIDS"); treatment for or history of drug or alcohol abuse; and/or mental or behavioral health or psychiatric care.

I specifically authorize the use and disclosure of the following PHI:
(Please provide a detailed description of the particular data and period of time you are requesting)

_X_Complete health record(s) for date(s) of service from study enrollment to 5 years after study enrollment, which may contain all of the documents listed below, as well as other notes or documents relating to my treatment or hospitalization.

_____History and physical exam_____

_____Hospital Inpatient Records_____

_____Clinic/Outpatient Records_____

_____ Consultation reports _____

_____Laboratory test results_____
_____Radiology Reports_____
_____Pathology Reports_____
_____Discharge Summary_____
_____Progress Notes_____
_____Photographs, videotapes_____
_____X-Ray films/images, digital or other images_____
_____Diagnosis and Treatment Codes_____
_____Complete billing record_____
_____Other: _____

I understand that copies of the records indicated above will be:

- Used by employees of LSUHSC-NO and/or Children's Hospital including treatment providers, and/or other members of its workforce.

- Disclosed to LSUHSC-NO and/or Children's Hospital, government officials or government agencies, such as the Food and Drug Administration study sponsors, study monitors, or others responsible for oversight of the research project.

- Sent to collaborating researchers outside LSUHSC-NO and/or Children's Hospital if and to the extent indicated in the attached Informed Consent document(s).

I understand that by signing this form, I am allowing LSUHSC-NO and/or Children's Hospital and their researchers to use or disclose my health information in connection with the attached Informed Consent and for the purpose of the research that is described in the Informed Consent. For example, the researchers may need the information to verify that I am eligible to participate in the study, or to monitor the results, including expected or unexpected side effects or outcomes. Other University/Hospital and government officials, safety monitors, and study sponsors may need the information to ensure that the study is conducted properly. Also, I understand that my health information may be disclosed to insurance companies or others responsible for my medical bills in order to secure payment.

I understand that any privacy rights not specifically mentioned in this Authorization are contained in the Notice of Privacy Practices that I received or will receive from the Principal Investigator or at the facility that I attend.

I understand that I may revoke this authorization at any time, except to the extent that LSUHSC-NO and/or Children's Hospital has already relied on the authorization, by sending or transmitting of a facsimile, a written notice to the contact person listed in the attached Informed Consent document(s).

I understand that if my information already has been included in a research database or registry as described in the attached Informed Consent document(s), LSUHSC-NO and/or Children's Hospital

considers itself to have relied on it, and therefore my information will not be removed from those repositories. Unless otherwise revoked, I understand that this authorization (_X_) will not expire or (__) will expire upon {date or event}_____. I understand that if I do not sign this form, I will not be able to participate in the above research study or receive the study-related interventions, but that LSUHSC-NO and/or Children's Hospital cannot otherwise condition treatment on my signing this form.

While the research study is in progress, my right to access any research records or results that are maintained by the facility may be suspended until the research study is over. If my access is denied, I understand that it will be reinstated at the end of the research study.

I understand the information disclosed by this authorization may be subject to re-disclosure by the recipient and no longer be protected by the Health Insurance Portability and Accountability Act. The LSUHSC and/or Children's Hospital facilities, their employees, officers, and physicians are hereby released from any legal responsibility or liability for disclosure of the above information to the extent indicated and authorized herein.

I UNDERSTAND THAT THIS AUTHORIZATION SUPERSEDES ANY CONTRARY INFORMATION IN ANY OTHER DOCUMENTS I HAVE SIGNED RELATED TO THE ATTACHED STUDY.

Signature of Patient or Patient's Legal Representative:_____
Date:___/___/____

Printed Name of Legal Representative (if any):
_____

Representative's Authority to Act for Patient (e.g., relationship to patient):
_____

Verification of Representative's Authority: ( ) viewed driver's license ( ) viewed Power of Attorney
( ) viewed other_____(specify)

LOUISIANA STATE UNIVERSITY HEALTH SCIENCES CENTER

At New Orleans (LSUHSC-NO) and CHILDREN'S HOSPITAL

INSTITUTIONAL REVIEW BOARD/ADMINISTRATIVE REVIEW COMMITTEE

****

AUTHORIZATION FOR USE AND DISCLOSURE OF PROTECTED HEALTH INFORMATION FOR RESEARCH PURPOSES – Biological Father

Title of Research Project: **South-seq: DNA sequencing for newborn nurseries in the South**

Name of Sponsor: National Institutes of Health (NIH) National Human Genome Research Institute
If applicable IRB Number: N/A

Principal Investigator: Jessica Patrick-Esteve, MD IRB or Protocol Number: new / ARC #new

I hereby request and authorize the LSUHSC-NO and/or Children's Hospital to use and disclose protected health information from the record(s) of:
Patient's Name/Address:
_____

Birth Date: ____/____/____

Specifically, I request and authorize any part of my health information relevant to the research project, identified above and in the Informed Consent document, to be used and/or disclosed to the Principal Investigator identified above or his/her designee, in connection with the research project. (NOTE: The following sentence may be deleted if not appropriate): I understand that this may include information relating to: Human Immunodeficiency Virus ("HIV") infection or Acquired Immunodeficiency Syndrome ("AIDS"); treatment for or history of drug or alcohol abuse; and/or mental or behavioral health or psychiatric care.

I specifically authorize the use and disclosure of the following PHI:
(Please provide a detailed description of the particular data and period of time you are requesting)

_X__Complete health record(s) for date(s) of service from study enrollment to 5 years after study enrollment, which may contain all of the documents listed below, as well as other notes or documents relating to my treatment or hospitalization.
_____History and physical exam_____
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_____Clinic/Outpatient Records_____
_____ Consultation reports _____
_____Laboratory test results_____

_____Radiology Reports_____
_____Pathology Reports_____
_____Discharge Summary_____
_____Progress Notes_____
_____Photographs, videotapes_____
_____X-Ray films/images, digital or other images_____
_____Diagnosis and Treatment Codes_____
_____Complete billing record_____
_____Other: _____

I understand that copies of the records indicated above will be:

- Used by employees of LSUHSC-NO and/or Children's Hospital including treatment providers, and/or other members of its workforce.

- Disclosed to LSUHSC-NO and/or Children's Hospital, government officials or government agencies, such as the Food and Drug Administration study sponsors, study monitors, or others responsible for oversight of the research project.

- Sent to collaborating researchers outside LSUHSC-NO and/or Children's Hospital if and to the extent indicated in the attached Informed Consent document(s).

I understand that by signing this form, I am allowing LSUHSC-NO and/or Children's Hospital and their researchers to use or disclose my health information in connection with the attached Informed Consent and for the purpose of the research that is described in the Informed Consent. For example, the researchers may need the information to verify that I am eligible to participate in the study, or to monitor the results, including expected or unexpected side effects or outcomes. Other University/Hospital and government officials, safety monitors, and study sponsors may need the information to ensure that the study is conducted properly. Also, I understand that my health information may be disclosed to insurance companies or others responsible for my medical bills in order to secure payment.

I understand that any privacy rights not specifically mentioned in this Authorization are contained in the Notice of Privacy Practices that I received or will receive from the Principal Investigator or at the facility that I attend.

I understand that I may revoke this authorization at any time, except to the extent that LSUHSC-NO and/or Children's Hospital has already relied on the authorization, by sending or transmitting of a facsimile, a written notice to the contact person listed in the attached Informed Consent document(s).

I understand that if my information already has been included in a research database or registry as described in the attached Informed Consent document(s), LSUHSC-NO and/or Children's Hospital considers itself to have relied on it, and therefore my information will not be removed from those

repositories. Unless otherwise revoked, I understand that this authorization (_X_) will not expire or (___) will expire upon {date or event}_____. I understand that if I do not sign this form, I will not be able to participate in the above research study or receive the study-related interventions, but that LSUHSC-NO and/or Children's Hospital cannot otherwise condition treatment on my signing this form.

While the research study is in progress, my right to access any research records or results that are maintained by the facility may be suspended until the research study is over. If my access is denied, I understand that it will be reinstated at the end of the research study.

I understand the information disclosed by this authorization may be subject to re-disclosure by the recipient and no longer be protected by the Health Insurance Portability and Accountability Act. The LSUHSC and/or Children's Hospital facilities, their employees, officers, and physicians are hereby released from any legal responsibility or liability for disclosure of the above information to the extent indicated and authorized herein.

I UNDERSTAND THAT THIS AUTHORIZATION SUPERSEDES ANY CONTRARY INFORMATION IN ANY OTHER DOCUMENTS I HAVE SIGNED RELATED TO THE ATTACHED STUDY.

Signature of Patient or Patient's Legal Representative:_____
Date:___/___/____

Printed Name of Legal Representative (if any):
_____

Representative's Authority to Act for Patient (e.g., relationship to patient):
_____

Verification of Representative's Authority: ( ) viewed driver's license ( ) viewed Power of Attorney
( ) viewed other_____(specify)

CONSENT FORM

Title of Research:	South-seq: DNA sequencing for newborn nurseries in the South (NIH Grant Number 2U01HG007301-05)
Site:	University of Louisville (17.1333) and Norton Healthcare
UAB IRB Protocol #:	IRB-300000328
Principal Investigators:	Kyle Brothers, MD, PhD
Sponsor:	NIH National Human Genome Research Institute (Contact: Lucia Hindorff PhD, MPH)

For Children (persons under 18 years of age) participating in this study, the term "You" addresses both the participant ("you") and the parent or legally authorized representative ("your child").

Purpose of the Research

We are asking you to take part in a research study. The purpose of this research study is to use whole genome sequencing (WGS), looking at your DNA, to identify the genetic cause of conditions like those observed in your child. For individuals with rare, undiagnosed diseases and their families, this experimental genetic test may provide information about what is causing the disease or condition. This information may be beneficial to your family in directing your child's health care, medical treatments, and your family planning decisions. Educational tools about your child's condition may also become available with a confirmed genetic diagnosis.

In addition, due to the limited number of genetic counselors available to support patients that may benefit from WGS, we will be comparing two results delivery methods: genetic counselors (standard of care), and healthcare providers (e.g. neonatologists and neonatology nurse practitioners) who undergo specific genetics results delivery training. In this clinical trial, we aim to demonstrate that both delivery methods are equivalent (i.e. there is no difference between the two methods).

Due to the experimental nature of this research study, data generated is based upon the knowledge currently accepted in the field. As more genomes are sequenced and as sequencing techniques improve, we will be better at identifying and understanding extremely rare variants (rare changes in DNA). In doing this, we will also improve and we will learn more about how certain variants may cause disease. For this reason, we plan to store samples for future research.

There will be approx. 1500 newborn participants enrolled for WGS and 800 parents and/or caregivers enrolled for the clinical trial across 4 NICU sites: UAB/Children's of Alabama, University of Mississippi Medical Center (UMMC), Woman's Hospital, University of Louisville and Norton Healthcare (UofL). Samples will also be collected from biological mothers and fathers (up to 2,250 individuals), when available, so that we can use their samples to determine inheritance of any variants we find in their child. We also hope to include a diverse group of participants so we are planning to offer this test to

all populations, especially those underrepresented in science and genomic research such as African Americans and those from rural areas.

Explanation of Procedures

If you agree to join the study, you are agreeing to:

- Give us permission to collect a blood sample for DNA analysis
    - Adults will give approximately 8mL (approx. 1.6 tsp) of blood that will be drawn from the arm.
    - Newborns will give no more than the maximum amount allowed for their body weight according to the University of Louisville and Norton Children's Hospital guidelines.
- Give us permission to fully analyze your DNA (or other related material, like RNA or protein) and determine the health significance of your genetic results.
- Allow us to return health information to you that we feel may be important to your child's health or other biological relatives.
- Allow key study personnel to access your child's personal medical records to aid in analysis. Study personnel may collect information about the child's symptoms, health history, medications/treatments, etc.
- Provide key study personnel with information about your child's health history, pregnancy and birth history, information about your health and that of other family members, if you know it, etc. Study personnel will not access your medical record. They will only have access to the information that you choose to share with them.
- Allow us, if you so choose, to return genetic results that are not related to your child's condition but are medically important for other reasons.
- Answer survey questions at the time of consent, return of results (ROR), 1-month post ROR, 4-months post ROR, and 4.5-months post ROR that will take approximately 20-35 minutes to complete.

You will be asked to take part in two clinic visits here in the nursery or at the outpatient clinic. During the first visit, you will be asked to enroll in the study and give a blood sample (1.5hrs) and during the second visit you will receive the results of your child's DNA test either by a genetic counselor or a trained healthcare provider (1.5-2hrs). The return of results visit can either take place in-person or over the phone. A certified letter with results will be sent to those who do not participate in either in the in-person or phone ROR appointment.

More than one parent/guardian/caregiver of a child receiving WGS can participate in the study. It is important that anyone participating in the survey portion of the study be present at ROR and complete every survey.

Collecting samples from both biological parents increases the chances of identifying genetic variation in your child that might be causing his or her symptoms. However if both parents are not available, we can still analyze eligible patients and potentially find valuable information. In cases where we enroll family members, our DNA test can identify whether a person is the biological parent or not. We will not tell you or your family members if we find out that one or both parents are not biologically related to the child, however we are less likely to discover diagnostic information about your condition without both biological parents.

Your blood samples will be labeled with a unique code (coded) and sent to researchers at the HudsonAlpha Institute for Biotechnology, a non-profit genetics research center located in Huntsville, AL. Some relevant, health information will also be given to the research staff, and coded with a unique study identifier, to aid in their analysis.

We will use state-of-the-art technologies to generate large amounts of information about the DNA from you and your child. A group of experts, including medical doctors and researchers, will use scientific findings and genetic databases to help decide what genetic information may be important to the health of your child. The sequence of all results believed to be medically relevant or important to your child's or your own health will be validated at HudsonAlpha Clinical Services Laboratory in Huntsville, AL or another independent clinical laboratory. We expect the entire DNA analysis process to take 2-4 months.

We do intend to perform analysis of each sample within our budgetary and technical means. If we are unable to analyze your samples you will be notified within 6 months of enrollment and sample collection. There is no cause for concern if you are told that we could not complete the analysis and provide you with results.

Return of results is at the discretion of the clinicians and researchers involved with this study. If they identify results that may impact your child's health, they may return those results to you. You will be scheduled for an appointment to discuss these findings with a genetic counselor or trained healthcare provider. Only a subset of results believed to be important to your child's medical care or those in line with the goals of this study will be reported to you. We will not provide you with all of the genetic information that we generate. At your results appointment, you may be provided with information regarding:

- Primary findings - These findings will include information about a variant(s) (DNA change) that may potentially be the reason for your child's phenotype (symptoms) or condition.
    - Most children will not receive a primary finding (or diagnosis). If no diagnosis is found, we will tell you. Even if we do not find a genetic diagnosis, your condition may still be the result of a change in your DNA that we are currently unable to identify.
    - If you receive a genetic diagnosis, this may not change your child's prognosis or medical treatment. However it may help you and your doctor to better understand the cause of your child's condition and the risks of similar conditions affecting your biological children.
- Secondary findings – These findings may be reported to any study participant and may include any genetic changes that might impact your health or the health of your current or future children. These may include:
    - Whether there are any changes in your DNA that could put you at a higher risk for developing a disease unrelated to your child's condition in the future, such as cancer or heart disease.
        1. Some of these diseases may be medically useful and some may not be medically useful. We will not return results that are not medically useful.

2. Some of these diseases will appear in childhood and others will appear when you are an adult.

- Carrier status – In the event that we discover that your child's symptoms are caused by a recessive genetic condition where he or she inherited one variant (DNA change) from each parent, we may provide information about whether or not you are a "carrier" for a genetic change that may be passed on to your biological children.

We will arrange for a genetic counselor or a trained healthcare provider to discuss the results of the test with you. Educational materials will also be made available to you to help you better understand any results that you may or may not receive as part of this study.

You will be actively enrolled in this study for up to one year however we may continue to access your medical record for up to 5 years. We plan to use coded information from our medical record to determine the impact of whole genome sequencing and genetic diagnosis on medical care. After you receive the results of the genetic test, you may be contacted by your physician or key study personnel to check on you or to ask follow-up questions. Your DNA samples may be stored indefinitely for future research unless you choose to withdraw from the study. Please note that participation in this study is voluntary and you may withdraw from this study at any time.

You will also be presented with a baseline survey at the time of enrollment that you can complete online using Genome Gateway. The survey will ask you questions about basic demographics, how you feel about your child's health and your experience in the hospital, how well you understand medical terms, math and genetics. After you receive results from this testing, you will be asked some of these same questions and some additional ones related to your health, your understanding of the genetic results returned, and how the results influence future life planning at 1-month post ROR, 4-months post ROR, and 4.5 months post ROR.

Risks and Discomforts

The risks of drawing blood include pain, bruising, lightheadedness, and fainting. Infection at the site of the needle stick is a rare side effect. These are the same risks you face any time you have a blood test.

The main concerns associated with genetic testing are anxiety, depression, or other forms of emotional distress that may result from receiving genetic information about the suspected cause of your child's condition. This is especially true for those diseases that are not treatable or preventable. Though some treatments have been shown to help individuals with certain genetic conditions, there is no "cure" for most.

When performing genetic testing, it may be discovered that family relationships are not as predicted. For example, a child might not be biologically related to his/her father, or two people who are married might turn out to be biologically related. These findings will not be disclosed as part of this study.

In some cases, you may receive information about your carrier status and/or changes in your DNA that may impact your health. These findings will only be returned if they were inherited by your child

who is enrolled in this study and suspected to contribute to their condition. Genetic changes in children that affect development may be inherited from one or both parents, even if the parents appear to be healthy. This information may affect the way you view or evaluate yourself or your family. It may also influence, or generate anxiety about, future family planning decisions.

It is also important to keep in mind that you and your biological relatives have similar DNA sequences. This means that genetic information about your child may also have implications for your relatives if the variation was inherited.

You may be referred to an additional physician or clinic for further testing or advice depending on the type of genetic information we generate from your sample. If you experience psychological distress or other difficulties, we can also refer you to an appropriate resource for care and/or support.

There may be unforeseeable risks associated with receiving genetic information and the potential decisions, actions, or inactions that may be required in response to that information. Please consider this carefully and ask any questions that you may have before deciding whether or not to participate in this study.

It is important that you consider the risks and uncertainties of this research study that make it different from traditional medical testing.

We will make sure that the information that you are given is as accurate as possible to the best of our ability. We will use the best standards, practices, and technologies available to researchers. However, the technologies available to analyze DNA and our knowledge of how DNA affects health are changing rapidly. They are also subject to much uncertainty. Some DNA changes that are important to health may be missed, and other DNA changes that are not important may be incorrectly identified as if they are important. There are also moral and ethical questions about using genetic information on which scientific and medical communities have not yet reached a consensus. Therefore, we do NOT guarantee that our test will have the same levels of completeness, accuracy, or standardization associated with more traditional medical tests.

Before offering your consent to participate in this research study, please consider all of the risks associated with:

- The return or possible lack of return of results;
- Whether our interpretation of those results is accurate;
- How you and/or your family will choose to act upon or not act upon the information or lack of information.

Benefits

You may not benefit directly from taking part in this study. However, your participation may lead to new discoveries that help to advance medical research and improve patient care, especially, but not only, newborn patient care in the future. Your participation in this study may help to make health care and access to health care broader and more representative.

You may find out if there is a change in your child's DNA that has altered their development. You might also find out if this change could affect future biological children.

A genetic diagnosis may help you connect with other families in the community who face similar medical problems. While unlikely, it is possible that a genetic diagnosis may point your doctor to a better medical and/or educational treatment.

You may discover that you or your child are at an increased risk for developing other diseases and that information may be of medical benefit.

None of the above benefits are guaranteed, and it is expected that many participants will not receive specific information that is relevant to their health.

Alternatives

This is not a treatment study. Your alternative is not to participate in this research study.

HIPAA Research Authorization

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) provides federal safeguards for your protected health information (PHI). State and federal privacy laws also may also require your health information to be protected. By signing this form you provide your permission, called your "authorization," for the use and disclosure of PHI.

If you sign this form, the research team working on this study will use and share your health information to answer the research questions described in this document, and to make sure that the research was done correctly. This includes things learned from the procedures described in this consent form. They may also collect other information including your name, address, date of birth, medical history, and other information from your medical records from this institution and other institutions involved with this research, as well as from your other healthcare providers (which may include information about HIV status, drug, alcohol, or sexually transmitted disease treatment, genetic test results, or mental health treatment). Those persons who receive your health information may not be required by Federal privacy laws (such as the HIPAA Privacy Rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

In most cases, the health information that identifies you can be used or shared by the research team only if you give your permission by signing this form. Your health information may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability, and conducting public health surveillance, investigations or interventions.

The time period when information can be used or shared ends when all activities related to this study are completed.

You do not have to sign this form. If you do not sign this form, you may not participate in the study and health information that identifies you will not be shared for research purposes.

Revocation of Research Authorization

You may withdraw the authorization you have given to use and share your protected health information at any time. This means you can tell us to stop using and sharing your protected health information. If you withdraw/revoke your authorization:

- We will stop collecting information about you.
- You may not withdraw information that we had before you told us to stop.
    - We may already have used it or shared it.
    - We may need it to complete the research.
    - We may need it to search records that are available to the public.
- Staff may ask your permission to follow-up with you if there is a medical reason to do so.

To withdraw your authorization, you will be requested to complete a written "Revocation of Research Authorization" form located at the end of this document. You may also obtain a copy from your study doctor, designated personnel or from the Human Subjects Protections Program Office website (https://louisville.edu/research/humansubjects/templates/biomedical-forms).

Confidentiality

Information obtained about you for this study will be kept confidential to the extent allowed by law. However, research information that identifies you may be shared with people or organizations for quality assurance or data analysis, or with those responsible for ensuring compliance with laws and regulations related to research. They include:

- the UAB Institutional Review Board (IRB). An IRB is a group that reviews the study to protect the rights and welfare of research participants.
- The University of Louisville Institutional Review Board, Human Subjects Protection Program Office, Privacy Office, others involved in research administration and research and legal compliance at the University, and others contracted by the University for ensuring human subjects safety or research and legal compliance
- The local research team
- People responsible for billing, sending and receiving payments related to your participation in the study
- the NIH National Human Genome Research Institute (NHGRI)
- the Office for Human Research Protections (OHRP)
- Office of Civil Rights

The information from the research including your child's clinical information, family history, and genetic variants may be published for scientific purposes; however, your identity will not be given out to anyone outside of the clinical team involved with the study.

Your consent form will be placed in your child's medical record. This may include either a paper medical record or electronic medical record (EMR). An EMR is an electronic version of a paper medical record of your care within this health system. Your child's EMR may indicate that you and your child are enrolled in this study and provide the name and contact information for the principal investigator.

Results of research tests or procedures that have been clinically validated (i.e. Sanger reports) may be placed in your child's medical record. All information within your medical record can be viewed by individuals authorized to access the record.

Information relating to this study, including your name, medical record number, date of birth and social security number, may be shared with the billing offices of University of Louisville so costs for clinical services can be appropriately paid for by either the study account or by your insurance.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and some employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware this federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance, nor does it protect you against genetic discrimination by some employers.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Voluntary Participation and Withdrawal

Whether or not you take part in this study is your choice. There will be no penalty if you decide not to be in the study. If you decide not to be in the study, you will not lose any benefits you are otherwise owed. You are free to withdraw from this research study at any time. Your choice to leave the study will not affect your relationship with any institution participating in this study.

In the event that you chose to withdraw from the study:

- No further genetic information from the study will be reported to you.
- Your blood samples will be destroyed.
- You will not be contacted to provide new information, additional samples, or participate in additional studies related to this project.
- If the analysis of your DNA has been completed, this information will be retained for the study.

If you would like to withdraw from the study, please contact Dr. Brothers or the study team at 502-629-5820.

Cost of Participation

There will be no cost to you for taking part in this study. The blood draw, genomic sequencing and analysis, and genetic counseling related to this study will be provided to you at no cost during the study period.

After you receive your research results, you may decide with your doctor or your child's doctor to get more testing. The costs of your standard medical care or any services rendered in response to a genetic finding identified by this research project will be billed to you and/or your insurance company in the usual manner. This type of follow-up medical testing will be considered part of your clinical care, and will not be paid for by the research study.

Payment for Participation in Research

Participation in this study is voluntary and $25 will be provided for each survey completed for a total of $125 for your completion of all 5 study-related surveys. Ask the study staff about the method of payment that will be used for this study (e.g., check, cash, gift card, direct deposit); payment may take up to 4 weeks to process.

Because you will be paid by UAB, to be in this study the University of Louisville may collect your name, address, social security number, and keep records of how much you are paid and will need to send this information to UAB. You may or may not be sent a Form 1099 by the UAB. This will only happen if you are paid $600 or more in one year by the University. This will not include payments you may receive as reimbursement for actual expenses based on receipts or actual miles traveled. We are required by the Internal Revenue Service to collect this information and you may need to report the payment as income on your taxes.
You can still be in the study even if you don't want to be paid

Payment for Research-Related Injuries

UAB, UMMC, HudsonAlpha, Woman's Hospital, University of Louisville, and NIH/NHGRI/sponsors of this research project have not provided for any payment if you are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge.

Significant New Findings

The study doctor or study staff will tell you if new information becomes available that might affect your choice to stay in the study. Please note that HudsonAlpha may, but is not required to, reanalyze your sample or report any new findings after results have been returned.

Storage of Specimens for Future Use

As part of this study, we would like to store some of the blood and DNA specimens collected from you and your child for validation of variants (to determine if a variant was inherited from a parent, etc.) identified by this project and for future research relevant to rare disease or other genetic disorders. The future research may be conducted by the study doctor or by other researchers that obtain IRB approval for their research. The specimens will be labeled with a code that only the study doctor can link back to you. Results of any future research will not be given to you or your doctor. The specimens obtained from you in this research may help in the development of a future commercial product. There are no plans to provide financial compensation to you should this occur. You do not have to agree to allow your specimens to be stored in order to be part of this study.

You may at any time withdraw from the study and request that your specimens be removed from storage and not be used for future research. If you decide you want your specimens removed, you may contact Dr. Bruce Korf at 205-934-9411. Once the request is received, and if your samples have not already been used for other research, they will be destroyed. If you do not make such a request, your specimens will be stored indefinitely or until used.

Initial next to your choice below:

___I agree to allow my specimens to be kept in the HudsonAlpha CSL and used for future genetics research.

___I do NOT agree to allow my specimens to be kept and used for future research.

Genomic Data Sharing (GDS)

We consider the privacy of your information to be of high priority and will take a variety of steps to ensure that privacy. However, it is important for researchers to share some of the information that they learn from studying human samples. We will never share personally identifiable information, like names and addresses, with anyone outside of the research study. However, parts of your information may be shared.

Some of your genetic information, limited to a very small subset that will not cause privacy loss risks to you, may be published in scientific journals or other unrestricted-access public venues to encourage sharing of the knowledge that may be learned by analyzing your DNA and DNA from other individuals. This could include information about your child's symptoms, their age, and any genetic findings that we discover.

We may share coded lists of the DNA differences that we identify in public genetic databases. These databases gather genetic information from large groups of people and are pooled together such that no specific participant can be identified.

There is a very small chance that some commercial value may result from the use of your donated samples or genetic information. If that happens, you will not receive a share in any profits.

Unless you opt out, we may submit your complete genomic data along with some of your coded health information to an NIH-designated Data Repository such as dbGAP (http://www.ncbi.nlm.nih.gov/gap), AnVIL (https://anvilproject.org/), or another controlled access database. Access to dbGAP and AnVIL is only available to qualified researchers at qualified institutions who have agreed to abide by certain privacy safeguards, obligating them, both legally and ethically, to protect your privacy and to maintain information confidentiality. However, since your genetic information is unique to you, there is a small chance that someone could trace your information back to you. This risk is very small, but may grow in the future. Some risks and benefits are listed below:

Risks: The risk of sharing your genomic data is that someone could link the information stored in the databases back to you. If your information suggests something about your health such as increased risk for disease, it could be misused. For example, it could be used to make it harder for you to get or keep a job or insurance or be used to discriminate against you or your family. There may also be other unknown risks. As stated above (confidentiality section of this form), there are federal protections against the misuse of your data (i.e. the Genetic Information Nondiscrimination Act, GINA).

Benefits: There is no direct benefit to you from sharing your genomic data with NIH-designated repositories, however allowing researchers to use your data may lead to a better understanding of how genes affect health which may help other people in the future.

Initial next to your choice below:

____ I agree for my genetic and other relevant study data, such as health information, to be shared with NIH-designated repositories such as dbGAP and AnVIL in a coded form for future research or analysis

____ I do NOT agree for my genetic and other relevant study data, such as health information, to be shared with NIH-designated repositories such as dbGAP and AnVIL in a coded form for future research or analysis

Contact For Future Research

As new research opportunities are identified, the researchers may wish to perform additional tests on fresh samples or invite eligible participants to enroll in new studies. We would like permission to contact you in the future, however this is not a requirement to participate in this study. A separate consent form will be obtained if you wish to participate in future research.

Initial next to your choice below:

____ You have permission to contact me about new research opportunities that may interest me.

____ You do NOT have permission to contact me about new research opportunities.

Secondary Findings

One unanimous decision to receive or not to receive secondary findings must be made by each participant family. Because parental samples are only used for confirmation of variation identified in the child's whole genome sequence for this project, only those secondary findings identified in the child will be confirmed in the parental samples. Participant families may opt to receive this information, if available. If a family chooses to do so, information about an identified secondary finding will be included in the child's medical record. Nothing will be placed in the parent's medical record.

Initial next to your choice below:

____ We (child and parent(s), if enrolled) would like to receive information about secondary findings.

____ We (child and parent(s), if enrolled) would NOT like to receive information about secondary findings.

Questions

If you have any questions, concerns, or complaints about the research or a research-related injury including available treatments, please contact the study PI Dr. Bruce Korf (UAB) at 205-934-9411 or call Dr. Brothers (the site PI) and the UofL study team at 502-629-5820.

If you would prefer to write, you may contact Dr. Brothers or the study team at the University of Louisville, 231 East Chestnut Street, Louisville, KY 40202 or email Dr. Brothers at kyle.brothers@louisville.edu.

If you have concerns or complaints about the research or research staff and you do not wish to give your name, you may call the toll free number 1-877-852-1167. This is a 24 hour hot line answered by people who do not work at the University of Louisville. If you have questions about your rights as a research participant, or concerns or complaints about the research, you may also contact the UAB Office of the IRB (OIRB) at (205) 934-3789 or toll free at 1-855-860-3789. Regular hours for the OIRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday.

Legal Rights

You are not waiving any of your legal rights by signing this consent form.

Signatures

Your signature below indicates that you have read (or been read) the information provided above and agree to have your child participate in this study. You will receive a copy of this signed consent form.

Your signature below indicates that you have read (or been read) the information provided above and agree to participate in this study. You will receive a copy of this signed consent form.

_____

Name of Proband Child (printed)

_____

Signature of Parent or Legally Authorized Representative Date

Mother/Father/Caregiver

_____

Name of Parent Participant (printed) Relationship

_____

Signature of Parent Participant Date

Mother/Father/Caregiver

_____

Name of Parent Participant (printed) Relationship

_____

Signature of Parent Participant Date

_____

Signature of Person Obtaining Consent Date

In this research study, one consent form may be used to waive consent for the infant and capture informed consent of both parents; however, a separate HIPPA Authorization form will be completed for each participant.

Waiver of Assent

The assent of _____(name of child/minor) was waived because of:
Age _____ Maturity _____ Psychological state of the child _____

REVOCATION OF AUTHORIZATION FOR USE AND DISCLOSURE OF YOUR HEALTH INFORMATION FOR RESEARCH

PI Address: 231 East Chestnut St. N-97
Louisville, Kentucky 40202
PI Phone: 502-629-5820

Return To:

OR

Institutional Review Board
MedCenter One, Suite 200
501 E. Broadway
Louisville, KY 40202

Do not sign this letter unless you are withdrawing from this research. You will be sent confirmation that this notice was received.

To Whom It May Concern:
I would like to discontinue my participation in the research study noted above. I understand that health information already collected will continue to be used as discussed in the Authorization I signed when joining the study.
Your options are (choose one):

☐ Withdraw from Study & Discontinue Authorization:
Discontinue my authorization for the future use and disclosure of protected health information. In some instances, the research team may need to use your information even after you discontinue your authorization, for example, to notify you or government agencies of any health or safety concerns that were identified as part of your study participation.

☐ Withdraw from Study, but Continue Authorization:
Allow the research team to continue collecting information from me and my personal health information. This would be done only as needed to support the goals of the study and would not be used for purposes other than those already described in the research authorization

☐ Withdraw authorization for use of PHI in optional sub-study. Please describe the change below.
_____

_____ _____
Printed Name and Signature of Subject Date Signed

_____ _____
Signature of Subject's Legal Representative Date Signed
(if subject is unable to sign)

_____ _____
Printed Name of Subject's Legal Representative Birthdate of Subject

_____
Relationship of Legal Representative to Subject

_____ _____
Subject's Address Subject's Phone Number

Optional:
I am ending my participation in this study because:_____

Appendix 4: Patient Resources and Learning Topics

Summary of changes made:

Based on feedback from Community Engagement Studio

General

- Made key points briefer and no longer verbatim repeats of detailed text
- Broke up text with more headers and subheaders
- Added examples for unexpected result and genetic discrimination sections
- Added in-text definition of terms
- Shortened page titles to prevent menu title cut-offs

New Section

- Added glossary of common genetics terms
- Added topic of instructions on how to use Genome Gateway
- Hyperlinked key words in other topics to glossary

New Videos

- SouthSeq overview
- Genome sequencing
- Dominant inheritance
- Recessive inheritance
- X-linked inheritance

New Graphics

- Made “Secondary Findings” graphic more specific to SouthSeq study
- Increased font for “What to Expect” and “What to Expect Next” graphic text

Learning assigned at time of consent/enrollment:

Instructions

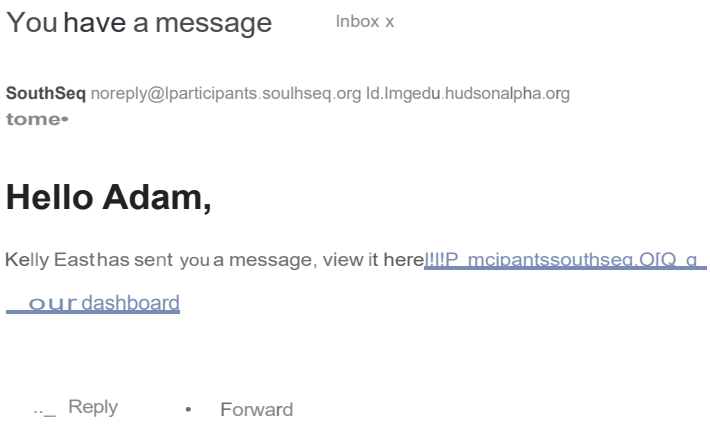
Key Points:

- Genome Gateway is an online tool that helps you participate In the SouthSeq study.
- In Genome Gateway you can build your family health history.
- In Genome Gateway *you* can explore learning topics.
- In Genome Gateway you can answer important surveys about the study.
- In Genome Gateway you can see and download files, including your child's test results.
- In Genome Gateway *you* can message with the SouthSeq study team.

Read more...

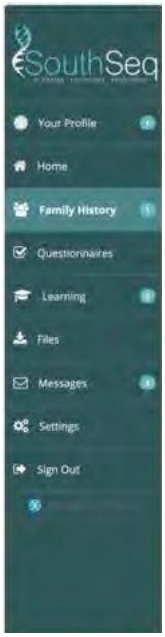
Receiving Notifications

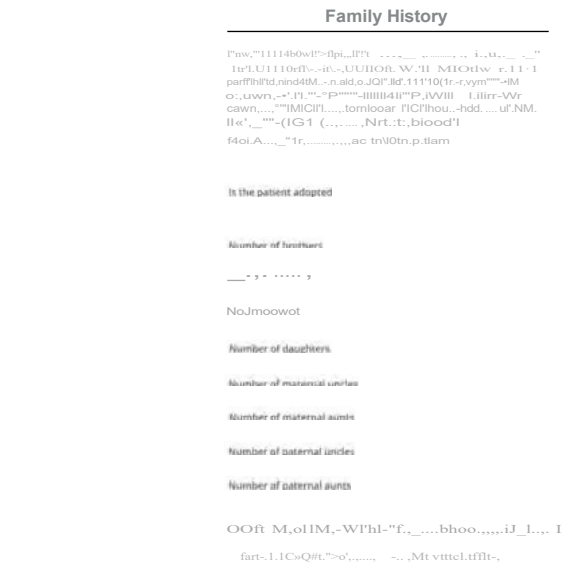
When you there is something new to look at or do in Genome Gateway, you should receive an email and/or text message from the system. The message will tell you what kind of new information is available and will have a link to click to get to the Genome Gateway website. The picture below shows what an email message from Genome Gatewaylooks like. Please keep an eye out for these messages.

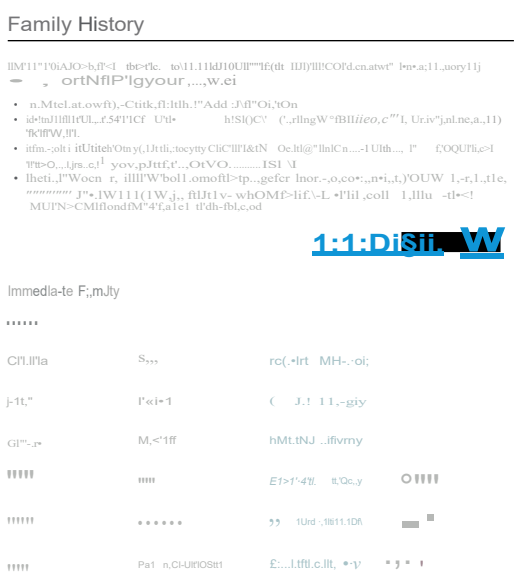


Building your family health history

From your main page in Genome Gateway, click on the family history icon to build your child's family health history. By answering a few simple questions about your child's relatives, the system will make your child's family tree. You can add details about your child's relatives including their age and any medical conditions they have. This information can be very helpful for the study team when the genome sequencing test is done. Watch the following video to learn more about how *to* build your child's family health history in Genome Gateway.

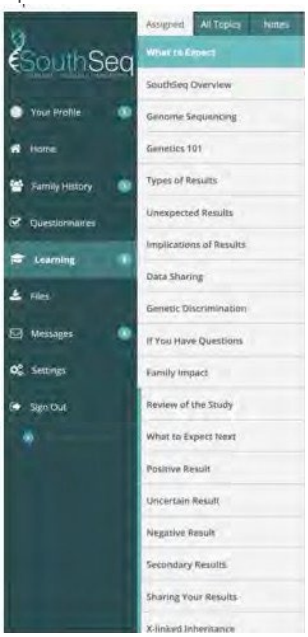


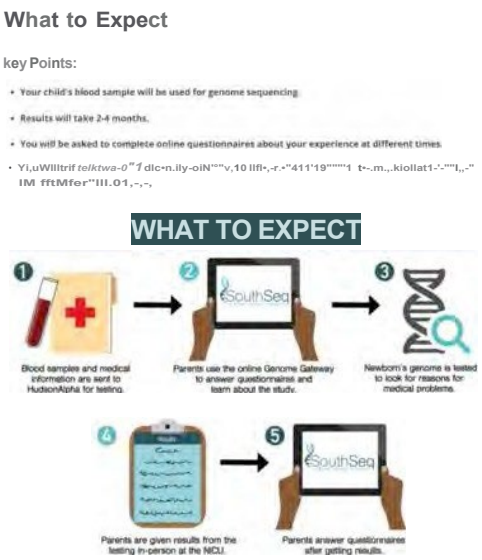




Explore learning topics

From the home page, you can find your assigned learning topics. You will be assigned learning topics at different points throughout the SouthSeq study. You can also find learning topics by clicking on the learning tab on the left menu bar. When you first enroll, your learning will include topics about the study and genome sequencing testing in general. You will also have learning assigned after you receive results from the study. These learning topics are available throughout the study. You can log into Genome Gateway at any point during the study to look at learning topics.





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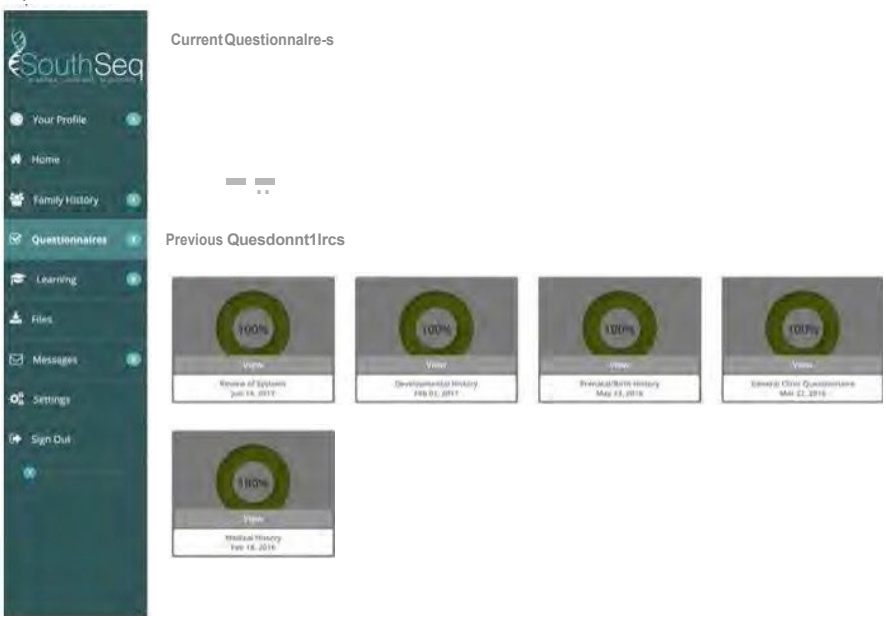
Answer surveys

From the home page, you can find your assigned questionnaires. You will be assigned questionnaires at different points of the SouthSeq study. You can also find questionnaires by clicking on the questionnaires tab on the left menu bar. These questionnaires will help the research team learn more about your experiences with the study. We hope that your answers to questionnaires will help families in the future with their genetic testing process and experience.



Download flies

You can find new files on your home page or click to view previous files from the SouthSeq study. You can also find files by clicking on the files tab on the left menu bar. Thisis where you can find your study consent and study results files. You can open or download your files by clicking on their name. These files will be kept in Genome Gateway throughout the study.

Message the study team

You can find messages in Genome Gateway from the messages tab in the left menu bar. Members of the study team can message you through Genome Gateway, and you can respond to messages in message threads. Thisis another way you can ask questions and talk to the study team. To respond to a message, you can click the text bar at the bottom of the page to type. You will get a text or email from Genome Gateway when there is a new message to read.

SouthSeq Overview

Key Points:

- **SouthSeq is a study that will enroll newborns in NICUs from across the Southeastern United States.**
- **Each newborn will have a genetic test called Genome Sequencing to look for causes of the newborn's medical problems**
- **Results of the study may include a reason for a newborn's medical problems.**
- **Results may include information about the chance the newborn or other family may develop other medical problems.**

Read more...

SouthSeq

You are being told about the SouthSeq study because your baby has medical problems that may have a **genetic** cause.

This study uses a new kind of genetic test, called **genome sequencing** that looks at your baby's entire genetic code.

Link to video: https://vimeo.com/287113637

Doing this test in a NICU may allow a diagnosis to be made earlier and may help your baby's doctors provide better care and treatments.

Study Goal

The goal of this study is to enroll about 1,500 newborns in the southeastern US. We want to learn if this test is helpful in a NICU and to understand the impact this impact has on patients and their families.

Results

Results from the genome sequencing test will be given back to you and your baby's doctors. **It may take 2-4 months to get the results.**

Results may include:

1. If the test was able to find the reason for your baby's medical problems
2. Genetic changes that may be important for your family's medical care

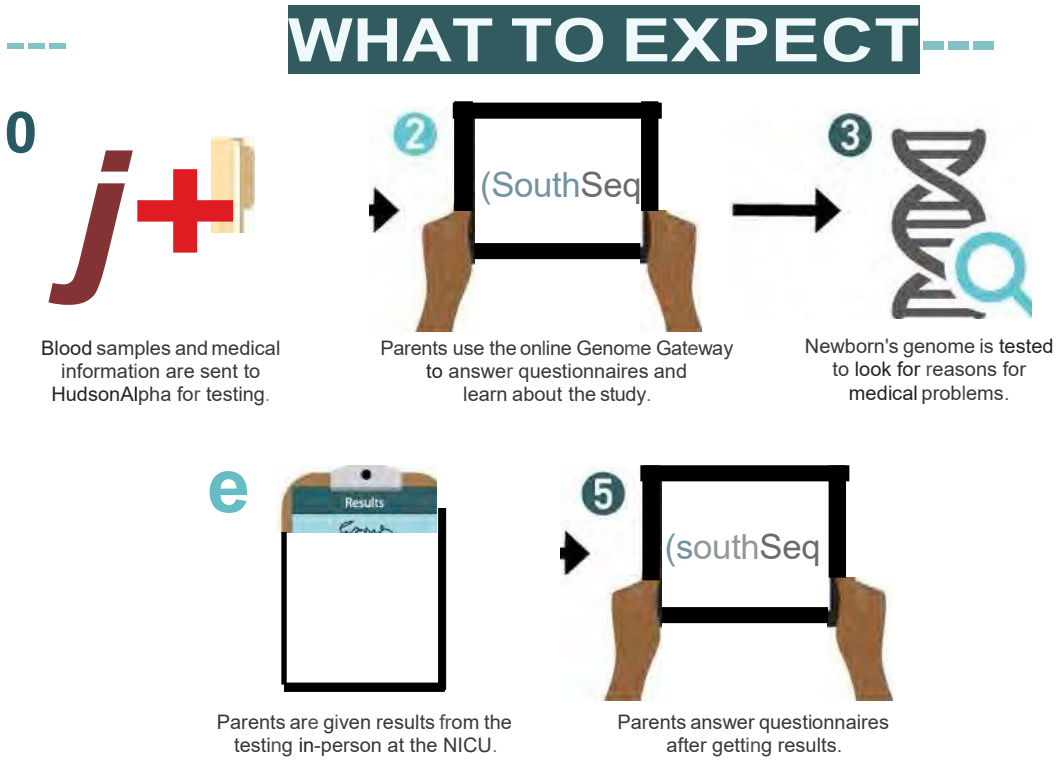
Learning

The learning topics here in Genome Gateway will give you more information about the study.

What to Expect

Key Points:

- **Your child's blood sample will be used for genome sequencing.**
- **Results will take 2-4 months.**
- **You will be asked to complete online questionnaires about your experience at different times.**
- **You will be followed by the study staff for up to one year, and the study team maylook at your chlld's medical record for up to 8 years.**



Read more...

Here is a look at what you can expect from your participation in the SouthSeq study.

Genome sequencing testing

Through the SouthSeq study, a genetic test called genome sequencing will be done for your baby. Genome sequencing is a test that looks at all of a person's genetic information called DNA. A blood sample will be collected from your baby as well as the biological parents if possible. Genome sequencing will not be done on parent samples, rather these samples will be used for follow-up testingdepending on the baby's results. See Genome Se uencing for more information on the test.

SouthSeq Steps

1. Blood samples and information about your baby's medical history will be sent to a lab at the HudsonAlpha Institute for Biotechnology, in Huntsville, AL for testing.
2. You will be asked to complete several questionnaires, complete your baby's family history, and read educational information inside Genome Gateway.
3. The lab will look at your baby's DNA sequence and look for anygenetic changes that could be the reason for medical problems.
4. Results from the genome sequencing test **will take 2-4 months to complete.** You will be notified when results are ready and a time will be scheduled for you to discuss your results with a healthcare provider in the NICU.
5. After you receive results from the study you will be asked to complete several additional questionnaires and new educational information in Genome Gateway.

Questionnaires

Questionnaires help us learn more about how this type of testing can be used in a NICU and the impact genomic results have on patients and their families. We appreciate your participation in this study and willingness to share your family's experiences with us.

Genome Gateway for files and communication

Throughout the study you will have access to Genome Gateway. Within Genome Gateway you will have access to files such your study consent form and your baby's results once they they have been discussed with you. You are also able to communicate with your SouthSeq study team using the message feature within Genome Gateway.

You will be sent an email and/or text message whenever there is a new questionnaire or new educational topic to complete.

You may be contacted by your child's healthcare team or study staff to ask follow-up questions. You will be actively involved in the study up to one year. During the year you're involved in the study, researchers will be able to give you results, give you questionnaires, and see how medical providers use genome sequencing results in your baby's care.

Privacy

This study will use some of your baby's medical information. Your baby's medical information is kept confidential. Names, date of birth, and other information that can be used to identify someone are not shared with anyone outside of the research study. Information about this study and genetic results will be in your baby's medical record. See the Genetic Discrimination section for more information about genetic privacy.

Withdrawing

It is important for you to know that you can leave the study and withdraw your consent to participate from the SouthSeq study at any time. To withdraw please contact the study coordinator at the NICU where your baby was enrolled. If you choose to withdraw from this study, your child's medical care will not be affected.

If You Have Questions

Contact Us:

We understand that you may have questions that come up that are not addressed in these learning topics. Use the information below as a guide to the best person to contact depending on your specific question or need.

Genome Gateway Messages

You may have messages through Genome Gateway from members of the study team. You can ask questions on message threads.

General health questions

If you have questions or concerns about your child's health and medical care, please contact your child's healthcare providers.

Genome sequencing test questions

If you have questions about the status of your genome sequencing test or your results, please contact the study coordinator where you were enrolled into the study.

- University of Alabama at Birmingham Medicine: (205-934-6452)
- Woman's Hospital in Baton Rouge: (225-924-8310)
- University of Mississippi Medical Center: (601-815-3070)

Overall SouthSeq project questions

If you have questions, concerns, or complaints about the research project, please contact Dr. Bruce Korf at 205-934-9411.

If you have questions about your rights as a research participant, you may also contact the UAB Office of the Institutional Review Board (IRB) at 205-934-3789.

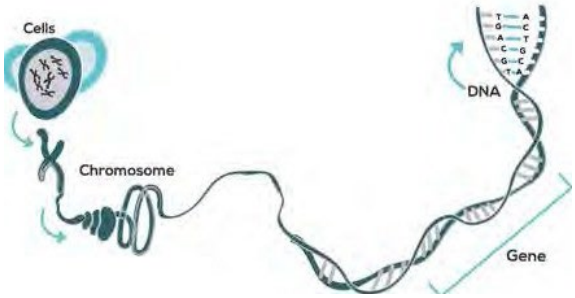
Genetics 101

Key Points:

- **A human body is made of cells, and inside our cells Is a complete set of DNA.**
- **DNA contains genetic "instructions" that ourbodies use and that we canpass to our children.**
- **A gene Is a section of DNA that tells our bodyhow to do a specific task.**
- **A person's entire setof DNA is called the genome.**

Read more...

Understanding genetics



Our understanding of **genetics** is increasing rapidly. We are learning more and more about how changes in a person's **genes** can affect their health and risk of developing disease. Newspapers, TV, and the Internet often talk about new genes or genetic tests related to medical conditions. Genetics can be complicated, and it is often difficult to separate fact from what is not true. The first step begins with a basic understanding of our genes and the human genome. Understanding these can help a person make informed decisions when faced with genetic questions.

Our bodies are made of cells

A **cell** is the basic building block of all living things. Adults have an estimated 10 trillion cells that make up their bodies. Inside a cell there is a command center, called the **nucleus**, that contains the cell's genetic information. This genetic information is in the form of **DNA**.

Cells have DNA

DNA (deoxyribonucleic acid) contains the genetic instructions that pass information from onegeneration to the next. DNA is found in long strands called **chromosomes** and is very tightly wound to fit inside the nucleus of a cell. DNA is made up of four building blocks: Adenine, Thymine, Cytosine, and Guanine, abbreviated A,T,C, and G.

The term **genome** refers to all of the genetic information present in a cell. There are nearly 3 billion DNA letters in a human's genome.

Genesare DNA instructions

A **gene** is a specific stretch of DNA that give the cells instructions. These instructions are like a recipe or a blueprint for the body. Often, but not always, these instructions tell the cellhow to put together a certain **i:iroteln**. For example, the human genome includes an insulin gene that tells a cell how to produce insulin - a protein that is important for digesting sugar. Some genes help decide whether a person is brown or blue-eyed, tall or short. Other genes decide the chance that a person will develop a wide variety of diseases.

Genes in the human genome

The human genome contains about 22,000 genes, which makes up only a small part of the total DNA sequence (about 2%). The rest of the DNA is made up of sections that control how genes work and sections that are not yet well understood.

Genome Sequencing

Key Points:

- Genome sequencing looks at all of a person's DNA.
- Genome sequencing looks for changes or differences in a person's DNA sequence.
- DNA changes are common, and most changes in DNA do not cause a problem. Some DNA changes can cause disease.
- Finding out if a disease is caused by a genetic change can be important for patients, families and doctors.

Link to video: https://vimeo.com/287114652

Read more...

Genome sequencing

Genome sequencing is a test that reads all of our DNA also called a genome. Every person's DNA is made up of four letters (A, T, C, G). We all have about 6 billion of these letters - 3 billion that were **inherited** or passed down from each parent. Your baby's genome contains a lot of information!

How the test works

Genome sequencing is usually done using a blood sample. DNA is taken from blood cells and put into a machine that reads the DNA letter sequence (A, T, C,G). The test looks at the order of DNA letters and compares it to a standard human genome sequence. Then the lab looks for chances or differences in your baby's DNA. This is like spell-check looking for spelling mistakes in a book.

How DNA changes affect health

Having differences or changes in DNA is not necessarily a bad thing. In fact, everyone has millions of DNA changes. Most DNA changes do not affect health. However, sometimes a DNA change can lead to disease.

DNA changes found by this test might be causing current medical problems or cause medical problems that may happen in the future. The test may help doctors make a diagnosis that would not be possible using other tests. The information can sometimes help doctors and patients make a better decision about treatment.

Genome sequencing finds rare DNA changes

Genome sequencing is very powerful but not perfect. We are not able to find and understand all the changes in DNA. Genome sequencing is best at finding very rare changes and rare medical problems. Genome sequencing is not good at finding genetic changes that cause common medical problems like Type 2 diabetes or high blood pressure.

Glossary of Terms

Here is a list of some of the genetic terms and definitions used in the learning sections.
Some of these words may be new to you. Some of these words you might already know, but they may have a different meaning in genetics.

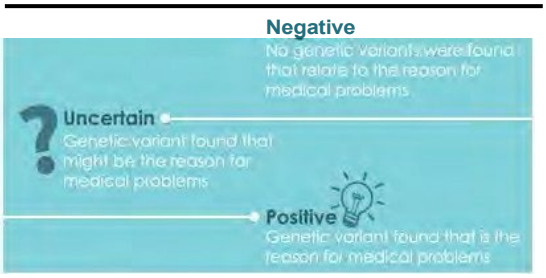
- **Benign:** harmless, does not cause disease
- **Carrier:** having one genetic change in a gene where two changes are needed to cause a disease
- **Cell:** building blocks of life found in every part of the body
- **Chromosome:** structures that hold long strands of DNA together inside the cells
- **dbGAP:** research database (run by the National Institutes of Health) with genome sequencing and symptom information
- **De-novo Inheritance:** a genetic change that is new in a person and not inherited from parents
- **DNA:** genetic information made of the letters A, T, C, and G
- **Dominant inheritance:** when one genetic change in a gene causes someone to have a disease
- **Gene:** a piece of DNA that has specific instructions for the body to grow and work, humans have more than 20,000 genes
- **Genetic counselor:** a health professional with special training in genetics and counseling who helps people understand genetics and how genetic changes can impact their health
- **Genetic discrimination:** being treated differently or unfairly based on your genetic information
- **Genetic testing:** testing that looks for differences in someone's DNA
- **Genome:** all of a person's genetic information, a person's entire sequence of DNA
- **Genome sequencing:** a test that reads through all of a person's DNA to look for differences
- **GINA (Genetic Information Nondiscrimination Act):** federal law that prevents health insurance and employers from making decisions based on genetic information
- **Maternal:** relatives or information from mom's side of the family
- **Nucleus:** special area of a cell that stores DNA
- **Paternal:** relatives or information from dad's side of the family
- **Pathogenic:** causes a disease or disorder
- **Primary result:** a result related to the reason for testing (current or past symptoms)
- **Protein:** gene products that help the body function
- **Recessive Inheritance:** when two genetic changes in a gene are needed for someone to have a condition
- **Secondary result:** result not related to the reason for testing (future disease risks)
- **Sex chromosomes:** the X and Y chromosomes that help determine if someone is born male or female
- **Variant of uncertain significance (VUS):** genetic change that is not understood enough to be called pathogenic or benign
- **X-linked Inheritance:** genetic changes passed down on the X chromosome
- **X-inactivation:** process in women where one of the X chromosomes is 'turned off' in every cell of the body

Types of Results

Key Points:

- Results related to why the genetic test was done are primary results.
- There are 3 primary results: positive, negative, and uncertain.
- **A negative result means nothing was found that's thought to be the cause of your child's medical problems.**
- **An uncertain result might be the cause of your child's medical problems**, but **the lab is not sure.**
- **A positive result is thought to be the cause of your child's medical problems.**

Read more...



Primary results

Genome sequencing results that have to do with the reason the testing has been done are called primary results. Genome sequencing looks at all of a person's DNA. This test can find genetic changes or differences in DNA that can cause medical problems. In this study, results that explain why your child is having medical problems in the NICU would be primary findings. There are three possible types of primary results you may receive: positive, negative, or uncertain.

Negative results

A negative result means that the lab did not find any genetic changes thought to be the cause of your baby's symptoms. A negative test result does not mean that your baby's symptoms are not due to a genetic change. It is possible that your baby has a genetic change that is not yet well understood or able to be found. In some cases, negative results can be looked at again in the future and a diagnosis may be possible at that time.

Uncertain results

An uncertain result means that the lab found a genetic change that is not currently able to be understood. This genetic change may be the cause for your baby's symptoms but there is not enough proof to be certain. This genetic change may also not be the cause of symptoms and just part of typical DNA differences between people. Your baby's healthcare provider should not treat an uncertain result as a diagnosis, and should not make medical decisions based on this kind of result alone. Over time, many of these uncertain results will be better understood and changed to either a positive or negative result.

Positive results

A positive result means that the lab found a genetic change that is believed to be the cause for your baby's medical problems. A positive result can lead to a diagnosis that has clear treatment and support resources. In other cases, a baby may be diagnosed with a new or less understood condition.

Unexpected Results

Key Points:

- **Geneticchanges might be found that aren't causing your child's medical problems. These are called secondary results.**
- **Secondary results might change a person's medical care.**
- **You will begiven a choice to learn about any secondary results that are found.**
- **SouthSeq will not provide information about paternity or other family relationships.**

Types of Secondary Results in SouthSeq

Cancer Risk

For example:
Changes in the *MSH6* gene lead to a higher chance of colon and other cancers

Heart Risk

For example:
Changes in the *LMNA* gene lead to a higher chance of heart problem called cardiomyopathy

Other Health Risks

c2

For example:
Changes in the *RYR1* gene lead to a higher chance of bad reaction when exposed to some anesthesia medicines

Read more....

Secondary results

Genome sequencing is a test that looks at all of a person's genetic information. During genome sequencing, the lab might find a genetic change that is not related to your baby's medical problems, but may still impact the health of your child and your family. These types of results are called secondary results. Secondary results returned in SouthSeq are genetic changes that put a person at an increased risk of future disease. You can choose whether or not you would like to receive secondary results.

This kind of result may explain a known family history of a disease. In other cases, a secondary result may increase risk for a disease that is not in the family history. It's important to know that SouthSeq secondary results do not include every genetic future disease risk.

Knowing about secondary results can help lower future disease risk

If you know about an increased disease risk from a secondary result, there may be steps that can be taken to lower the risk for the disease. For example, finding an increased risk for cancer could lead to more cancer screening.

The SouthSeq study is only returning secondary results that are treatable or have ways to lower disease risk.

Example secondary result

A SouthSeq secondary result may find a genetic change in a baby that increases the risk for breast cancer. This increased risk would be important when the child is an adult. Genetic testing for the child's parents could tell if a parent also has the genetic change that increases risk for breast cancer. If a parent has the genetic change, they could talk to their doctors about their risk and possibly start breast cancer screenings early.

Family relationships

In some cases, genome sequencing may find unexpected information about family relationships. For example, genetic information may reveal that a child is not biologically related to his or her father or that the parents of a child are related to each other. This type of unexpected information **will not be reported as part of the SouthSeq study.**

Implications of Results

Key Points:

- **The most common result in SouthSeq will be a negative result.**

  A negative result does not rule out a genetic cause for your baby's medical problems.

- **A variant of unknown significance (VUS) result means a genetic change has been found, but we need more information before we can be certain it is the cause of your baby's medical problems.**

- **A positive result means a genetic change has been found that explains the reason for your baby's medical problems.**

- **In many cases, results do not change your baby's medical care.**

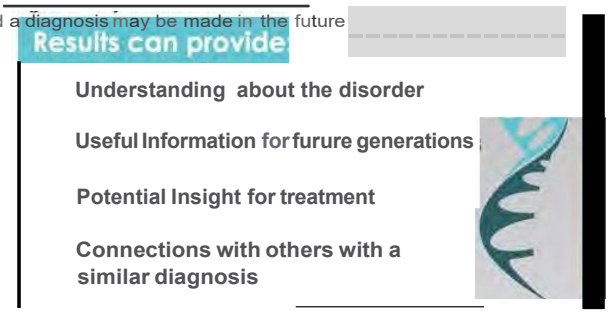
Read more....

Negative results

A negative result is the most common result. This means that genome sequencing looked at all of your baby's genetic information but did not find a reason for your baby's medical problems. This does not mean that your baby's symptoms are not genetic. There is no perfect test that can find and understand all genetic changes. Your baby's doctor may choose to do other types of tests to continue looking for a reason for symptoms. In the future, your doctor may also ask that scientists re-read your child's genome sequence. As scientific knowledge grows, the test results may be better understood and a diagnosis may be made in the future.

Variant of uncertain significance results

Sometimes, a genetic change is found that might be the cause of your baby's symptoms. This is called a variant of uncertain significance (VUS). More information is needed to find out if the change is actually the cause of the symptoms or a harmless genetic change. Because it is uncertain, this type of result should NOT be used to help doctors make decisions about medicines or other care for your baby.



Positive results

In some cases, genome sequencing will find a genetic change that explains the reason for your baby's symptoms and gives your family a diagnosis. This means that doctors can stop looking for why your baby has medical problems. Sometimes, it also allows family members to learn the chance that someone else in the family could have the same symptoms.

What happens if we find a diagnosis?

Sometimes, getting a genetic diagnosis for your baby can help their doctors better care for them. For example, it may tell doctors they should think about using a certain medicine or therapy to treat your baby's symptoms. The result may also help doctors decide to stop using medicines or therapies that are not working, or inform them about treatments that are unlikely to work. Some results may even tell doctors that they should be on the lookout for other problems your baby does not currently have. This hopefully keeps more problems from happening later.

In many cases getting a genetic diagnosis does not change how doctors treat a baby's symptoms. It is possible to receive a diagnosis for which there are no approved medications or therapies. However, families can sometimes use the result to connect with other families who have children with a similar diagnosis. This can help the families feel supported in caring for their child. It can also lead to the chance to be a part of more research, which may at some point help doctors learn how to better care for children with the same diagnosis.

Family Impact

Key Points:

- **It is important to think about what findings from SouthSeq could mean for your family.**
- **A primary result may provide other family members with a diagnosis.**
- **A primary result may tell you about the chance other children will have similar problems.**
- **A secondary result can give future disease risk information to close relatives.**

Read more....

Family members share DNA

The impact that genetic test results may have on family members is important to think about with genome sequencing. Your baby's genome sequencing will look at all of their genetic information called DNA. Genome sequencing is different from most other medical tests. It can give health information about both the patient and their family members related by blood. This is because people share their DNA with their family.

Primary result

Finding a diagnosis for one person may provide a diagnosis for other family members who have similar medical problems. Finding a genetic cause for your baby's medical problems may also tell you about the chance for future children to have the same condition.

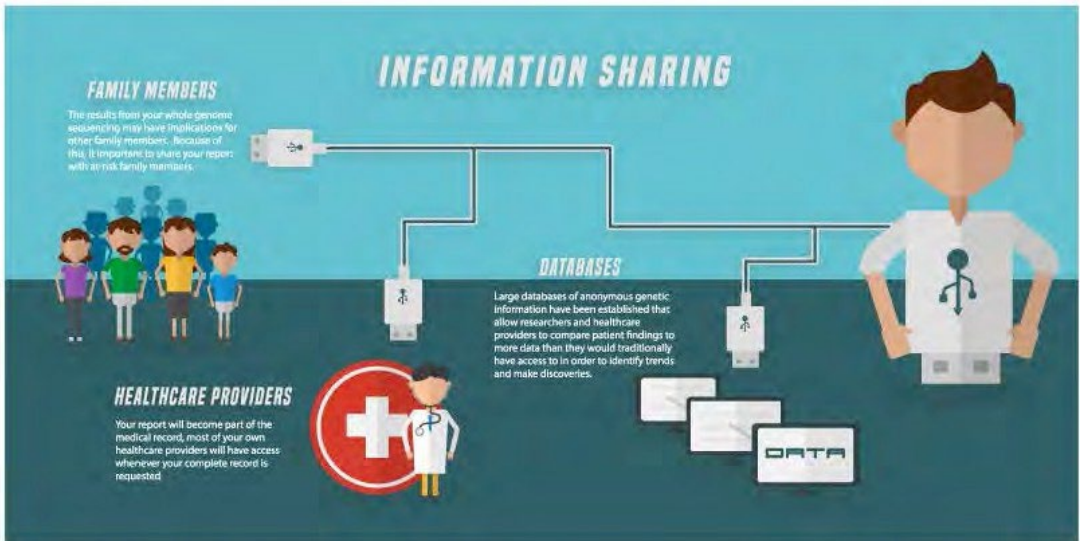
Secondary result

Secondary results can have important family impacts as well. For example, finding a strong genetic risk factor for certain types of cancer in a person means that some of their close relatives likely share the genetic change and also have an increased cancer risk. Learning some of these results can be emotionally charged for patients. This is especially true if the results impact both the health of the person being tested, as well as the health of their siblings, parents, and other family members.

Data Sharing

Key Points:

- You can choose how much information you want to share. Your choices have no impact on your results or medical care.
- The consent form andresults from this study will bein your child's medical record.
- Some of your child's genetic and medical information (but not name, address or other identifying information) will be shared with public genetic databases and published in scientific journals.
- You can share your child's fullgenome sequence with a private database for scientists called dbGAP.
- You can allow your child's genome sequence data and left over blood sample to be used in future research.



Read more....

Information sharing in the study

As part of this research study, some of your private information may be shared with different people and databases. Some of these are not required for you to take part in the study, and you can choose if you want to share you child's information.

Required information sharing

In medical records

Everyone who agrees to take part in this research study allows their signed consent form to be put into their child's medical record. This means that everyone who can see your child's medical chart will know your family agreed to take part in this study. This may include healthcare providers, as well as school systems, insurance companies, and anyone else that has access to your child's chart. Results you receive from the research study will also be put into their medical chart.

Databases andJournals

The information from genome sequencing may also be shared with others outside of this research study. Everyone who agrees to take part in this research study allows small parts of their unique genetic sequence to be shared to public databases and published in scientific journals. Along with these parts of genetic code, details such as your child's age and a list of their symptoms may also be shared. This is to help other doctors and researchers learn what this study finds out about genetic changes and how they play a role in illness. These small amounts of genetic information cannot be used to identify someone, so no one outside of the research study looking at these databases or journals will know that it was your family.

With the laboratory

In addition, everyone who agrees to take part in this research study allows their blood sample and the genetic information contained in their blood sample to be stored at the laboratory. These samples are used to help researchers better understand any results that come from this test. An example of this is using the genetic information stored at the laboratory to see if a genetic change in a child's blood is also present in their parent's blood.

Optional information sharing

Private database (dbGaP)

There are two more places where samples or genetic information can be shared, but neither of these are required in order to take part in this study. The first is a private database called dbGaP. If you agree to have information shared to dbGaP, your child's complete genome sequence and some information about their medical problems will be included. No names or dates of birth are included, and this is not a public database. The only people that can use this database are researchers who have applied for access and agreed to keep it private. A complete genome sequence is unique to a person just like a fingerprint, so there is a small chance this could someday be used to identify your child. If you are not comfortable with this, you can say "no" to dbGaP and still take part in the research study.

Additional research in the lab

The second place where your sample or information may be used is in the laboratory where the testing is done. As mentioned above, you are required to have your sample kept there to better understand the results of this test. However, researchers are also interested in using these blood samples to perform other types of genetic research on human disease. If you are not comfortable with your or your child's sample being used for any other research outside of this specific study, you can say "no" to sample storage and still take part in the research study.

Genetic Discrimination

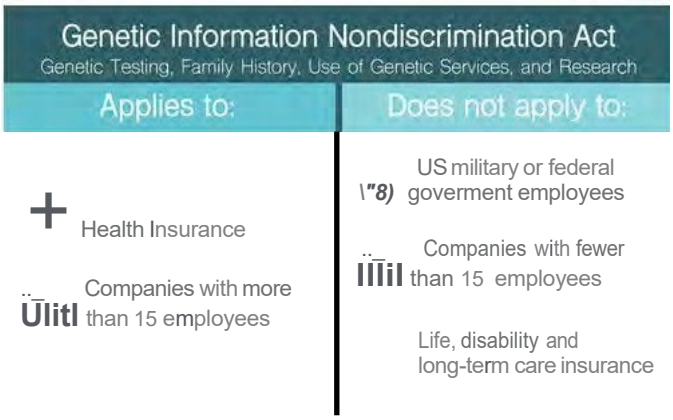
Key Points:

- **Some people are worried about how their genetic information could make it harder to get a job, insurance or other service.**
- **The Genetic Information Nondiscrimination Act (GINA) is a law preventing health insurances or jobs from using genetic information to make decisions.**
- **GINA does apply to members of the US military, small businesses, or life, disability, or long-term insurances.**

Read more...

Could someone use my or my child's genetic Information against them?

People who are thinking about genome sequencing may be worried about genetic discrimination, or how the genetic test results might be used against them in the future. You may be worried someone could use genetic information to make employment, insurance, or other services harder or impossible to get. **Genetic information** in this case means genetic test results, family health history, or the fact that a person has seen a genetics doctor or been a part of genetic research.



Federal law to prevent genetic discrimination

In 2008, the Genetic Information Nondiscrimination Act (GINA) was signed into law to reduce genetic discrimination. GINA makes it illegal for health insurance companies to decide if someone can have coverage or how much they pay for coverage based on genetic information. GINA also prevents insurance companies from requiring patients to have genetic testing or asking for the results. This act also keeps many companies from using genetic information against an employee to make hiring, firing, or promotion decisions.

What is not covered by the federal law

GINA does not apply in all cases. For example, companies with fewer than 15 employees do not have to follow GINA. GINA also does not apply to the US military or to federal government employees (however, these groups often have separate policies in place). Also, life, disability, and long-term care insurance policies are not protected by GINA. These companies could still use genetic information to make decisions about coverage.

For example:

The results of genome sequencing might show you or your child have an increased risk for cancer. A long-term care insurance company might ask about this result and make your coverage cost more because they think there's a higher chance you'll have to use the insurance. However, your job couldn't ask you about this result or fire you if they know you have an genetic test results that shows an increased risk for cancer.

Things to think about

You may want to think about possible results or who is able to see genome sequencing results. You can decide if you want secondary results that can tell about future disease risk. See Possible UnexP-ected Results for more information. You can decide where you want your child's information shared. See Data Access and Storagg for more information.

Should I get life, long-term care, or disability Insurance?

A person thinking about genetic testing may want to apply for life, long-term care, and disability insurance policies before genetic testing in case the results show an increased disease risk. In some cases, a genetic test result could actually show a person does not have a high chance to have the same disease that is in their family. In this case, the genetic test result could help the person applying for these insurance policies.

More questions?

If you have additional questions or concerns about the possibility of genetic discrimination, we encourage you to ask your healthcare provider or visit www.ginahelP-.org.

Learning assigned at time of result return:

Review of the Study

Key Points:

- **Your newborn had genome sequencing — a test that looked at all of their genetic information.**
- **SouthSeq's goal is to find out how genome sequencing in the NICU can help families.**
- **Results may include a genetic reason for your newborn's medical problems or other genetic information important for your family.**

Read more...

SouthSeq Study
You are enrolled in the SouthSeq study because your baby has medical problems that may have a **genetic** cause.

This study uses a new kind of genetic test, called **genome sequencing** that looks at your baby's entire genetic code.

Doing this test in a NICU may allow a diagnosis to be made earlier and may help your baby's doctors provide better care and treatments.

Goal
The goal of this study is to enroll about 1,500 newborns in the southeastern US. We want to learn if this test is helpful in a NICU and to understand the impact this impact has on patients and their families.

Results
Results from the genome sequencing test will be given back to you and your baby's doctors. Results may include:

1. If the test was able to find the reason for your baby's medical problems
2. Genetic changes that may be important for your family's medical care

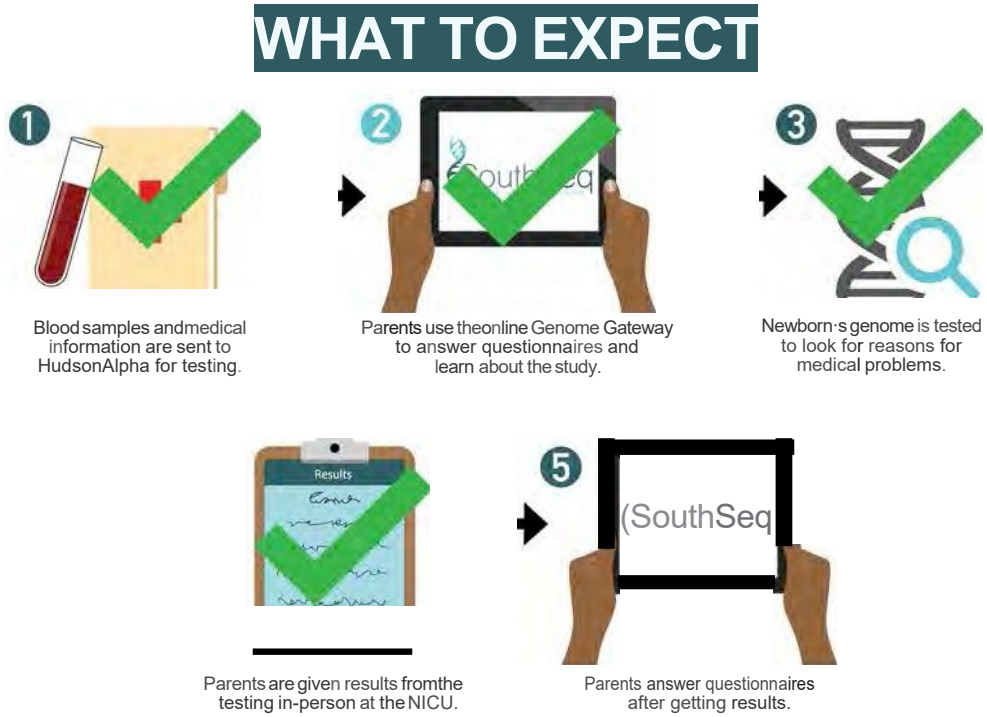
Genome Gateway
The learning topics here in Genome Gateway will give you more information about the study, possible results, and important things to consider.

Link to video: https://vimeo.com/287113637 (same as above in overview section)

What to Expect Next

Key Points:

- **You will be notified when your results are ready and a results appointment will be scheduled.**
- **New questionnaires and learning articles will be available to you after your results have been returned.**
- **You wlllbe actively enrolled In the trial for up to one year.**
- **We will continue to review your records for up to 8 years and update you with any new information If you give permission to be re-contacted.**



Read more...

Next steps to receive study results

By taking part in SouthSeq, a **genetic** test called **genome sequencing** was done for your baby. When results are ready, you will be notified and a time will be scheduled for you to discuss the results with a healthcare provider in the NICU. A healthcare provider will go over whether any genetic changes were found that are thought to be the cause of your baby's symptoms. The provider will also discuss any medical recommendations based on the test result and answer any questions that youmay have. You will be given a copy of the test results as well.

Questionnaires

When you first enrolled in SouthSeq you were asked to fill outseveral online questionnaires. There are additional questionnaires we will ask you to fill out now that results are ready and again in several months. Questionnaires help us learn more about how to return genome sequencing results. This may be helpful to other families in the future. These questionnaires will be filled out online in Genome Gateway. You will be sent an email and/or text message whenever there is a new survey to complete.

Questionnaires will be assigned:

- At return of results appointment
- 1 month after results
- 4 months after results
- 4 and a half months after results

Learning topics and files will be available in Genome Gateway

Educational topics, like this one, will continue to be available to you in Genome Gateway until the study closes. We encourage you to come back and review this information in the future as needed. You will also continue to have access to the shared files (including your consent form and test results) and messaging features within Genome Gateway.

Future contact

You may also be contacted by your child's healthcare team or study staff to answer follow-up questions. You will be actively involved in the study for up to one year. It is possible that new information will be discovered about your child's genome sequence, even after you have received results from the SouthSeq study. If you have given permission to be re-contacted, your child's healthcare team or study staff may contact you with updated information about your child's genetic test result.

The study team will continue to look at information in your child's medical record for up to eight years. This is to understand the impact of genome sequencing on your child's medical care. After eight years, the data will be kept for further research but personal identifiers like name and date of birth will be removed.

Withdrawing

It is important for you to know that you can leave the study and withdraw your consent to participate from the SouthSeq study at any time. To withdraw, please contact the study coordinator at the NICU location where your baby was enrolled. If you choose to withdraw from this study, your child's medical care will not be affected.

Positive Result

Key Points:

A positive primary result is a genetic change that likely caused your child's medical problem.

Many genetic conditions do not have a cure or specific treatment.

- A positive result may impact your or your child's future family planning.
- There may be support groups or specific organizations for your child's genetic condition.

Read more...

Primary results

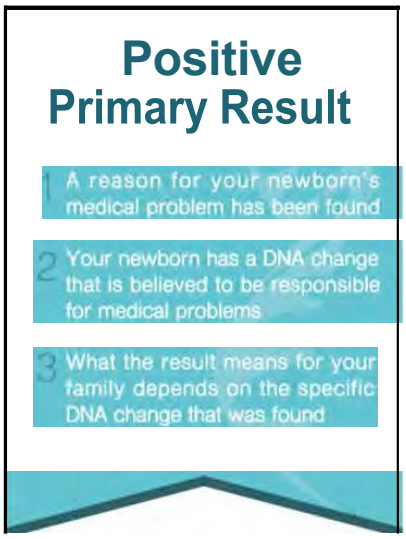
Primary results are those related to your newborn's **medical problems and the reason genome sequencing** testing was done.

Positive result

A positive primary result from a genome sequencing test means that a genetic change was found that is **likely the cause of your newborn's symptoms.**

How are positive results used?

A positive primary result may lead to changes in medical care. This information may help doctors **better care for your child. However, many genetic conditions do not have specific treatments or cures. Sometimes having a genetic diagnosis can provide a** better picture of what the condition might be like in **the future. Keep in mind that it is not possible to** know the exact symptoms that will occur and how severe they **will** be.



Family impacts

Receiving a positive result could have an impact on your or your family's future family planning. Some genetic changes are new in a one person and not found in other relatives. Some genetic changes are inherited and passed down through a family. Knowing whether the genetic change found in your child was new or passed down **can help your healthcare provider give you a more specific estimate of the chance that other family members,** such as future children, may have the same condition or symptoms.

Result letter

When you discuss your child's results from the SouthSeq study with the healthcare provider you will also receive a **copy of the test results and a letter explaining the results in detail. If you receive a positive result, the healthcare provider will go over the specific genetic change that was found and what it means for your child's medical care** and your family.

Finding support

For some families, receiving a positive result allows them to connect with specific support groups, resources and/or research studies specific for the genetic condition that their child has. Your result report will include information about currently available resources specific to your child's positive result. In addition, the following **resources for the larger, rare disease community may also be of interest to you:**

The National Organization for Rare Disorders (NORD)

Global Genes: Allies in Rare Disease

Alabama Rare

Mississippi Rare Action Network

Uncertain Result

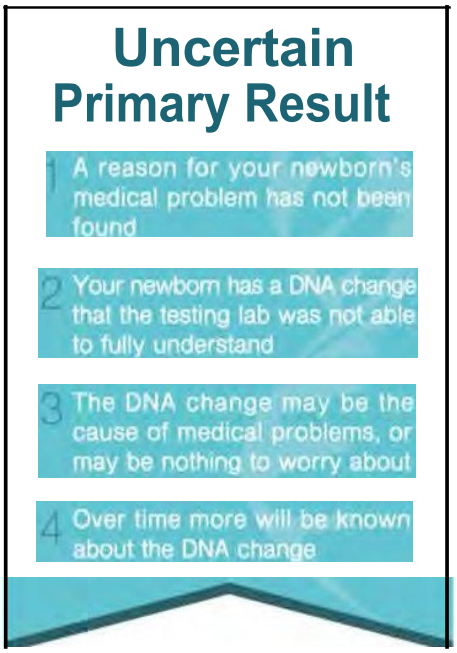
Key Points:

- **An uncertain primary result means we found a genetic change that might be the cause of your child's medical problem.**
- **There Is not enough Information about the genetic change. There might be more information In the future.**
- **You may be contacted by your healthcare provider or SouthSeq staff for result updates.**

Read more...

Primary results

Primaryresults are those related to your child's medical problems and the reason the g q!!..!mQ.Og_testing was done.



Uncertain result

An uncertain primary result means the study found a genetic change that is not well understood. There is not enough information available to decide if the change is actually the cause of symptoms or a harmless genetic change. This kind of result is called a variant of uncertain significance (¥U . It is important to figure out if this genetic change could cause symptoms. We all have millions of genetic changes and most of them are harmless.

How are uncertain results used?

Because it is uncertain, this type of result should not be viewed as *a* definite diagnosis. This result may not help doctors make decisions about medical care. Doctors might recommend more testing for your child or family members to get more information about the genetic change. Our hope is that over time more will be learned about the genetic change and experts will be able to decide whether it is the cause of symptoms. Our knowledge of genetics and disease is constantly improving.

Result Letter

When you discuss your child's results from the SouthSeq study you will receive a copy of the test results and a letter explaining the results in detail. If you receive an uncertain result, the healthcare provider will go over the specific genetic change that was found.

What if more information Is found?

During the SouthSeq study, the testing lab might learn more about the variant of uncertain significance. More information can help the lab decide whether it is the likely cause of symptoms. You may be contacted by your healthcare provider or study staff with new information about your test result. We encourage people who have an uncertain result to stay in touch with their healthcare and SouthSeq study team. They can help you find out if new information is available for your child's genetic change.

Negative Result

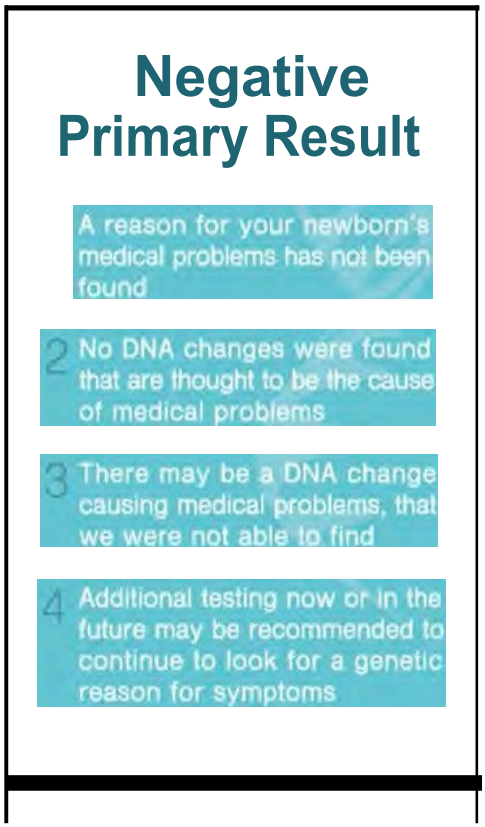
Key Points:

- **A negative primary result means we did not find a genetic change that caused your child'smedical problem.**
- **Your child'smedical problems could still have a genetic cause.**
- **It Is possible to find a genetic cause with a new genetic test or If the SouthSeq lab looks at your child's results again In the future.**

Read more...

Primary results

Prima!',)' results are those that are related to your child's medical problems and the reason that the genome sequencing testing was done.



Negative result

A negative primary result means no genetic changes were found that are thought to have caused your child's symptoms. It would be easy to think that this means the symptoms are not caused by a genetic disorder. However, this is not the case. There are many reasons that a person might receive a negative result.

Reasons for a Negative Result

It is possible that your child's symptoms were not caused by a single genetic change. Sometimes symptoms are caused by many genetic and environmental factors. These cases are very difficult to diagnose with the types of testing available today.

It is also possible that your child's symptoms were caused by a single genetic change that is not able to be found with current testing options. There are certain types of genetic changes that are very difficult to find. We may have found genetic changes in your child that are not fully understood. We might understand these changes better in the future with more research.

Future Testing

We will continue to learn more about how genetic changes cause symptoms and human disease. Sometimes, a person who had a negative result when they were first tested will later receive a genetic diagnosis. This could happen through a new genetic test that might be ordered, or by the laboratory taking another look at your child's genome sequence in the future. It is important for you to keep in touch with your child's healthcare providers to stay up to dateon testing options and new information.

Secondary Results

Key Points:

- **A secondary result is a genetic change not related to your newborn's medical problems.**
- **These results are associated with increased risk for other diseases in the future.**
- **Steps can be taken to prevent or reduce disease risk with these results.**
- **This genetic change was probably inherited from a parent who also has an increased disease risk.**

Read more...

A secondary result or finding is a genetic change that is not related to the reason for testing but may still be important to know about.

What kinds of secondary results does SouthSeq look for?

In addition to searching for a reason for your newborn's medical symptoms, the SouthSeq study also looks for changes in a small list of other genes. These genes are related to the possibility of developing other diseases in the future, like cancer or heart disease. The study only reports secondary results that have ways to prevent or reduce risk of disease. Knowing that someone has a risk to develop a certain disease in the future may mean that they need to see a certain kind of doctor or have special tests to check for symptoms.

What does it mean to receive a secondary result?

Receiving a secondary result means that a genetic change was found that is known to cause an increased risk of a particular disease in the future. Sometimes getting a secondary result can explain a person's family history of disease. Other times a secondary result is surprising, and found in a person who does not have any family history of the disease. Based on the specific result there may be medical changes recommended that lower risk or detect disease at an earlier stage. Many of these diseases happen in adulthood. This result will be important to know about as your child gets older.

Where did this genetic change come from?

While it is possible that a secondary result is a brand new genetic change in your child, it is more likely that it was passed down from a parent. If the study received blood samples from both parents' samples, we may be able to tell you which side of the family the secondary result came from. Knowing which side of the family the result came from can help parents know their disease risk. It is important to talk with your child's genetics team or with your own doctor about this finding and whether you and your relatives may need genetic testing as well.

Sharing Your Results

Key Points:

- **Your child's genetic results will be included in their medical record, and small parts of their genome sequence will be shared on public databases.**
- **You may have decided to share your child's genome sequence on a private database.**
- **You may have decided to let your child's sample be used for future research.**
- **You should think carefully about what other medical providers and family members you might like to share your child's results with.**

Read more...

By participating in SouthSeq, some of your child's private information may be shared with different people and databases. Some of these were required for all SouthSeq participants. Other types of sharing were optional. You get to decide what types of information you feel comfortable having shared and with whom.

Where was my data automatically shared?

Everyone who agreed to take part in SouthSeq had their signed consent form put into their child's medical record. The **genome se9uencing** results you received from the study will also be automatically put into your child's medical record. Everyone who agreed to take part in this research study also allowed small, unidentifiable parts of their child's unique genetic sequence to be shared to public databases and published in scientific journals. This information cannot be used to identify your child or your family.

What choices did I have for more data sharing?

When you consented to participate in the SouthSeq study you were given the option to share your child's **genetic** information with two other places. The first is a private database called **dbGaP** to which only researchers have access. The second is the laboratory where the genetic testing was done. If you forgot what choices you made for data sharing, they are marked on your consent form in the files section of Genome Gateway. For more information about the places that your child's data may be shared, review the section on Data Access.

Who should I share my study results with?

You might want to share your child's SouthSeq study results with other people. As you think about who else might need or want to see your child's results, it is important to remember that their genetic test results are private health information. Parents can choose how to use and share their child's results. There may be benefit to your child, yourself and others in knowing this information. There could also be risks and implications in having your child's information shared with others. For more information about these risks and implications, see the learning on Genetic Discrimination.

Sharing with Healthcare Providers

Participants may choose to share their child's results with other healthcare providers besides the study physician. The results you receive may impact multiple aspects of your child's medical care. It may be helpful for providers in multiple specialties to see the test results.

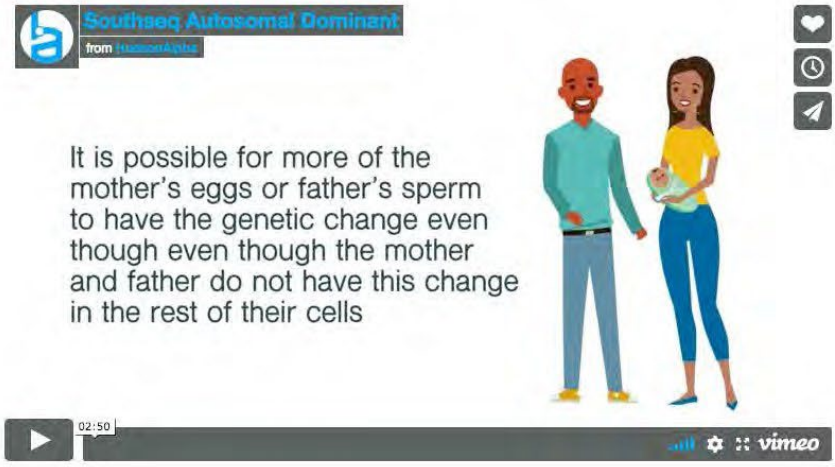
Sharing with Family Members

Results from agenome sequencing test may have implications for you and your family members. In some cases, a genetic test result may explain medical symptoms in family members. In other cases, a result mayshow that family members are at risk of developing a disease in the future or being a **carrier** for a genetic condition they could pass on to their children. There may be genetic tests that your relatives are interested in having themselves based on your family's test results. Your child's healthcare provider will go over any potential impacts on family **members during your result discussion.**

Dominant Inheritance

Key Points:

- **Gene comes in pairs. One gene comes from mom and one gene comes from dad.**
- **A dominant inheritance pattern is when a change in one of the genes is enough to cause a problem.**
- **A person with a dominant condition has a 1 in 2 chance of passing on the changed gene to a child.**
- **Not all people with the same gene change will have the same symptoms.**



Read more...

How dominant inheritance works

Dominant inheritance is one way that a genetic trait or condition can be **inherited** or passed down in a family. For most genes, each person has two copies. One gene copy is inherited from mom and the other is inherited from dad. A condition is inherited in a dominant pattern when a disease-causing (pathogenic) change in just one copy of a gene is enough to cause the condition. This happens even though the other copy of the gene is working.

How are dominant conditions inherited?

A person with a dominant condition has a **1 in 2 (50%)** chance to pass on the changed gene copy to a child. The child that gets this copy will have the condition. There is also a 1 in 2 (50%) chance that the parent with the condition will pass the typical copy of the gene to a child. The child that gets this typical copy will not have the condition. This 1 in 2 chance is like the chance you land on heads with the flip of a coin. There is the same 1 in 2 chance for every pregnancy. It does not matter how many children you already have with or without the condition.

Symptoms can look different even in the same family

It is important to keep in mind that two people with the same condition may not have the same exact symptoms. Even in the same family, people with the gene change may have no symptoms, mild symptoms, or severe symptoms. A mildly affected adult with a dominant condition may have a child with serious medical problems related to the condition. A person with more serious symptoms may also have children that have milder symptoms.

New genetic changes can happen

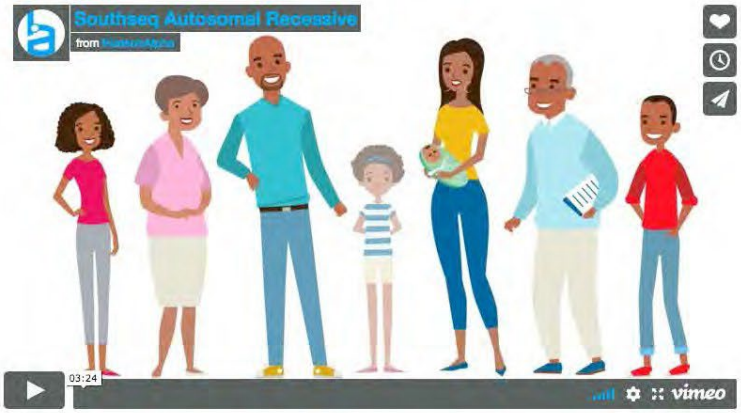
Sometimes a person is the first person in their family with a dominant condition. For these people, the change was present in either the egg or sperm from which they developed. This random change in a gene is called a new (also called de novo) genetic change. See the New Genetic Changes learning for more information.

Link to video: https://vimeo.com/293432650

Recessive Inheritance

Key Points:

- **Gene comes in pairs. One gene comes from mom and one gene comes from dad.**
- **A recessive inheritance pattern is when *both* copies of a gene have to be non-working to cause a problem.**
- **A carrier has one working and one non-working copy of a recessive gene.**
- **When carriers of the same condition have a child together, there's a 1 in 4 chance the child has the condition.**



Read more...

How recessive inheritance works

Recessive inheritance is one way that a genetic trait or condition can be **inherited** or passed down in a family. For most genes, everyone has two copies. One copy is inherited from mom, and one copy is inherited from dad. When a condition is recessive, both copies must have harmful changes to cause the condition.

Carriers of recessive conditions

A person with one working copy of the gene and one non-working copy with a disease-causing (pathogenic) change is considered a carrier of the condition. Carriers of a recessive condition usually do not have any symptoms. Most people don't know they are carriers of a recessive condition until they have genetic testing or a child with the condition.

How are recessive conditions inherited?

When both a mother and father are carriers of the same recessive condition, they have a chance of having a child with the disease. If both parents happen to pass on their non-working copy, the child will have symptoms of that condition.

When both parents are carriers of a recessive condition, three different outcomes are possible:

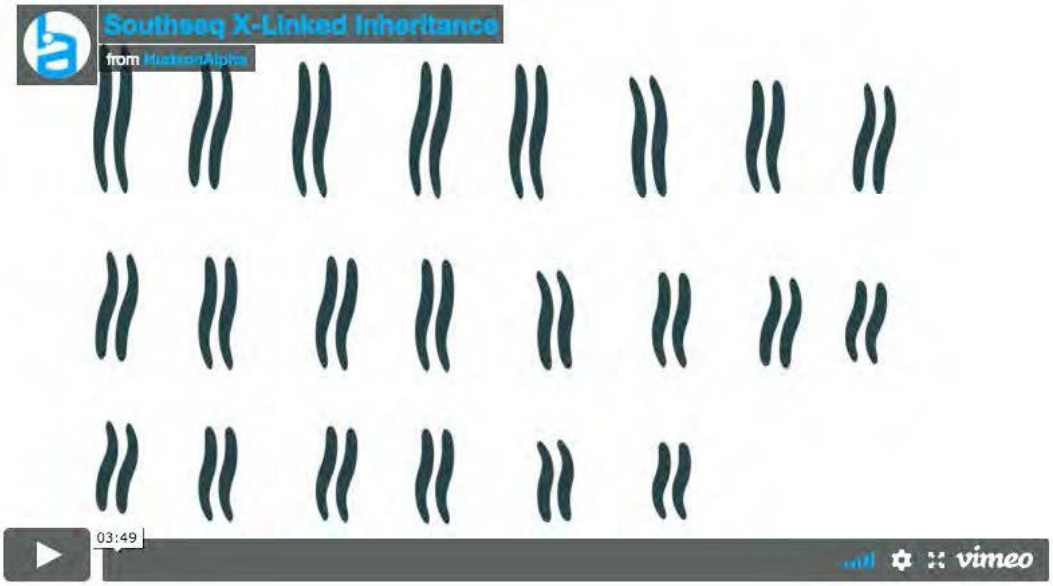
1. The child *is not affected* and *is not a carrier*. This occurs when the child inherits a working copy from each parent. Each child has a 1 in 4 chance (25%) of not being affected and not being a carrier. This child does not have to worry about having the condition or passing the condition on to future generations.
2. The child *is not affected* but *is a carrier*. This occurs when the child inherits one parent's working copy and the other parent's non-working copy. Each child has a 2 in 4 chance (50%) of being a carrier of the condition but not being affected. This child does not have to worry about having the disease, but may be concerned about passing their non- working copy on to their own children in the future.
3. The child *is affected* and *has symptoms* of the condition. This occurs when the child inherits a non-working copy from each parent. Each child has a 1 in 4 chance (25%) of having the condition. This child would pass on one of their non-working copies to their own children. The chance for their children to also be affected depends on if their partner is also a carrier.

Link to video: https://vimeo.com/292783767

X-linked Inheritance

Key Points:

- **Women usually have two X chromosomes and men usually have an X and a Y chromosome.**
- **Sometimes genetic changes are on the X chromosome, these are called X-linked conditions.**
- **Men with a disease-causing change on the X chromosome will have the condition.**
- **Women with only one disease-causing change on the X chromosome will usually not have the disease. They are carriers.**



Read more...

What is an X chromosome?

X-linked inheritance, also called sex-linked inheritance, is one way that a genetic trait or condition can be **inherited** or passed down in a family. Two of the 46 chromosomes found in each cell of the body are called the sex chromosomes. One of these is called the X chromosome and the other is called the Y chromosome. These chromosomes determine our sex. Women usually have two X chromosomes and men usually have an X and a Y. Women pass an X chromosome to each of their children. Men pass either the X or the Y chromosome which decides a child's sex.

Link to video: https://pod02857.catalyzeapps.com/learning/xlinked-inheritance

X-linked Genetic Conditions

A medical condition caused by a change in a gene on the X chromosome is called an X-linked condition.

Males have only one X chromosome. This means that a male has only one copy of each of the genes that are on the X chromosome. If he has a disease-causing change on his X chromosome, he will have the condition.

Females have two X chromosomes. This means that a female has two copies of each gene on the X chromosome. If one of her X chromosomes has a disease-causing change, she will usually not have the condition. This is because her other X chromosome contains a working copy of the gene. She would be a carrier for the condition. She can pass on the disease-causing change to her children.

How are X-linked Conditions Inherited?

When a **mother** is a carrier for an X-linked condition, four different outcomes are possible:

1. The child *is a boy* and *is affected* and has symptoms of the condition. This happens when a male child inherits the genetic change from his mother. Each son has a 1 in 2 chance (50%) of having the condition.

2. The child *is a boy* and *is not offected.* This happens when a male child inherits the working gene copy from his mother. Each son has a 1 in 2 chance (50%) of not being affected. This child does not have to worry about having the condition or passing the condition on to future generations.

3. The child *is a girl* and *is a carrier (but likely not affected).* This happens when a female child inherits the genetic change from her mother. Each daughter has a 1 in 2 chance (50%) of being a carrier.

4. The child *is a girl* and *is not a carrier (and is not affected).* This happens when a female child inherits the working copy of the gene from her mother. Each daughter has a 1 in 2 chance (50%) of not being a carrier. This child does not have to worry about having the condition or passing the condition on to future generations.

When a **father** has an X-linked condition, two outcomes are possible:

1. *All daughters will be carriers* of that condition. This happens because he has to pass on his X chromosome with the genetic change to his daughters.

2. *None of the sons will be affected.* This happens because he has to pass on his Y chromosome to his sons. These children don't have to worry about passing the condition on.

Can girls be affected with an X-linked condition?

Early in a female's development, one of her two X chromosomes is randomly and permanently "turned off" in each of her cells. This is a process called **X-Inactivation**. X-inactivation is random, so the X chromosome from the mother is active in some cells, and the X chromosome from the father is active in other cells.

Most females who are carriers of an X-linked condition do not have any symptoms of the condition. Some females do have X-linked condition symptoms. This is a result of uneven, or skewed, X-inactivation. Sometimes, the working copy of the gene will be "turned off" in so many cells that the female will have symptoms of the condition. The severity of her symptoms depends on the amount of cells where the working copy of the gene remains active.

New Genetic Change

Key Points:

- **De novo genetic changes aren't Inherited. They happen for the first time in a child.**
- **De novo genetic changes are new in the egg or sperm that made a child. These changes aren't found in a parent's blood.**
- **A person with a de novo condition can pass their genetic change to their children.**
- **The chance for a parent to have other children with the same change is less than 1 in 100.**

Read more...

What does de novo mean?

In some cases, **genetic** changes are not **inherited** or passed on from either parent but instead occur for the first time in a child. These new genetic changes are called **de novo**. The word de novo is a Latin word for "new."

How do new genetic changes happen?

De novo changes happen when an egg or sperm **cell** has a genetic change that the rest of the parent's cells do not. These new genetic changes occur due to random chance as egg and sperm cells are made. If a de novo change happens in a gene that causes a **dominant** disorder, the person will have that disease while the rest of the family will not. This is because in a dominant disease, having a single disease-causing change in one copy of the gene is enough for someone to have the disease. See Dominant Inheritance for more information.

How does a new genetic change affect risk in family members?

Even though a person with a de novo change did not inherit the change from a parent with the disease, they do have a chance to pass the change on to their children. Each child of a person with a de novo dominant genetic condition has a 50%, or 1 in 2, chance to have the same disease as their parent.

For parents of a child with a de novo dominant inherited condition, the chance to have another child with the same condition is very low. In rare cases, other eggs or sperm may have the same change as the child with symptoms, which would increase the risk for another affected child. We are not able to test all the cells in a parent's body to find out if other cells may carry the change. We usually say that the chance for a sibling of a child with a de novo dominant condition to be affected is less than 1%, or 1 in 100. This means that if you have more children, the chance for them to be born with the same condition as your child is less than 1 in 100.

Appendix 5: Study Flyer

DNA sequencing for newborn nurseries in the South

Consent Form Summary

(version 2/18/19)

General Information	You are being asked to take part in a research study. This research study is voluntary, meaning you do not have to take part in it. The procedures, risks, and benefits are fully described further in the consent form.
Purpose	The purpose of the study is to perform a genetic test (whole genome sequencing) on babies in the hospital who have symptoms that have not yet been diagnosed, but may be genetic. We will also be doing a clinical trial; some families will receive results from non-genetics providers and others will receive findings from genetic counselors.
Duration & Visits	If you agree to be in the study, you will be asked to complete 5 surveys and have 2 clinic visits (to enroll in the study and to get results).
Overview of Procedures	There will be one initial visit where we will collect a blood sample from your baby and from the child's biological parents who are willing to give blood samples. At this appointment you will also be asked to complete an enrollment survey. This initial visit will take approximately 1.5 hours. When your results are ready, a nurse will call you to schedule another appointment. At that appointment, someone will discuss your results with you and you will be asked to complete another survey. We will be audio recording the session, but the recordings will not be shared with anyone outside of the study team. This result visit will take approximately 1 hour. Three other surveys (at 1 month, 4 months, and 4.5 months after you have received your results) will be assigned to you online. You will receive an email when the survey is available for you to complete. For each survey that you complete, we will mail you a $25 check. If you do not have internet at home, just tell the nurse and you can use the study iPad in the clinic. There is a chance that someone from the research team might call you to ask if you would be interested in taking part in an interview. If you are interested, they will schedule a time to talk and you will be compensated for your time.
Risks	The most likely risks are temporary pain or bruising from the blood draw. Completing surveys may cause some individuals to become upset, frustrated or tired. Additionally, genetic testing can sometimes provide unexpected results which may cause some people to be anxious. If you have any questions about the testing performed for this study, please ask the nurse coordinator who provided you with this flyer.
Benefits	We hope that by sequencing your child's genome we will be able to determine the reason for their symptoms. We also hope to learn more about how to best deliver genetic information to families. The knowledge gained from your participation will be helpful to patients with rare disease and researchers in the future.
Alternatives	If you do not want to take part in the study, your alternative is to not participate.

SouthSeq

ALABAMA KENTUCKY LOUISIANA MISSISSIPPI

SouthSeq a NIH-funded':' research study looking at how a new kind of genetic test, called whole genome sequencing, can be used to try to find the reason for medical problems among newborns in a neonatal intensive care unit (NICU).

What to Expect

1. A small blood sample will be taken from the newborn and if possible from one or both of the biological parents.
2. Results from the test will take about 3-4 months to complete.
3. When results are ready, families will be notified and given a time to discuss the results with a healthcare provider.
4. Parents in this study will be asked to fill out several questionnaires online. If you do not have a computer or access to the Internet, we will help you fill out these questionnaires.
5. Parents may also be contacted by the newborn's healthcare team or study staff to ask follow-up questions.

Genes and the Genome

Genes are the sections of DNA that provides instructions for the human body to grow and work properly. A human genome contains about 22,000 genes. All of a person's DNA is called his or her genome.

Genetic Changes

All people have changes in their DNA. Genetic changes can range from very small to very large. Most genetic changes are not related to a medical problem. Some changes are harmful and cause disease. These are the types of changes we look for in this study.

If you have any additional questions about this study, please contact 205-934-5771.

hudsonalpha.org/ southseq

*The SouthSeq project (U01HG007301) is supported by the Clinical Sequencing Evidence-Generating Research (CSER) consortium which is funded by the National Human Genome Research Institute (NHGRI) with co-funding from the National Institute on Minority Health and Health Disparities (NIMHD) and the National Cancer Institute (NCI). More information about CSER can be found at https:/ /cser-consortium.org/.

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If you have any additional questions about this study, please call 601-815-5180 or visit **hudsonalpha.org/southseq.**

Principle Investigator: Renate Savich, MD

SouthSeq

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If you have any additional questions about this study, please call 225-924-8310 or visit **hudsonalpha.org/southseq.**

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SouthSeq

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SouthSeq a research study looking at how a new kind of genetic test, called whole genome sequencing, can be used to try to find the reason for medical problems among newborns in a neonatal intensive care unit (NICU).

The whole genome sequencing test looks at a person's entire genetic code. The test looks for a genetic change that may be the cause of a medical problem. We believe doing this test in a NICU can allow diagnoses to be made earlier and may help doctors provide better care and treatments.

To be included in the study, a newborn must have medical problems or unusual physical findings that may have a genetic cause. Results from the whole genome sequencing test will be given back to families and their doctors.

Results may include:

- The reason for the newborn's medical problems or unusual physical findings.
- Other genetic changes that may be important for the family's medical care.

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4. Parents in this study will be asked to fill out several questionnaires online. If you do not have a computer or access to the Internet, we will help you fill out these questionnaires.
5. Parents may also be contacted by the newborn's healthcare team or study staff to ask follow-up questions.

If you have any additional questions about this study, please call 504-251-2810 or visit hudsonalpha.org/southseq.

Site PI: Jessica Patrick-Esteve, MD

SouthSeq

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If you have any additional questions about this study, please call the KCPCRU at 502-629-5820, option 1. M-F 8:00-4:30

*The SouthSeq project (U01HG007301) is supported by the Clinical Sequencing Evidence-Generating Research (CSER) consortium which is funded by the National Human Genome Research Institute (NHGRI) with co-funding from the National Institute on Minority Health and Health Disparities (NIMHD) and the National Cancer Institute (NCI). More information about CSER can be found at https:/ /cser-consortium.org/.

Appendix 6: Provider Training Resources and Fact Sheets

SouthSeq Provider Live Training

Purpose: Equip healthcare providers with the knowledge and skills needed to be able to understand genome sequencing results and discuss results with patients and families in a NICU setting.

Background: A major goal of the SouthSeq study is to test a hypothesis that with adequate training and support, genome sequencing can be deployed in a NICU setting without the direct involvement of genetic specialists. Babies receiving genome sequencing will be randomized to either receive results from a genetic specialist (i.e. genetic counselor) or a NICU provider (i.e. neonatologist or neonatal nurse practitioner). Results will be discussed with the participant family in-person (ideally) or over the phone. Following result disclosure, the participant family will complete questionnaires to help the SouthSeq research team understand their experience and outcomes allowing us to test the stated hypothesis.

Description: Live training of participating SouthSeq healthcare providers will occur at each study site and will in total last approximately 4 hours. The study team will work with each NICU to determine the structure of the training to best meet provider's needs. The training may take place in one session or be broken up into multiple sessions over several days. The training will incorporate didactic learning, hands-on learning, and small group discussions to achieve the desired learning objectives. In addition to live training, materials from the training will be stored in the online Genome Gateway education platform for providers to review as needed throughout the study.

Learning Objectives:

1. Explain the benefits and limitations of genome sequencing and how it compares to other types of genetic tests
2. State the purpose of the SouthSeq study and the hypothesis being tested through result disclosure
3. Identify the role of the non-genetics NICU provider in the SouthSeq study
4. Demonstrate familiarity and proficiency completing provider tasks in the online Genome Gateway platform
5. Interpret a SouthSeq genome sequencing result letter and report
6. Develop a plan for disclosing various types of genome sequencing results (positive, negative, uncertain) including key points and next steps
7. Describe common questions among patients receiving genome sequencing results
8. Attend to psychosocial needs of families surrounding genome sequencing result disclosure
9. Identify and critique patient support resources relevant to genome sequencing results

SouthSeq Provider Live Training

Tentative Schedule (order and timing to be modified per site):

15 minutes	Meet and greet; Get refreshments	
15 minutes	Introductions; Overview of the SouthSeq study *Didactic*	Candice Finnila (Project Manager)
15 minutes	Logistics of return of results in SouthSeq *Didactic*	Kelly East (Genetic Counselor)
10 minutes	Q/A	Kelly East
15 minutes	Logistics of the trial *Didactic*	Liz Rahn (Clinical Trial Team)
45 minutes	Genome Gateway training *Hands-on*	Kelly East
15 minutes	Whole genome sequencing (WGS) *Didactic*	Meagan Cochran (Genetic Counselor)
60 minutes	Returning WGS results *Didactic; Hands-on; Small group discussion*	Overview: Kelly East Role Plays: All GCs
60 minutes	Psychosocial skills *Didactic; Simulation*	Whitley Kelley Veronica Greve (Genetic Counselors)
30 minutes	Wrap up; Q/A	Kelly East

Description of non-didactic portions of training:

- **Genome Gateway Training**: providers will use their own device (tablet, laptop) or a provided device to log into the Genome Gateway system. They will be led through a series of step by step instructions to learn how to 1) review patient information, 2) view files, 3) review educational materials, and 4) answer questionnaires.
- **Returning WGS results**: this session will begin with a brief didactic overview of what SouthSeq results look like. Next providers will be given 6 example reports to review. As they review these reports they will be asked to answer questions about each result on a written table. The goal of this activity is to become familiar with reports and know where to find information. Following this activity, attendees will break into smaller groups for a discussion facilitated by a genetic counselor. Genetic counselors will have a discussion guide to scaffold conversations, highlighting important take home messages and nuances of each example result.
- **Psychosocial skills**: this session will begin with a brief didactic presentation where genetic counselors will share their experiences giving genome results to patients and the possible range of psychosocial responses. We will also discuss strategies for assessing patient understanding and avoiding information overload when presenting genomic information. The final activity of the training includes a one-on-one simulation between each participating provider and a genetic counselor. The provider will be given the opportunity to practice describing an example result to the genetic counselor as well as responding to some typical (and not so typical) patient questions.

Returning Genome Sequence Results in SouthSeq

Provider Training Session

SouthSeq

Introductions

SouthSeq

During this training we will discuss:

- An overview of the SouthSeq study
- Logistics of returning SouthSeq results
- Logistics of the trial aspect of SouthSeq
- How to use the online Genome Gateway system
- What whole genome sequencing is, and what it is not
- How to prepare for and give back genome results
- Psychosocial considerations in genetics

SouthSeq

Overview of the SouthSeq Study

SouthSeq

Primary Goal/Hypothesis

- Early WGS offers best chance of genetic diagnosis in symptomatic newborns
- WGS can be efficiently and safely performed outside major academic medical centers
- WGS will ultimately reduce the costs of care for symptomatic newborns

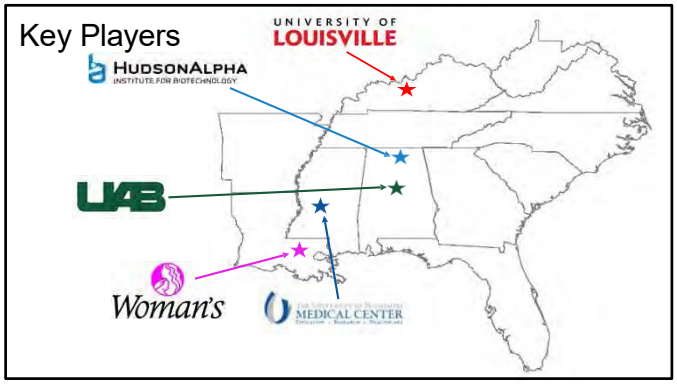
SouthSeq

Specific Aims

- Aim 1: Perform WGS on 1,500 infants in nurseries with symptoms that prompt a genetics referral
- Aim 2: Enable non-geneticist clinicians to return WGS results
- Aim 3: Conduct trial to compare return of WGS results by non-geneticist providers vs genetic counselors
- Aim 4: Conduct facilitated deliberative process with key stakeholders to develop guidelines for future implementation

SouthSeq

Key Players



Randomization

"Standard of Care" Arm	"Experimental" Arm
Informed Consent by Site Research Nurse	**Informed Consent by Site Research Nurse**
Genome Sequencing, Analysis; Results Generated at HudsonAlpha	*Genome Sequencing, Analysis; Results Generated at HudsonAlpha*
Results Returned by Site Genetic Counselor	**Results Returned by Site NICU Provider (YOU!)**

SouthSeq

Enrollment Criteria

When in doubt, enroll!

Inclusion

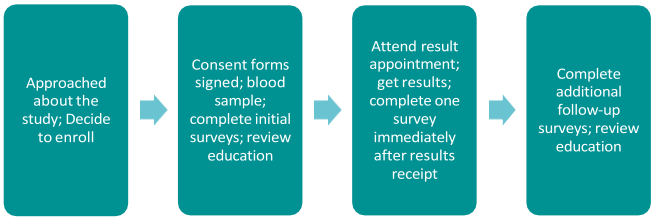
- 2 or more major congenital anomalies
- 1 major and 2 or more minor anomalies
- 1 major anomaly and an unexplained major medical condition that is not explained by prematurity
- 1 major anomaly and a first degree relative with the same major anomaly
- **OR, suspicion of a potential underlying genetic condition**

Exclusion

- Known or strong suspicion for a chromosomal aneuploidy (T13, T18, T21, Monosomy X)
- Disorders with established low genetic yield, e.g., gastroschisis, hydronephrosis, isolated congenital heart defects
- ~~confirmed teratogenic exposure~~
- confirmed congenital infection

SouthSeq

Patient experience



SouthSeq

Logistics of return of results

SouthSeq

Return of results is a process by which participant families, and the local clinical team, are notified about the findings of the genome sequencing test.

- Begins when a result report is ready
- Ends when the results have been documented in the medical record and communicated with the clinical team

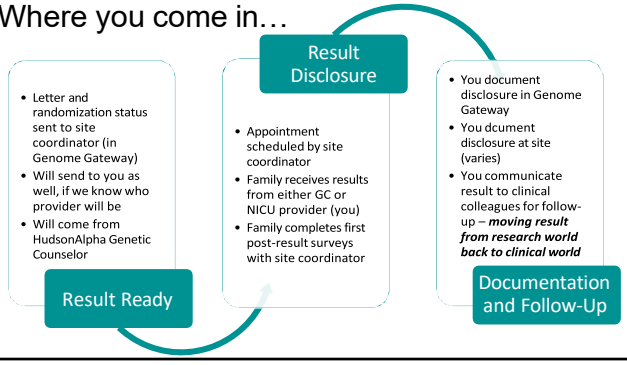
SouthSeq

From blood sample to result report

- Blood samples sent to HudsonAlpha for sequencing and analysis
- Any findings are confirmed in the lab by a second test
- Any findings are discussed at a Variant Review Committee (VRC) meeting
- HudsonAlpha genetic counselors translate decisions made at the VRC into patient-friendly result report letters

SouthSeq

Where you come in…



It doesn't end there…

- The lab at HudsonAlpha may learn new information about the results, and issue an updated report
  - Disclosed by the same provider who gave initial results
- The patient may experience new problems/symptoms that could be communicated to the lab
- The patient may have additional questions or concerns that need to be addressed

SouthSeq

The goal of this training is to equip you, the healthcare provider, with information, skills, and confidence to give genome sequencing results back to patients/families in the "experimental arm" of SouthSeq

SouthSeq

Safety Nets

- HudsonAlpha GCs here to be a "just-in-time" resource for you throughout the study
- Specific patient situations that will automatically trigger disclosure by control arm (site genetic counselor)
  - i.e. secondary findings
- Audio recording of result disclosures (all), monitoring and tracking of errors***

SouthSeq

****Not meant to be anxiety inducing.*

Result recording review

High-risk Safety Error

Errors in critical details that are likely to lead to patient harm

Ex. invasive testing recommended based on misinterpreted test result

Notify safety board; Real-time Feedback

Major Errors

Errors in critical details that are likely to have an impact on patient care and decision making

Ex. the recurrence risk is 25% (instead of <1%)

Real-time Feedback

Minor Errors

Errors in non-critical details that are unlikely to have an impact on patient care or decision making

Ex. this gene is on chromosome 6 (instead of 16)

End-of-study Feedback

SouthSeq

Logistics, and some edge cases

Baby has been discharged prior to results	Come back to NICU to receive results in person
Baby has passed away prior to results	Come back to NICU to receive results in person
Family moves or is unwilling to return to NICU for results	Scheduled phone disclosure by same provider who would have done in-person disclosure, rest of process stays same
Family is completely lost to follow-up	Letter sent to family notifying of available results, results put in medical record

SouthSeq

Questions?

Logistics of the trial

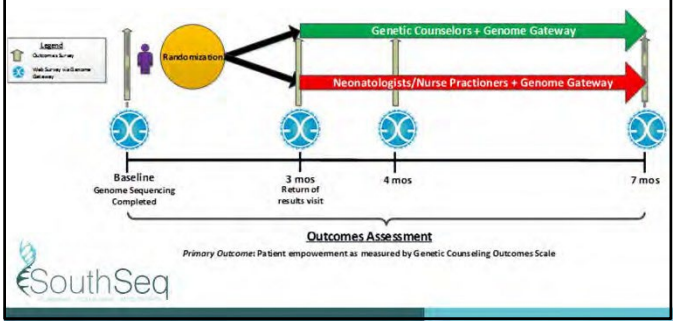
SouthSeq

Study Population and Timeline

- ~1,100 families will be enrolled into the clinical trial
- Start of clinical trial
  - Site-dependent based on provider training
  - Onboarding of new sites
- Trial planned to end 6 months into year 4 (Jan. 2021)

SouthSeq

SouthSeq - Workflow



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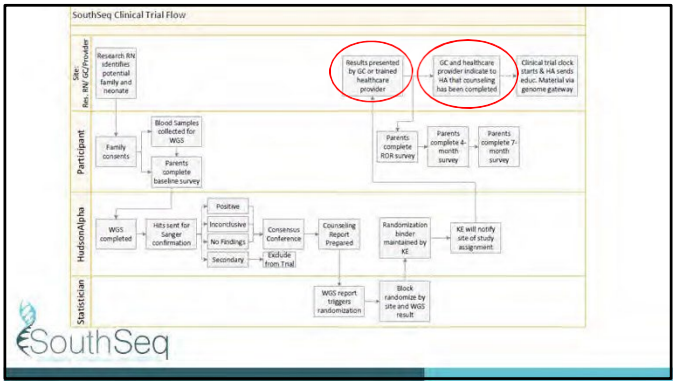


SouthSeq

Hypotheses

Primary Hypothesis: No clinically relevant difference in the **parental empowerment** between the two arms (trained healthcare provider vs. genetic counselor)

Secondary Hypothesis: Trained health care provider arm will be non-inferior to the genetic counselor arm in terms of **personal utility** and **uncertainty**

X = Y

SouthSeq

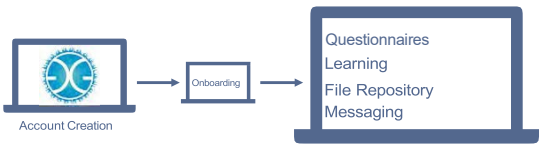
Take Away Messages

- The healthcare provider delivering results should not be the babies' current NICU attending MD/NP
  - The purpose of return of results does not include care/management of the condition (can discuss likely care changes/guidelines but not trigger that care during disclosure)
- Documentation by the healthcare provider to study staff about the disclosure session is critical to the fidelity of the trial
  - How disclosure was done
  - Who attended (which specific parents/caregivers)

SouthSeq

Genome Gateway

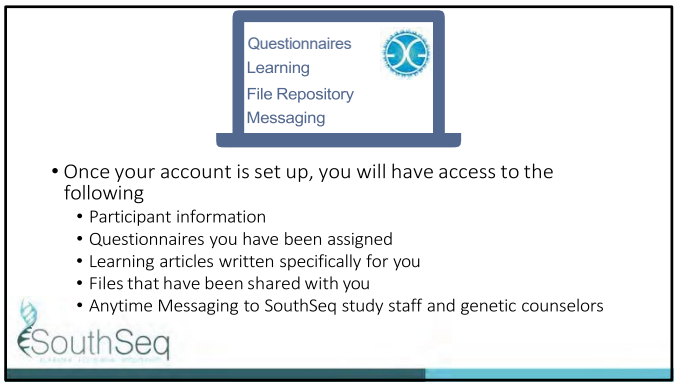
SouthSeq



- A provider account has been created for you. This initiated an email to you with a link to finish the setup of your account.
- You will be asked some basic demographic questions and create a unique password for your Genome Gateway account

  (passwords must be at least 8 characters, contain upper and lower case letters, at least one number and one special character)

SouthSeq



- Once your account is set up, you will have access to the following
  - Participant information
  - Questionnaires you have been assigned
  - Learning articles written specifically for you
  - Files that have been shared with you
  - Anytime Messaging to SouthSeq study staff and genetic counselors

SouthSeq

Log In

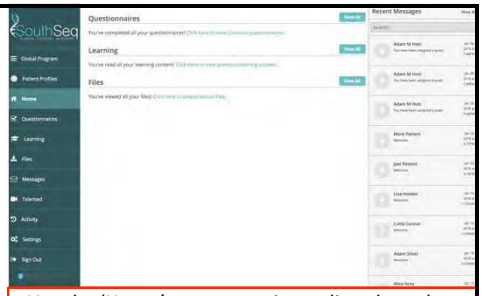
Bookmark this URL!

participants.southseq.org

- Once initial setup is completed, use your email address and the unique password for your Genome Gateway account

SouthSeq

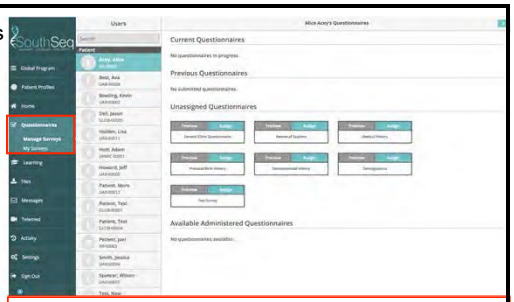
Navigating



- Use the 'Home' page to navigate directly to the most relevant areas easily

SouthSeq

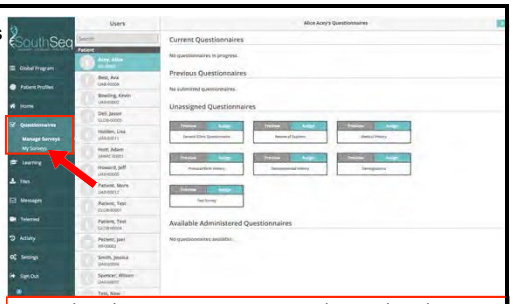
Questionnaires



- Navigate to 'Questionnaires' from the homepage

SouthSeq

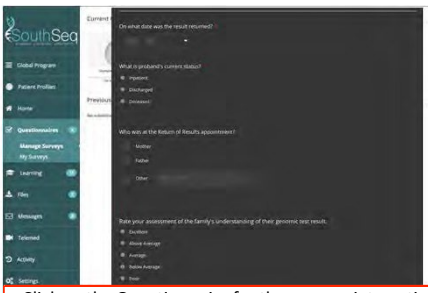
Questionnaires



- Complete the Questionnaires assigned to you by selecting 'My Surveys'

Questionnaires

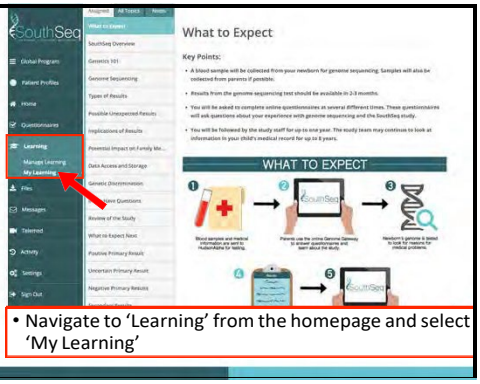
- Questions with a red Asterix are required
- Please click 'Submit' when finished



- Click on the Questionnaire for the appropriate patient to complete it. Note the patient ID is listed with each questionnaire

Learning

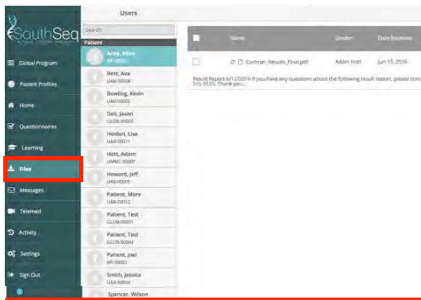
- A predetermined set of learning articles will be assigned to you
- You are able to see all learning topics (including participant topics) by clicking the "All Topics" tab at the top of the list.



- Navigate to 'Learning' from the homepage and select 'My Learning'

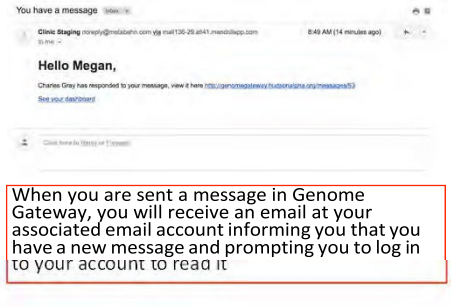
Files

- Files can be viewed in the internet browser or downloaded to your computer by clicking on the file name



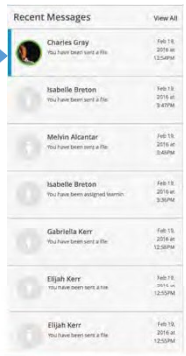
- Navigate to 'Files' from the homepage and select the appropriate patient from the list of users

Messages



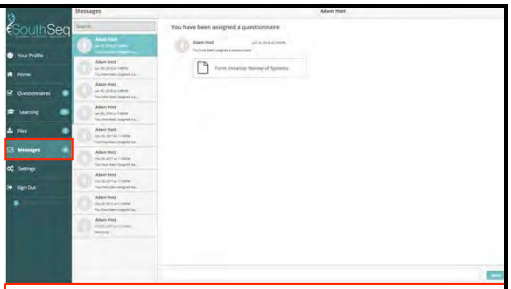
When you are sent a message in Genome Gateway, you will receive an email at your associated email account informing you that you have a new message and prompting you to log in to your account to read it

Messages



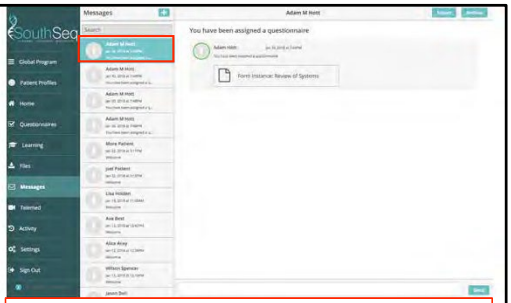
The most recent message threads are on the right side of the 'Home' screen. New messages will have a blue bar on the left side. Click on a message thread to open.

Messages



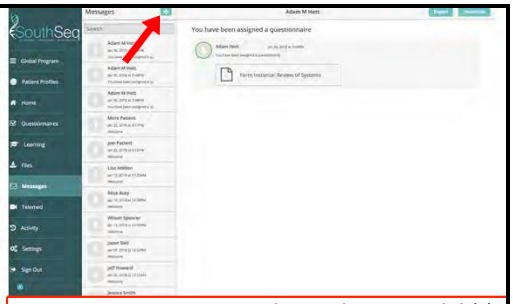
To access all messages, navigate to 'Messages' from the homepage

Messages



- Click on message to open the thread of messages

Messages



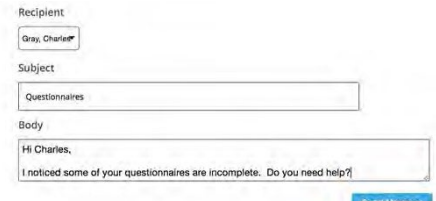
To start a new conversation with a SouthSeq user, click '+'

Messages

Use drop-down menu to select recipient; you will be able to message SouthSeq study staff or patients.

Please do not message patients directly.

Messages



Add a subject for the message and text in the body, then click 'send message' to start a conversation

Genome Gateway Technical Support

- Technical support can be obtained by contacting SouthSeq study staff
  - Susan Hiatt (shiatt@hudsonalpha.org)
  - Candice Finnila (cfinnila@hudsonalpha.org)
  - Adam Hott (ahott@hudsonalpha.org)

Whole Genome Sequencing

SouthSeq

In this section we will:

- Review the technology and possible results of whole genome sequencing (WGS)
- Discuss how WGS differs from other available genetic tests
- Review limitations and important considerations to keep in mind when discussing WGS with patients

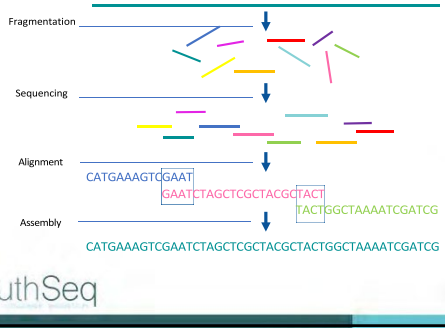
SouthSeq

WGS sequencing pipeline

1. Isolate DNA from participant sample(s)
2. Sequence genome of proband
3. Identify and align sequence fragments
4. Detect variants
5. Determine clinical relevance
6. Perform Sanger confirmation of variants
7. Report results to healthcare team

SouthSeq

WGS…inside the box

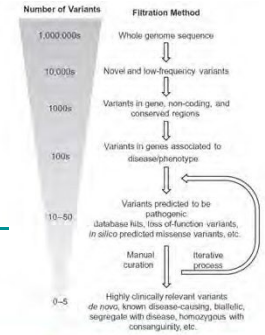


SouthSeq

Variant filtration

computer programs

people



SouthSeq

Classifying variants

- make up vast majority of variation found
- typically don't even get reported

- conflicting or absent evidence about disease association
- treat as innocent until proven guilty

- strong evidence about disease association
- should alter medical management based on result if indicated

SouthSeq

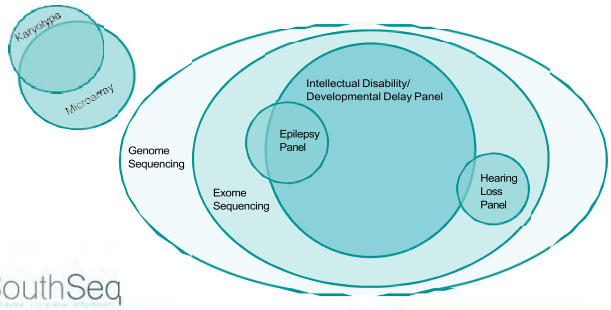
WGS vs other genetic tests

Karyotype and Microarray	Single-Gene and Panel Testing	Whole Genome Sequencing
Helpful in detecting large-scale chromosomal changes and gains/losses of genetic information	Uses Sanger or NextGen sequencing to thoroughly interrogate a list of genes of interest for single nucleotide variation	Massively parallel sequencing allows investigation of a person's entire** genetic code with "future-proof" data output
Best as a first-line test or when a specific diagnosis is highly likely (ex: Trisomy 21)	Best when the gene list is small and the diagnostic suspicion is high	Best when the phenotype is nonspecific or the gene list is large
Low resolution – a normal result does not rule out much	Limited possibility for reanalysis	Higher likelihood of VUS/GUS and secondary findings

SouthSeq

**in actuality there are some limitations in coverage

WGS vs other genetic tests



SouthSeq

Limitations of WGS

Technical limitations:

- Lower depth of coverage overall
- Does not reliably detect certain kinds of genetic changes (CNVs, repeats, pseudogenes)

Analytical limitations:

- High likelihood of variants of uncertain significance
- Many genes not currently associated with a specific disease or phenotype

Logistical limitations:

- Labor-intensive → results in higher costs and longer turnaround times
- Massive amounts of data

SouthSeq

Words of caution

- Not all variants are harmful
- Disease-causing variants are not blinking lights
- Increased detection = increased uncertainty
- A negative result does NOT mean "not genetic"

SouthSeq

Questions?

SouthSeq

Returning Genome Sequencing Results

SouthSeq

In this section we will:

- Review the format and contents of SouthSeq result reports
- Discuss how to use result reports to prepare for the result disclosure conversation
- Practice preparation for result disclosure using a series of example case reports

  → *through individual hands-on work time and small group discussion*

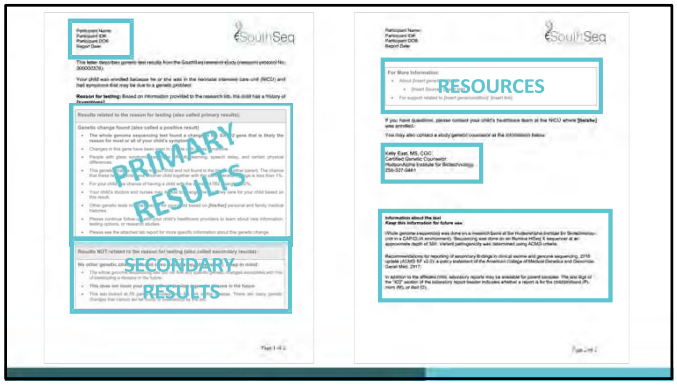
SouthSeq

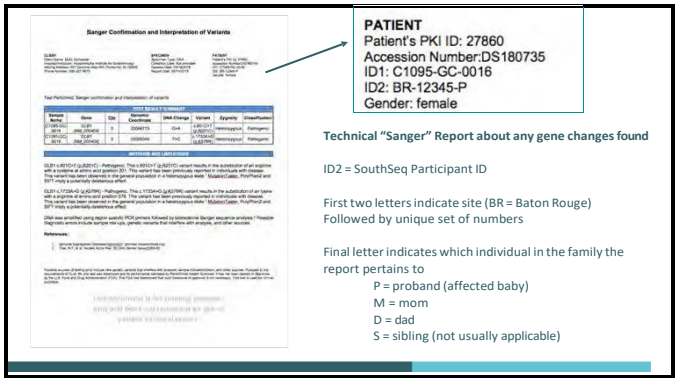
Contents and structure of SouthSeq result reports

All SouthSeq participants will receive a letter from HudsonAlpha summarizing their results.

If a genetic variant is being returned, a technical "Sanger" lab report will accompany the letter.

SouthSeq





What you will not find in the result report

- Confirmation of paternity or non-paternity
  not reported by the study
- Consanguinity (parental relatedness)
  not reported by the study
- Secondary findings
  would automatically put the case in the control arm (for return by GC)

SouthSeq

The result report/letter is your guide

Key talking points and take home messages

Resources to share with participant/family

Written in patient-friendly language

SouthSeq

If you have questions…

Your HudsonAlpha GC:

[Birmingham: Meagan Cochran; Jackson: Whitley Kelley; Baton Rouge: Veronica Greve]

Genome Gateway messaging best and most secure communication method (can discuss PHI/clinical details).

SouthSeq

Let's Practice…

- 6 example result reports, cover a wide range of possible results and implications
- Read result report as if you are preparing to disclose it to a family
  - Think about key messages, likely questions, if there is other information you want or need to gather prior to patient interaction
  - Highlight words/topics you want clarification on
  - Fill out chart
- Next will break up into small groups for in-depth discussion about the results with a genetic counselor

SouthSeq

Psychosocial considerations in the context of genetics

Veach, P., LeRoy, B., & Callanan, N. (2018). *Facilitating the Genetic Counseling Process Practice-Based Skills* (2nd ed. 2018.. ed.). Cham: Springer International Publishing : Imprint: Springer.

Delivering Genomic Results

- Are genomic result disclosures different from other patient interactions? How?

Kaphingst, K. A., Ivanovich, J., Elrick, A., Dresser, R., Matsen, C., & Goodman, M. S. (2016). How, who, and when: preferences for delivery of genome sequencing results among women diagnosed with breast cancer at a young age. *Molecular genetics & genomic medicine*, *4*(6), 684-695.

Delivering Genomic Results

- Understanding the familial context of the result makes information more meaningful
- Counseling the family, not the result

Delivering Genomic Results

- Avoid information overload
  - Proceed slowly and divide up information
- Try to use terminology participants understand

Delivering Genomic Results

- What if participants don't want to hear part or all of results?
  - Inheritance
  - Recurrence risks
  - Prognosis
  - Medical management recommendations

Assessing Patient Understanding - Questions

- Questions are helpful to clarify patient meaning and check your assumptions
- Avoid over-questioning and interrogating patients
- Open-ended questions are helpful for assessment
- Try to avoid close ended questions

Assessing Patient Understanding - Information

- Start from relevant basics
- After concepts, pause to assess
  - "What's your understanding of what we've just discussed?"
- Look for nonverbal cues
- Emotional reactions may impede information understanding

Assessing Patient Understanding – Emotional Reaction

- Anger
- Grief
- Guilt
- Shame
- Relief

Krabbenborg, L., Vissers, L. E. L. M., Schieving, J., Kleefstra, T., Kamsteeg, E. J., Veltman, J. A., ... & Van der Burg, S. (2016). Understanding the psychosocial effects of WES test results on parents of children with rare diseases. *Journal of genetic counseling*, *25*(6), 1207-1214.

Assessing Patient Understanding - Emotional Reaction

- Positive coping strategies:
  - Seek social support
  - Plan
  - Positive reappraisal
- Negative coping strategies:
  - Confrontative
  - Distancing
  - Self-controlling
  - Self-denigrating
  - Escape-avoidance

SouthSeq

Assessing Patient Understanding - Misconceptions

- Participants may have underlying misconceptions about genetics and disease
- Numerical risk information may be difficult for participants to understand
- Consider whether you are challenging a family's misconception or cultural perspective

SouthSeq

Let's Practice

- Case assignment
- Review the case and list on your result return sheet:
  - Three key points you want to convey to the participants
  - Three key points you think participants want to know

SouthSeq

Simulation

- 15 minutes for case simulations
- Deliver these results as if the genetic counselor is an actual participant
- Feel free to use the resources and information identified in the previous activities

SouthSeq

Role-play Wrap-up

Did you feel adequately prepared?

What happened that was expected? Unexpected?

What opportunities were missed?

What additional information or resources would you have liked to have had?

SouthSeq

Case F

Singleton with UNC13A *VUS (no associated syndrome)*

Connecting with other families

"Do you know other people that have this?"

Utility

*"Why did you give me this result if there is no way to help him? I don't care **why** it happened."*

Overinterpretation

"If a mutation was found, it must be bad."

SouthSeq

Case B

Mother-proband duo with likely pathogenic HDAC8 *variant (Cornelia de Lange syndrome)*

Assumption of inheritance

"If it didn't come from me, it came from her dad, and he's fine, so my child will be fine too."

Blame

"This must be her dad's fault."

SouthSeq

Case B

Mother-proband duo with likely pathogenic HDAC8 *variant (Cornelia de Lange syndrome)*

Misunderstanding of natural history of condition

"I know this came from her dad's side because his mother has heart problems."

Discussion of intellectual disability during neonatal period

"Will my child be able to live independently as an adult?"

SouthSeq

Case C

Trio, proband with GLB1 *compound heterozygous variants inherited from parents (GM1 gangliosidosis)*

Misunderstanding of inheritance

"No one in our family has anything like this. The test must be wrong."

Seeking solutions

"Is there anyone who can help her? We will try anything."

Religious/cultural beliefs + potential denial

"God will heal my baby."

SouthSeq

Case E

Trio, proband with NF1 *likely pathogenic variant inherited from mother (neurofibromatosis type 1)*

Guilt

"This is my fault."

"Why are his symptoms so much worse than mine? Did I do something to make them worse?"

Misunderstanding of variable expressivity

"You're saying I have this too, but I'm not sick. The test must be wrong."

SouthSeq

Case D

Trio, proband with de novo *likely pathogenic* CDKN1C *variant (Beckwith-Wiedemann syndrome)*

Misunderstanding of natural history and purpose of surveillance guidelines

"Will doing the tests you're talking about cure her?"

Misunderstanding of inheritance

"Does this mean he is not/I am not the father?"

Guilt/blame, misunderstanding of de novo *variants*

"This is because of the chemicals on the farm I grew up on."

SouthSeq

Case A

Negative result

Misunderstanding of limitations

"So this isn't genetic?"

"Now I can tell my sister this isn't something her kids can get."

Guilt, personal narrative

"I knew nothing was going to come back, because I drank a glass of wine when I was 10 weeks pregnant and that's what caused this."

SouthSeq

Example of Complex Result

Child born with multiple congenital anomalies and hearing loss

Result: maternally inherited pathogenic PALB2 *variant*

PALB2*: tumor suppressor; homozygous or compound heterozygous variation causes Fanconi anemia*

- *Heterozygous variation causes increased breast and pancreatic cancer risk*

SouthSeq

Example of Complex Result

Primary result with secondary implications

Unable to identify "second hit" in PALB2

- *Uncertain diagnostic result*

Discussing increased adulthood cancer risk for an infant

Disclosing increased risk of cancer to a parent for whom this should have immediate medical management implications

SouthSeq

Resource-finding

Take 2-3 minutes to Google your case's result (including Google images)

- *What do you find?*
- *What, if anything, would be helpful for families?*
- *What, if anything, would you rather families NOT see immediately after receiving their result?*

SouthSeq

Resource-finding

SouthSeq

Recap of your role: for each result you disclose

1. Review letter/report, prepare
2. Return the results to the family
3. Complete survey in Genome Gateway
3. Transition result knowledge to clinical team

SouthSeq

Wrap Up
Questions?
Next Steps

SouthSeq

Pre-Training Survey

1. What is your primary role as a healthcare provider?
   - ☐ Physician (MD/DO)
   - ☐ Nurse practitioner (APRN/MSN/DNP)
   - ☐ Physician's Assistant (PA-C)
   - ☐ Genetic counselor
   - ☐ Other _____

2. What is your specialty? (select all that apply)
   - ☐ General Internal Medicine
   - ☐ Internal Medicine Subspecialty _____
   - ☐ General Pediatrics
   - ☐ Pediatrics Subspecialty _____
   - ☐ Family practice
   - ☐ General Med/Peds
   - ☐ Med/Peds Subspecialty _____
   - ☐ Neurology
   - ☐ Ob/Gyn
   - ☐ General Surgery
   - ☐ Surgery Subspecialty _____
   - ☐ Psychiatry
   - ☐ Hem/Onc
   - ☐ Medical Genetics
   - ☐ Other _____

3. Have you received any of the following formal genetics education (not including college or professional degree)? (select all that apply)
   - ☐ Genetics residency or fellowship
   - ☐ Genetics education course/CME (online or in person)
   - ☐ Residency rotation in genetics
   - ☐ Graduate degree (in addition to your professional degree) focused on genetics
   - ☐ Other
   - ☐ I have had no formal genetics training.

4. How many years have you been in practice (since residency/training ended)?
   - ☐ 0-5 years
   - ☐ 6–10 years
   - ☐ 11–15 years
   - ☐ 16–20 years
   - ☐ 21–25 years
   - ☐ >25 years

5. Please pick the category that best describes your race/ethnicity: (select all that apply)

- ☐ American Indian or Alaska Native
- ☐ Asian
- ☐ Black or African American
- ☐ Hispanic or Latino
- ☐ Native Hawaiian or Other Pacific Islander
- ☐ White

6. Have often, on average, are you involved in ordering genetic testing (karyotype, microarray, gene sequencing, exome/genome sequencing) for a patient as part of your clinical practice? Pick the answer that best describes your experience.
   - ☐ Every day
   - ☐ Once per week
   - ☐ Once per month
   - ☐ Once per year
   - ☐ I have never ordered a genetic test

7. Which of the following types of genetic test results have you ordered for a patient as part of your clinical practice? (select all that apply)
   - ☐ Karyotype
   - ☐ Microarray
   - ☐ Single gene test or small panel test (<10 genes)
   - ☐ Large gene panel test (>10 genes)
   - ☐ Mitochondrial DNA testing
   - ☐ Exome sequencing
   - ☐ Genome sequencing
   - ☐ Other _____
   - ☐ I have never ordered a genetic test

8. How confident do you feel in your ability to read and interpret genetic test results?
   - ☐ Not at all confident
   - ☐ A little confident
   - ☐ Somewhat confident
   - ☐ Very confident

9. Have you ever seen a whole genome sequencing result report for a patient as part of your clinical practice?
   - ☐ Yes
   - ☐ No
   - ☐ Unsure

10. How confident do you feel in your ability to read and interpret a whole genome sequencing test result?
    - ☐ Not at all confident
    - ☐ A little confident

- ☐ Somewhat confident
- ☐ Very confident

11. How confident do you feel in your ability to explain a whole genome sequencing test result to a patient/family?
    - ☐ Not at all confident
    - ☐ A little confident
    - ☐ Somewhat confident
    - ☐ Very confident

12. How confident do you feel in your ability to manage a patient's care based on a whole genome sequencing result?
    - ☐ Not at all confident
    - ☐ A little confident
    - ☐ Somewhat confident
    - ☐ Very confident

13. Which of the following do you feel are significant barriers to the implementation of whole genome sequencing in routine NICU clinical care? (select all that apply)
    - ☐ Test cost
    - ☐ Lack of insurance coverage
    - ☐ Limited diagnostic value
    - ☐ Possibility of unexpected results
    - ☐ Possibility of uncertain results
    - ☐ Limited healthcare provider time
    - ☐ Lack of healthcare provider knowledge/training
    - ☐ Lack of patient understanding
    - ☐ Turn around time
    - ☐ Other _____
    - ☐ There are no barriers

Post-Training Survey

1. To what extent do you feel this training has increased your understanding of genomics and the role it can play in making a diagnosis?
   - ☐ Not at all
   - ☐ A little
   - ☐ Somewhat
   - ☐ Very

2. To what extent do you feel that this training has equipped you with the knowledge and skills needed to implement your role in the SouthSeq study?
   - ☐ Not at all
   - ☐ A little
   - ☐ Somewhat
   - ☐ Very

3. How confident do you feel in your ability to read and interpret a whole genome sequencing test result?
   - ☐ Not at all confident
   - ☐ A little confident
   - ☐ Somewhat confident
   - ☐ Very confident

4. How confident do you feel in your ability to explain a whole genome sequencing test result to a patient/family?
   - ☐ Not at all confident
   - ☐ A little confident
   - ☐ Somewhat confident
   - ☐ Very confident

5. How confident do you feel in your ability to manage a patient's care based on a whole genome sequencing result?
   - ☐ Not at all confident
   - ☐ A little confident
   - ☐ Somewhat confident
   - ☐ Very confident

6. What aspect of training was most valuable to you? _____

7. What aspect of training was least valuable to you? _____

8. Are there any topics that you wished had been covered, or covered more deeply? If so, what are they? _____

9. Do you feel that the format and structure of this training was appropriate for the topics (length, inclusion of discussion, hands-on, and simulation)?

   _____

10. How often do you expect to refer to the online version of training materials in the future?
    - ☐ Not at all
    - ☐ Rarely
    - ☐ Sometimes
    - ☐ Very often

11. Is there any other feedback you would like to provide about the training? _____

    _____

Appendix 7: Survey Measures by Time Point

Appendix 7.1

Enrollment Survey

1. ***Please identify the individual completing this survey.**
   - ☐ Mother
   - ☐ Father
   - ☐ Other (please specify): _____

2. ***What is your age?**

3. ***Do you speak another language besides English?** (Check one)*
   - ☐ Yes **(If marked, complete next 2 questions)**
   - ☐ No

   - How well do you speak English?
     - ☐ Native English-speaker
     - ☐ Very well
     - ☐ Well
     - ☐ Not well

   - What language do you prefer to speak with your child's doctors?
     - ☐ English
     - ☐ Another language **(If marked, please select language from the list below)**
     - ☐ I am equally comfortable discussing my child's medical care in both English and another language

   - Please tell us which language you prefer to speak with your child's doctors:
     - ☐ Spanish
     - ☐ Vietnamese
     - ☐ Chinese (Mandarin, Cantonese, or other Chinese language)
     - ☐ Tagalog
     - ☐ German
     - ☐ French
     - ☐ Korean
     - ☐ Russian
     - ☐ Arabic
     - ☐ Other (please specify): _____

4. ***What category or categories best describe you?** Check all that apply.
   - ☐ American Indian, Native American, or Alaskan Native
   - ☐ Asian
   - ☐ Black or African American
   - ☐ Native Hawaiian/Pacific Islander
   - ☐ White or European American
   - ☐ Middle Eastern or North African/Mediterranean
   - ☐ Hispanic/Latino(a)
   - ☐ Prefer not to answer

- ☐ Unknown/None of these fully describe me

5. ***What category or categories best describe your child?** Check all that apply.
   - ☐ American Indian, Native American, or Alaska Native
   - ☐ Asian
   - ☐ Black or African American
   - ☐ Native Hawaiian/Pacific Islander
   - ☐ White or European American
   - ☐ Middle Eastern or North African/Mediterranean
   - ☐ Hispanic/Latino(a)
   - ☐ Prefer not to answer
   - ☐ Unknown/None of these fully describe my child

6. ***Are you currently (please select one):**
   - ☐ Married
   - ☐ Living together but not married
   - ☐ Separated or Divorced
   - ☐ Widowed
   - ☐ Never married and currently not living together

7. ***What is your employment status from this past week?** (check all that apply)
   - ☐ Working for pay at a job or business
   - ☐ With a job or business but not at work
   - ☐ Looking for work
   - ☐ Working, but not for pay, at a family-owned job or business
   - ☐ Not working at a job or business
   - ☐ Not looking for work
   - ☐ Taking care of house or family
   - ☐ Going to school
   - ☐ Retired
   - ☐ Disabled
   - ☐ Other: _____
   - ☐ Prefer not to answer
   - ☐ Don't know

8. ***What was your household's total family income (before taxes) from all sources in the last year?** (Check one)
   - ☐ Less than $10,000
   - ☐ $10,000 to $14,999
   - ☐ $15,000 to $19,999
   - ☐ $20,000 to $24,999
   - ☐ $25,000 to $29,999
   - ☐ $30,000 to $39,999
   - ☐ $40,000 to $49,999
   - ☐ $50,000 to $59,999

- ☐ $60,000 to $69,999
- ☐ $70,000 to $79,999
- ☐ $80,000 to $99,999
- ☐ $100,000 to $119,999
- ☐ $120,000 to $139,999
- ☐ $140,000 or more
- ☐ Prefer not to answer

9. How many people (children and adults) were supported by this income in the last year?

_____

10. ***What is the highest grade or level of school you completed or the highest degree you received?** (Check one)
    - ☐ No schooling completed
    - ☐ Elementary school (kindergarten through 5th grade)
    - ☐ Middle school (6th, 7th, or 8th grade)
    - ☐ Some high school (9th, 10th, or 11th grade)
    - ☐ 12th grade, no diploma
    - ☐ High school graduate (diploma or GED or equivalent)
    - ☐ Some post-high school training (college or occupational, technical, or vocational training), no degree or certificate
    - ☐ Completed occupational, technical, or vocational program, received degree or certificate
    - ☐ Associate (2-year) college degree
    - ☐ Bachelor's degree (for example: BA, AB, BS)
    - ☐ Master's degree (for example: MA, MS, MEng, MEd, MSW, MBA)
    - ☐ Professional degree (for example: MD, DDS, DVM, LLB, JD)
    - ☐ Doctoral degree (for example: PhD, EdD)

11. ***Are you covered by health insurance or some other kind of health care plan?** (Include health insurance obtained through employment or purchased directly, as well as government programs like Medicare and Medicaid that provide medical care or help pay medical bills) (Check one)
    - ☐ No
    - ☐ Yes

12. If you answered yes for #11: What kind or kinds of health insurance or health care coverage do you have? (Check all that apply)
    - ☐ Private health insurance, employment based
    - ☐ Private health insurance, directly purchased
    - ☐ Government plan, Medicare
    - ☐ Government plan, Medicaid
    - ☐ Government plan, Military health care
    - ☐ Other type of insurance (Please Describe): _____

☐ No coverage of any type.

13. ***Is your child covered by health insurance or some other kind of health care plan?** (Include health insurance obtained through employment or purchased directly as well as government programs like Medicare and Medicaid that provide medical care or help pay medical bills) (Check one)
    ☐ No
    ☐ Yes

14. If you answered yes for #13: IF YOUR CHILD IS COVERED: What kind or kinds of health insurance or health care coverage do they have? (Check all that apply)
    ☐ Private health insurance, employment based
    ☐ Private health insurance, directly purchased
    ☐ Government plan, Medicare
    ☐ Government plan, Medicaid
    ☐ Government plan, Military health care
    ☐ Other type of insurance (Please Describe): _____
    ☐ No coverage of any type.

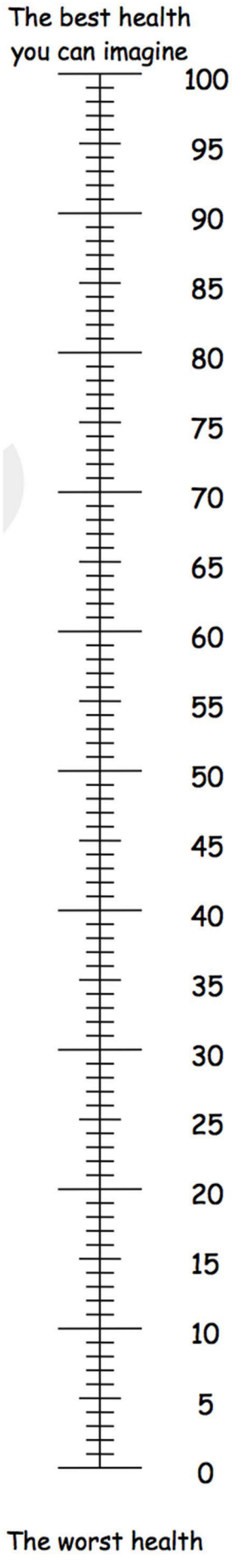
15. ***Which of the following currently applies to your child?**
    ☐ My child is currently in the hospital
    ☐ My child is now living outside the hospital
    ☐ My child is no longer living (if selected, skip to Question 17)

16. How good is your child's health TODAY?

- We would like know how good or bad your child's health is **TODAY**.
- This line is numbered **0** to **100**.
- **100** means the <u>best</u> health you can imagine. **0** means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your child's health is TODAY
- Now please write the number you marked on the scale in the box below

YOUR CHILD'S HEALTH TODAY= _____

- **N/A**



17. ***Considering your child's medical condition, please rank the degree to which you agree with the following statements:**

	Strongly Disagree	**Disagree**	**Somewhat Disagree**	**Neutral**	**Somewhat Agree**	**Agree**	**Strongly Agree**
I am clear in my own mind why my family has enrolled in SouthSeq.							
I can explain what the condition means to people in my family who may need to know.							
I understand the impact of the condition on my child(ren)/any child I may have.							
When I think about the condition in my family, I get upset.							
I don't know where to go to get the medical help I/my family need (s).							
I can see that good things have come from having this condition in my family.							
I can control how this condition affects my family.							
I feel positive about the future.							
I am able to cope with having this condition in my family.							
I don't know what could be gained from each of the options available to me.							
Having this condition in my family makes me feel anxious.							
I don't know if this condition could affect my other relatives (brothers, sisters, aunts, uncles, cousins).							

In relation to the condition in my family, nothing I decide will change the future for my children/any children I might have.							
I understand the reasons why my child's doctor referred my family to SouthSeq							
I know how to get the non-medical help I/my family need(s) (e.g. educational, financial, social support).							
I can explain what the condition means to people outside my family who may need to know (e.g. teachers, social workers).							
I don't know what I can do to change how this condition affects me/my children.							
I don't know who else in my family might be at risk for this condition.							
I am hopeful that my child(ren) can look forward to a rewarding family life.							
I am able to make plans for the future.							
I feel guilty because I (might have) passed this condition on to my children.							
I am powerless to do anything about this condition in my family.							
I understand what concerns led to my referral to SouthSeq							
I can make decisions about the condition that may change my child(ren)'s future/the							

future of any child(ren) I may have.							

18. For each item, rate yourself on the scale from “Not at all Good (1) to Extremely good (6)”

a. How good are you at working with fractions?

Not at all good					**Extremely Good**
1	2	3	4	5	6

b. How good are you at figuring out how much a shirt will cost if it is 25% off?

Not at all good					**Extremely Good**
1	2	3	4	5	6

c. How often do you find numerical information to be useful?

Never					**Very often**
1	2	3	4	5	6

19. ***Please mark the following statements as True or False.**

	True	**False**
It is possible to see a gene with the naked eye.		
Healthy parents can have a child with a hereditary disease.		
The onset of certain diseases is due to genes, environment and lifestyle.		
The carrier of a disease gene may be completely healthy.		
All serious diseases are hereditary.		
Genes are inside cells.		
The child of a disease gene carrier is always also a carrier of the same disease.		
A gene is a piece of DNA.		
A gene is part of a chromosome.		
All body parts have all of the same genes.		
It has been estimated that a person has about 20,000 genes.		
A person’s race and ethnicity can affect how likely they are to get a disease.		
Each of us has variations in our genes that make it more likely that we will get certain diseases.		
A “complex disease” is a health condition brought on by many genes and lifestyle and environment.		
A single nucleotide polymorphism or “SNiP” is a variation present in some individuals that stretches across a large section of DNA.		

20. Rate how certain you anticipate feeling about the following aspects of your child's upcoming sequence results:

	Very Uncertain (1)	2	3	4	Very Certain (5)
What my child's future test results may mean for his/her health					
What future actions I will need to take based on my child's test results					
How my child's physician may use the future results to improve my child's health					
Whether I will be worried or concerned about my child's future test results					
Whether my child's future test results will reveal something alarming					
Whether my child's future test results will disrupt my child's life					
Whether I will be able to trust my child's future test results					
Whether my child's future test results will be accurate					

21. ***Please rank the degree to which you agree with the following statements**

	Always	**Often**	**Sometimes**	**Occasionally**	**Never**
How often do you have someone (like a family member, friend, hospital/clinic worker, or caregiver) help you read medical materials?					
How often do you have problems learning about your medical condition because of difficulty reading written information?					
How often do you have a problem understanding what is told to you about your medical condition?					
	Not at all	**A little bit**	**Somewhat**	**Quite a bit**	**Extremely**
How confident are you filling out forms by yourself?					

22. ***In general, would you say your health is:**

Excellent	**Very Good**	**Good**	**Fair**	**Poor**

23. ***Here are some questions about the support that is available to you.**

a. About how many close friends and close relatives do you have (people you feel at ease with and can talk to about what is on your mind)?

Write in number of close friends and close relatives:_____

b. People sometimes look to others for companionship, assistance, or other types of support. How often is each of the following kinds of support available to YOU if you need it?

	None of the time	**A little of the time**	**Some of the time**	**Most of the time**	**All of the time**
Someone to help you if you were confined to bed…					
Someone you can count on to listen to you when you need to talk…					
Someone to give you good advice about a crisis…					
Someone to take you to the doctor if you needed it…					

Someone who shows you love and affection…					
Someone to have a good time with…					
Someone to give you information to help you understand a situation…					
Someone to confide in or talk to about yourself or your problems…					
Someone who hugs you…					
Someone to get together with for relaxation…					
Someone to prepare your meals if you were unable to do it yourself…					
Someone whose advice you really want…					
Someone to do things with to help you get your mind off things…					
Someone to help with daily chores if you were sick…					
Someone to share your most private worries and fears with…					
Someone to turn to for suggestions about how to deal with a personal problem…					
Someone to do something enjoyable with…					
Someone who understands your problems…					
Someone to love and make you feel wanted…					

Appendix 7.1A

Enrollment Survey for Deceased Probands

1. ***Please identify the individual completing this survey.**
   - ☐ Mother
   - ☐ Father
   - ☐ Other (please specify): _____

2. ***What is your age?**

3. ***Do you speak another language besides English?** (Check one)*
   - ☐ Yes **(If marked, complete next 2 questions)**
   - ☐ No

   - How well do you speak English?
     - ☐ Native English-speaker
     - ☐ Very well
     - ☐ Well
     - ☐ Not well

   - What language do you prefer to speak with your child's doctors?
     - ☐ English
     - ☐ Another language **(If marked, please select language from the list below)**
     - ☐ I am equally comfortable discussing my child's medical care in both English and another language

   - Please tell us which language you prefer to speak with your child's doctors:
     - ☐ Spanish
     - ☐ Vietnamese
     - ☐ Chinese (Mandarin, Cantonese, or other Chinese language)
     - ☐ Tagalog
     - ☐ German
     - ☐ French
     - ☐ Korean
     - ☐ Russian
     - ☐ Arabic
     - ☐ Other (please specify): _____

4. ***What category or categories best describe you?** Check all that apply.
   - ☐ American Indian, Native American, or Alaskan Native
   - ☐ Asian
   - ☐ Black or African American
   - ☐ Native Hawaiian/Pacific Islander
   - ☐ White or European American
   - ☐ Middle Eastern or North African/Mediterranean
   - ☐ Hispanic/Latino(a)
   - ☐ Prefer not to answer

- ☐ Unknown/None of these fully describe me

5. ***What category or categories best describe your child?** Check all that apply.
   - ☐ American Indian, Native American, or Alaska Native
   - ☐ Asian
   - ☐ Black or African American
   - ☐ Native Hawaiian/Pacific Islander
   - ☐ White or European American
   - ☐ Middle Eastern or North African/Mediterranean
   - ☐ Hispanic/Latino(a)
   - ☐ Prefer not to answer
   - ☐ Unknown/None of these fully describe my child

6. ***Are you currently (please select one):**
   - ☐ Married
   - ☐ Living together but not married
   - ☐ Separated or Divorced
   - ☐ Widowed
   - ☐ Never married and currently not living together

7. ***What is your employment status from this past week?** (check all that apply)
   - ☐ Working for pay at a job or business
   - ☐ With a job or business but not at work
   - ☐ Looking for work
   - ☐ Working, but not for pay, at a family-owned job or business
   - ☐ Not working at a job or business
   - ☐ Not looking for work
   - ☐ Taking care of house or family
   - ☐ Going to school
   - ☐ Retired
   - ☐ Disabled
   - ☐ Other: _____
   - ☐ Prefer not to answer
   - ☐ Don't know

8. ***What was your household's total family income (before taxes) from all sources in the last year?** (Check one)
   - ☐ Less than $10,000
   - ☐ $10,000 to $14,999
   - ☐ $15,000 to $19,999
   - ☐ $20,000 to $24,999
   - ☐ $25,000 to $29,999
   - ☐ $30,000 to $39,999
   - ☐ $40,000 to $49,999
   - ☐ $50,000 to $59,999

- ☐ $60,000 to $69,999
- ☐ $70,000 to $79,999
- ☐ $80,000 to $99,999
- ☐ $100,000 to $119,999
- ☐ $120,000 to $139,999
- ☐ $140,000 or more
- ☐ Prefer not to answer

9. How many people (children and adults) were supported by this income in the last year? _____

10. ***What is the highest grade or level of school you completed or the highest degree you received?** (Check one)
    - ☐ No schooling completed
    - ☐ Elementary school (kindergarten through 5th grade)
    - ☐ Middle school (6th, 7th, or 8th grade)
    - ☐ Some high school (9th, 10th, or 11th grade)
    - ☐ 12th grade, no diploma
    - ☐ High school graduate (diploma or GED or equivalent)
    - ☐ Some post-high school training (college or occupational, technical, or vocational training), no degree or certificate
    - ☐ Completed occupational, technical, or vocational program, received degree or certificate
    - ☐ Associate (2-year) college degree
    - ☐ Bachelor's degree (for example: BA, AB, BS)
    - ☐ Master's degree (for example: MA, MS, MEng, MEd, MSW, MBA)
    - ☐ Professional degree (for example: MD, DDS, DVM, LLB, JD)
    - ☐ Doctoral degree (for example: PhD, EdD)

11. ***Are you covered by health insurance or some other kind of health care plan?** (Include health insurance obtained through employment or purchased directly, as well as government programs like Medicare and Medicaid that provide medical care or help pay medical bills) (Check one)
    - ☐ No
    - ☐ Yes

12. If you answered yes for #11: What kind or kinds of health insurance or health care coverage do you have? (Check all that apply)
    - ☐ Private health insurance, employment based
    - ☐ Private health insurance, directly purchased
    - ☐ Government plan, Medicare
    - ☐ Government plan, Medicaid
    - ☐ Government plan, Military health care
    - ☐ Other type of insurance (Please Describe): _____
    - ☐ No coverage of any type.

13. ***Which of the following currently applies to your child?**

- ☐ My child is currently in the hospital
- ☐ My child is now living outside the hospital
- ☐ My child is no longer living

14. ***Considering your child's medical condition, please rank the degree to which you agree with the following statements:**

	Strongly Disagree	**Disagree**	**Somewhat Disagree**	**Neutral**	**Somewhat Agree**	**Agree**	**Strongly Agree**
I am clear in my own mind why my family has enrolled in SouthSeq.							
I can explain what the condition means to people in my family who may need to know.							
I understand the impact of the condition on any child I may have.							
When I think about the condition in my family, I get upset.							
I don't know where to go to get the medical help I/my family need (s).							
I can control how this condition affects my family.							
I feel positive about the future.							
I am able to cope with having this condition in my family.							
I don't know what could be gained from each of the options available to me.							
Having this condition in my family makes me feel anxious.							

I don't know if this condition could affect my other relatives (brothers, sisters, aunts, uncles, cousins).							
In relation to the condition in my family, nothing I decide will change the future for any children I might have.							
I understand the reasons why my child's doctor referred my family to SouthSeq							
I know how to get the non-medical help I/my family need(s) (e.g. educational, financial, social support).							
I can explain what the condition means to people outside my family who may need to know (e.g. teachers, social workers).							
I don't know what I can do to change how this condition affects me/my children.							
I don't know who else in my family might be at risk for this condition.							
I am able to make plans for the future.							
I feel guilty because I (might have) passed this condition on to my children.							
I am powerless to do anything about this condition in my family.							
I understand what concerns led to my referral to SouthSeq							
I can make decisions about the condition that may change the							

future of any child(ren) I may have.							

15. For each item, rate yourself on the scale from “Not at all Good (1) to Extremely good (6)”

a. How good are you at working with fractions?

Not at all good					**Extremely Good**
1	2	3	4	5	6

b. How good are you at figuring out how much a shirt will cost if it is 25% off?

Not at all good					**Extremely Good**
1	2	3	4	5	6

c. How often do you find numerical information to be useful?

Never					**Very often**
1	2	3	4	5	6

16. ***Please mark the following statements as True or False.**

	True	**False**
It is possible to see a gene with the naked eye.		
Healthy parents can have a child with a hereditary disease.		
The onset of certain diseases is due to genes, environment and lifestyle.		
The carrier of a disease gene may be completely healthy.		
All serious diseases are hereditary.		
Genes are inside cells.		
The child of a disease gene carrier is always also a carrier of the same disease.		
A gene is a piece of DNA.		
A gene is part of a chromosome.		
All body parts have all of the same genes.		
It has been estimated that a person has about 20,000 genes.		
A person’s race and ethnicity can affect how likely they are to get a disease.		
Each of us has variations in our genes that make it more likely that we will get certain diseases.		
A “complex disease” is a health condition brought on by many genes and lifestyle and environment.		
A single nucleotide polymorphism or “SNiP” is a variation present in some individuals that stretches across a large section of DNA.		

17. ***Please rank the degree to which you agree with the following statements**

	Always	**Often**	**Sometimes**	**Occasionally**	**Never**
How often do you have someone (like a family member, friend, hospital/clinic worker, or caregiver) help you read medical materials?					
How often do you have problems learning about your medical condition because of difficulty reading written information?					
How often do you have a problem understanding what is told to you about your medical condition?					
	Not at all	**A little bit**	**Somewhat**	**Quite a bit**	**Extremely**
How confident are you filling out forms by yourself?					

18. ***In general, would you say your health is:**

Excellent	**Very Good**	**Good**	**Fair**	**Poor**

19. ***Here are some questions about the support that is available to you.**

a. About how many close friends and close relatives do you have (people you feel at ease with and can talk to about what is on your mind)?

Write in number of close friends and close relatives:_____

b. People sometimes look to others for companionship, assistance, or other types of support. How often is each of the following kinds of support available to YOU if you need it?

	None of the time	**A little of the time**	**Some of the time**	**Most of the time**	**All of the time**
Someone to help you if you were confined to bed…					
Someone you can count on to listen to you when you need to talk…					

Someone to give you good advice about a crisis…					
Someone to take you to the doctor if you needed it…					
Someone who shows you love and affection…					
Someone to have a good time with…					
Someone to give you information to help you understand a situation…					
Someone to confide in or talk to about yourself or your problems…					
Someone who hugs you…					
Someone to get together with for relaxation…					
Someone to prepare your meals if you were unable to do it yourself…					
Someone whose advice you really want…					
Someone to do things with to help you get your mind off things…					
Someone to help with daily chores if you were sick…					
Someone to share your most private worries and fears with…					
Someone to turn to for suggestions about how to deal with a personal problem…					
Someone to do something enjoyable with…					
Someone who understands your problems…					
Someone to love and make you feel wanted…					

Appendix 7.2

ROR Survey

1. ***Please identify the individual completing this survey.**
   - ☐ Mother
   - ☐ Father
   - ☐ Other (please specify): _____

2. ***What is your age?**

3. ***In the past 3 months, has your marital status or employment changed?**
   - ☐ Yes
   - ☐ No

4. If you answered yes to question 3: Are you currently (please select one):
   - ☐ Married
   - ☐ Living together but not married
   - ☐ Separated or Divorced
   - ☐ Widowed
   - ☐ Never married and currently not living together

5. If answered yes to question 3: What is your employment status from this past week? (select all that apply)
   - ☐ No change
   - ☐ Working for pay at a job or business
   - ☐ With a job or business but not at work
   - ☐ Looking for work
   - ☐ Working, but not for pay, at a family-owned job or business
   - ☐ Not working at a job or business
   - ☐ Not looking for work
   - ☐ Taking care of house or family
   - ☐ Going to school
   - ☐ Retired
   - ☐ Disabled
   - ☐ Other: _____
   - ☐ Refused
   - ☐ Don't know

6. Is your child covered by health insurance or some other kind of health care plan? (Include health insurance obtained through employment or purchased directly as well as government programs like Medicare and Medicaid that provide medical care or help pay medical bills) (Check one)
   - ☐ No
   - ☐ Yes

7. If you answered yes for #6: IF YOUR CHILD IS COVERED: What kind or kinds of health insurance or health care coverage do they have? (Check all that apply)
   - ☐ Private health insurance, employment based
   - ☐ Private health insurance, directly purchased
   - ☐ Government plan, Medicare
   - ☐ Government plan, Medicaid
   - ☐ Government plan, Military health care
   - ☐ Other type of insurance (Please Describe): _____
   - ☐ No coverage of any type.

8. ***In the past 3 months, has your residential address changed?**
   - ☐ Yes (if yes, please notify your study coordinator)
   - ☐ No

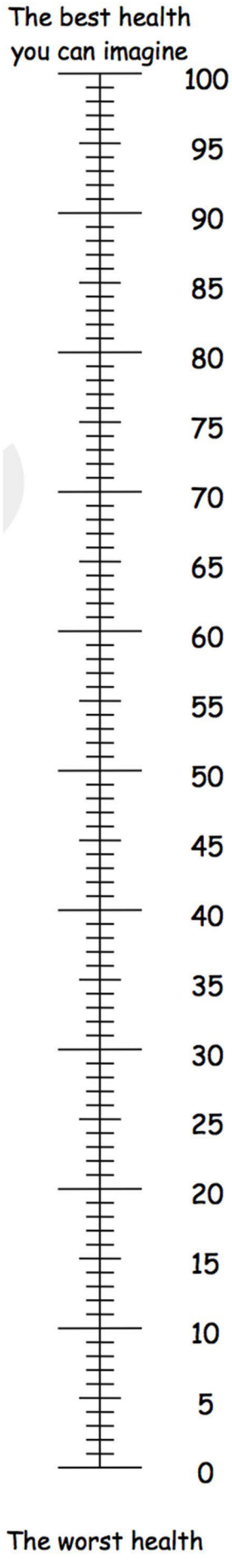
9. ***Which of the following currently applies to your child?**
   - ☐ My child is currently in the hospital
   - ☐ My child is now living outside the hospital
   - ☐ My child is no longer living (if selected, skip to Question 11)

10. How good is your child's health TODAY?

- We would like know how good or bad your child's health is **TODAY**.
- This line is numbered **0** to **100**.
- **100** means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your child's health is TODAY
- Now please write the number you marked on the scale in the box below

YOUR CHILD'S HEALTH TODAY= _____

- **N/A**



11. ***Considering your child's medical condition, please rank the degree to which you agree with the following statements:**

	Strongly Disagree	**Disagree**	**Somewhat Disagree**	**Neutral**	**Somewhat Agree**	**Agree**	**Strongly Agree**
I am clear in my own mind why my family has enrolled in SouthSeq.							
I can explain what the condition means to people in my family who may need to know.							
I understand the impact of the condition on my child(ren)/any child I may have.							
When I think about the condition in my family, I get upset.							
I don't know where to go to get the medical help I/my family need (s).							
I can see that good things have come from having this condition in my family.							
I can control how this condition affects my family.							
I feel positive about the future.							
I am able to cope with having this condition in my family.							
I don't know what could be gained from each of the options available to me.							
Having this condition in my family makes me feel anxious.							
I don't know if this condition could affect my other relatives (brothers, sisters, aunts, uncles, cousins).							

In relation to the condition in my family, nothing I decide will change the future for my children/any children I might have.							
I understand the reasons why my child's doctor referred my family to SouthSeq							
I know how to get the non-medical help I/my family need(s) (e.g. educational, financial, social support).							
I can explain what the condition means to people outside my family who may need to know (e.g. teachers, social workers).							
I don't know what I can do to change how this condition affects me/my children.							
I don't know who else in my family might be at risk for this condition.							
I am hopeful that my child(ren) can look forward to a rewarding family life.							
I am able to make plans for the future.							
I feel guilty because I (might have) passed this condition on to my children.							
I am powerless to do anything about this condition in my family.							
I understand what concerns led to my referral to SouthSeq							
I can make decisions about the condition that may change my child(ren)'s future/the							

future of any child(ren) I may have.							

12. ***The following questions ask about how you, as a parent, felt after receiving your child's genetic test results. Please indicate how much you had each specific feeling in the past week by choosing the one answer for each question.**

	Not at all	A little	Somewhat	A good deal	A great deal
How **upset** did you feel about your child's genetic test result?					
How **happy** did you feel about your child's genetic test result?					
How **anxious or nervous** did you feel about your child's genetic test result?					
How **relieved** did you feel about your child's genetic test result?					
How **sad** did you feel about your child's genetic test result?					
How **frustrated** did you feel about recommendations for your child's care based on the genetic test?					
How **uncertain** did you feel about what your child's genetic test result means for your child?					
How **uncertain** did you feel about what your child's genetic test result means for other family members' risk of disease?					
How much did you feel that **you understood clearly your child's choices** for care based on the genetic test result?					
How **concerned** did you feel that your child's genetic test result would affect his or her ability to get or keep health insurance?					
How **helpful** was the information you received from your genetic test result					

in planning for your child's future?					
How **concerned** did you feel that your child's genetic test result might make it hard for them to get or keep a job?					
How **guilty** did you feel about your child's genetic test result?					
How **much loss of control** over your child's life did you feel because of your child's genetic test result?					

13. ***Rate how certain you feel about the following aspects of your child's sequence results:**

	Very Uncertain (1)	2	3	4	Very Certain (5)
What my child's test results mean for his/her health					
What actions I need to take based on my child's test results					
How my child's doctor may use the results to improve my child's health					
Whether I am worried or concerned about my child's test results					
Whether my child's test results revealed something alarming					
Whether my child's test results disrupted my life					
Whether I can trust my child's test results					
Whether my child's test results are accurate					

14. ***Please indicate how useful you find the following outcomes of genome sequencing for you and your child**

	Not at all useful (1)	A little useful (2)	Somewhat useful (3)	Neutral (4)	Useful (5)	Very useful (6)	Extremely useful (7)
Help with my child's life planning							
Inform plans for my child's school or career							
Inform my child's decisions about having children							
Use for testing a future pregnancy, if appropriate							
Help me or our family mentally prepare for the future							
Help to better understand my child's health							
Contribute to my child's self-knowledge							
Help me cope with my child's health risks							
Help me feel more in control of my child's health							
Help me feel more in control of my child's life							
Simply to provide information							
Satisfy my curiosity about my child							
Help my child use social programs, like resources and services							
Improve communication with my family members							

Feel good about helping the medical community							
Feel good about having information for family members							
Feel good about taking responsibility for my child's health							

15. ***In general, would you say your health is:**

Excellent	Very Good	Good	Fair	Poor

16. **How well do you understand your child's test results?**

Not at all	A little bit	Moderately	Quite a bit	Extremely

17. ***Please tell us about your experience receiving your child's genetic test results.**

	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree	Not Applicable
I was treated with sensitivity and respect.						
I felt listened to.						
The clinical team checked to make sure I understood the information						
I trust the clinical team						
The clinical team explained complicated topics well						

I got clear, understandable information.						
I received too much information to understand						
It was hard to make sense out of the information						
I felt I had the information and support available to me to answer any questions I had after receiving my child's genetic results						
I felt comfortable asking questions and voicing my concerns						
The clinical team helped me cope with any uncertainty or unknowns						
It was hard to ask questions about this information						
I felt comfortable talking about sensitive issues or embarrassing subjects with the clinical team						
The clinical team noticed when I had problems understanding						
I had questions about this information that I was unable to ask						

18. ***Here are some questions about the support that is available to you**

a. About how many close friends and close relatives do you have (people you feel at ease with and can talk to about what is on your mind)?

Write in number of close friends and close relatives:_____

b. People sometimes look to others for companionship, assistance, or other types of support. How often is each of the following kinds of support available to YOU if you need it?

	None of the time	**A little of the time**	**Some of the time**	**Most of the time**	**All of the time**
Someone to help you if you were confined to bed…					
Someone you can count on to listen to you when you need to talk…					
Someone to give you good advice about a crisis…					
Someone to take you to the doctor if you needed it…					
Someone who shows you love and affection…					
Someone to have a good time with…					
Someone to give you information to help you understand a situation…					
Someone to confide in or talk to about yourself or your problems…					
Someone who hugs you…					
Someone to get together with for relaxation…					
Someone to prepare your meals if you were unable to do it yourself…					
Someone whose advice you really want…					
Someone to do things with to help you get your mind off things…					
Someone to help with daily chores if you were sick…					
Someone to share your most private worries and fears with…					
Someone to turn to for suggestions about how to deal with a personal problem…					
Someone to do something enjoyable with…					
Someone who understands your problems…					
Someone to love and make you feel wanted…					

Information Seeking V1 *(ROR)*

19. ***What sources, if any do you think you are likely to use to find more information about the genetic test results you received today? Please write below.**

_____

_____

Appendix 7.2A

ROR Survey for Deceased Probands

1. ***Please identify the individual completing this survey.**
   - ☐ Mother
   - ☐ Father
   - ☐ Other (please specify): _____

2. ***What is your age?**

3. ***In the past 3 months, has your marital status or employment changed?**
   - ☐ Yes
   - ☐ No

4. If you answered yes to question 3: Are you currently (please select one):
   - ☐ Married
   - ☐ Living together but not married
   - ☐ Separated or Divorced
   - ☐ Widowed
   - ☐ Never married and currently not living together

5. If answered yes to question 3: What is your employment status from this past week? (select all that apply)
   - ☐ No change
   - ☐ Working for pay at a job or business
   - ☐ With a job or business but not at work
   - ☐ Looking for work
   - ☐ Working, but not for pay, at a family-owned job or business
   - ☐ Not working at a job or business
   - ☐ Not looking for work
   - ☐ Taking care of house or family
   - ☐ Going to school
   - ☐ Retired
   - ☐ Disabled
   - ☐ Other: _____
   - ☐ Refused
   - ☐ Don't know

6. ***In the past 3 months, has your residential address changed?**
   - ☐ Yes (if yes, please notify your study coordinator)
   - ☐ No

7. ***Which of the following currently applies to your child?**
   - ☐ My child is currently in the hospital

- ☐ My child is now living outside the hospital
- ☐ My child is no longer living

8. *Considering your child's medical condition, please rank the degree to which you agree with the following statements:

	Strongly Disagree	Disagree	Somewhat Disagree	Neutral	Somewhat Agree	Agree	Strongly Agree
I am clear in my own mind why my family has enrolled in SouthSeq.							
I can explain what the condition means to people in my family who may need to know.							
I understand the impact of the condition on any child I may have.							
When I think about the condition in my family, I get upset.							
I don't know where to go to get the medical help I/my family need (s).							
I can control how this condition affects my family.							
I feel positive about the future.							
I am able to cope with having this condition in my family.							
I don't know what could be gained from each of the options available to me.							
Having this condition in my family makes me feel anxious.							
I don't know if this condition could affect my other relatives (brothers, sisters, aunts, uncles, cousins).							

In relation to the condition in my family, nothing I decide will change the future for any children I might have.							
I understand the reasons why my child's doctor referred my family to SouthSeq							
I know how to get the non-medical help I/my family need(s) (e.g. educational, financial, social support).							
I can explain what the condition means to people outside my family who may need to know (e.g. teachers, social workers).							
I don't know what I can do to change how this condition affects me/my children.							
I don't know who else in my family might be at risk for this condition.							
I am able to make plans for the future.							
I feel guilty because I (might have) passed this condition on to my children.							
I am powerless to do anything about this condition in my family.							
I understand what concerns led to my referral to SouthSeq							
I can make decisions about the condition that may change the future of any child(ren) I may have.							

9. *The following questions ask about how you, as a parent, felt after receiving your child's genetic test results. Please indicate how much you had each specific feeling in the past week by choosing the one answer for each question.

	Not at all	A little	Somewhat	A good deal	A great deal
How **upset** did you feel about your child's genetic test result?					
How **happy** did you feel about your child's genetic test result?					
How **anxious or nervous** did you feel about your child's genetic test result?					
How **relieved** did you feel about your child's genetic test result?					
How **sad** did you feel about your child's genetic test result?					
How **uncertain** did you feel about what your child's genetic test result means for other family members' risk of disease?					
How **guilty** did you feel about your child's genetic test result?					

10. *Please indicate how useful you find the following outcomes of genome sequencing for you and your child

	Not at all useful (1)	A little useful (2)	Somewhat useful (3)	Neutral (4)	Useful (5)	Very useful (6)	Extremely useful (7)
Use for testing a future pregnancy, if appropriate							
Help me or our family mentally prepare for the future							
Simply to provide information							
Improve communication with my family members							

Feel good about helping the medical community							
Feel good about having information for family members							

11. *In general, would you say your health is:

Excellent	Very Good	Good	Fair	Poor

12. How well do you understand your child's test results?

Not at all	A little bit	Moderately	Quite a bit	Extremely

13. *Please tell us about your experience receiving your child's genetic test results.

	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree	Not Applicable
I was treated with sensitivity and respect.						
I felt listened to.						
The clinical team checked to make sure I understood the information						
I trust the clinical team						
The clinical team explained complicated topics well						
I got clear, understandable information.						
I received too much information to understand						

It was hard to make sense out of the information						
I felt I had the information and support available to me to answer any questions I had after receiving my child's genetic results						
I felt comfortable asking questions and voicing my concerns						
The clinical team helped me cope with any uncertainty or unknowns						
It was hard to ask questions about this information						
I felt comfortable talking about sensitive issues or embarrassing subjects with the clinical team						
The clinical team noticed when I had problems understanding						
I had questions about this information that I was unable to ask						

14. *Here are some questions about the support that is available to you

a. About how many close friends and close relatives do you have (people you feel at ease with and can talk to about what is on your mind)?

Write in number of close friends and close relatives:_____

b. People sometimes look to others for companionship, assistance, or other types of support. How often is each of the following kinds of support available to YOU if you need it?

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
Someone to help you if you were confined to bed…					
Someone you can count on to listen to you when you need to talk…					
Someone to give you good advice about a crisis…					
Someone to take you to the doctor if you needed it…					
Someone who shows you love and affection…					
Someone to have a good time with…					
Someone to give you information to help you understand a situation…					
Someone to confide in or talk to about yourself or your problems…					
Someone who hugs you…					
Someone to get together with for relaxation…					
Someone to prepare your meals if you were unable to do it yourself…					
Someone whose advice you really want…					
Someone to do things with to help you get your mind off things…					
Someone to help with daily chores if you were sick…					
Someone to share your most private worries and fears with…					
Someone to turn to for suggestions about how to deal with a personal problem…					
Someone to do something enjoyable with…					
Someone who understands your problems…					
Someone to love and make you feel wanted…					

Information Seeking V1 *(ROR)*

15. *What sources, if any do you think you are likely to use to find more information about the genetic test results you received today? Please write below.

_____

_____

Appendix 7.3 1-month post-ROR Survey

1. **Please identify the individual completing this survey.**
   - ○ Mother
   - ○ Father
   - ○ Other (please specify): _____

2. **In the past 3 months, has your marital status or employment changed?**
   - ○ Yes
   - ○ No

If you answered yes to question 2:

3. **Are you currently (please select one):**
   - ☐ Married
   - ☐ Living together but not married
   - ☐ Separated or Divorced
   - ☐ Widowed
   - ☐ Never married and currently not living together

If answered yes to question 2:

4. **What is your employment status from this past week?** (select all that apply)
   - ☐ No change
   - ☐ Working for pay at a job or business
   - ☐ With a job or business but not at work
   - ☐ Looking for work
   - ☐ Working, but not for pay, at a family-owned job or business
   - ☐ Not working at a job or business
   - ☐ Not looking for work
   - ☐ Taking care of house or family
   - ☐ Going to school
   - ☐ Retired
   - ☐ Disabled
   - ☐ Other: _____
   - ☐ Refused
   - ☐ Don't know

5. **In the past month, has your residential address changed?**
   - ☐ Yes
   - ☐ No

If you answered yes to question 5:

6. What is the address where you currently live?

   Street: _____

   _____

   City: _____ State: _____ Zip Code: _____

7. In the past month, has your child's residential address changed?
   - ☐ Yes
   - ☐ No

If you answered yes to question 7:

8. What is the address where your child currently lives?

   Street: _____

   _____

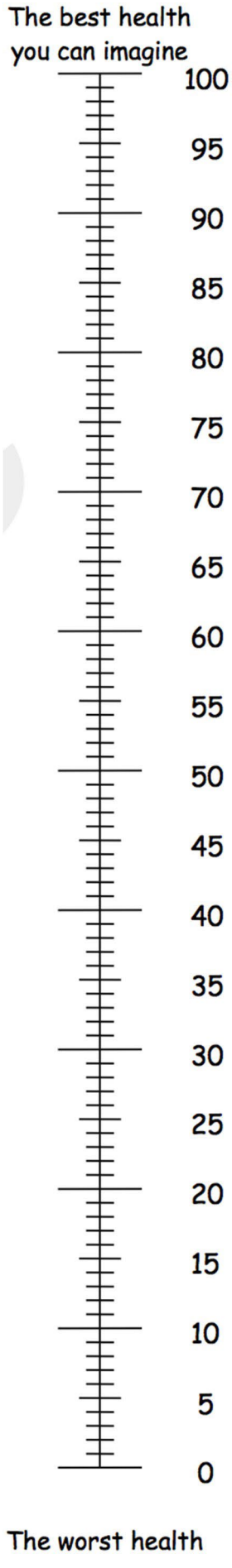
   City: _____ State: _____ Zip Code: _____

How good is your child's health TODAY?

- We would like know how good or bad your child's health is **TODAY**.
- This line is numbered **0** to **100**.
- **100** means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your child's health is TODAY
- Now please write the number you marked on the scale in the box below

YOUR CHILD'S HEALTH TODAY= _____

- **N/A**



9. **Considering your child's medical condition, please rank the degree to which you agree with the following statements:**

	Strongly Disagree	Disagree	Somewhat Disagree	Neutral	Somewhat Agree	Agree	Strongly Agree
I am clear in my own mind why my family has enrolled in SouthSeq.							
I can explain what the condition means to people in my family who may need to know.							
I understand the impact of the condition on my child(ren)/any child I may have.							
When I think about the condition in my family, I get upset.							
I don't know where to go to get the medical help I/my family need (s).							
I can see that good things have come from having this condition in my family.							
I can control how this condition affects my family.							
I feel positive about the future.							
I am able to cope with having this condition in my family.							
I don't know what could be gained from each of the options available to me.							
Having this condition in my family makes me feel anxious.							
I don't know if this condition could affect my other relatives (brothers, sisters, aunts, uncles, cousins).							

In relation to the condition in my family, nothing I decide will change the future for my children/any children I might have.							
I understand the reasons why my child's doctor referred my family to SouthSeq							
I know how to get the non-medical help I/my family need(s) (e.g. educational, financial, social support).							
I can explain what the condition means to people outside my family who may need to know (e.g. teachers, social workers).							
I don't know what I can do to change how this condition affects me/my children.							
I don't know who else in my family might be at risk for this condition.							
I am hopeful that my child(ren) can look forward to a rewarding family life.							
I am able to make plans for the future.							
I feel guilty because I (might have) passed this condition on to my children.							
I am powerless to do anything about this condition in my family.							

10. The following questions ask about how you, as a parent, felt after receiving your child's genetic test results. Please indicate how much you had each specific feeling in the past week by choosing the one answer for each question.

	Not at all	A little	Somewhat	A good deal	A great deal
How **upset** did you feel about your child's genetic test result?					
How **happy** did you feel about your child's genetic test result?					
How **anxious or nervous** did you feel about your child's genetic test result?					
How **relieved** did you feel about your child's genetic test result?					
How **sad** did you feel about your child's genetic test result?					
How **frustrated** did you feel about recommendations for your child's care based on the genetic test?					
How **uncertain** did you feel about what your child's genetic test result means for your child?					
How **uncertain** did you feel about what your child's genetic test result means for other family members' risk of disease?					
How much did you feel that **you understood clearly your child's choices** for care based on the genetic test result?					
How **concerned** did you feel that your child's genetic test result would affect his or her ability to get or keep health insurance?					
How **helpful** was the information you received from your genetic test result in planning for your child's future?					
How **concerned** did you feel that your child's genetic test result might make it hard for them to get or keep a job?					

How **guilty** did you feel about your child's genetic test result?					
How **much loss of control** over your child's life did you feel because of your child's genetic test result?					

11. **Rate how certain you feel about the following aspects of your child's sequence results:**

	Very Uncertain (1)	2	3	4	Very Certain (5)
What my child's test results mean for his/her health					
What actions I need to take based on my child's test results					
How my child's doctor may use the results to improve my child's health					
Whether I am worried or concerned about my child's test results					
Whether my child's test results revealed something alarming					
Whether my child's test results disrupted my life					
Whether I can trust my child's test results					
Whether my child's test results are accurate					

12. **Please indicate how useful you find the following outcomes of genome sequencing for you and your child**

	Not at all useful (1)	A little useful (2)	Somewhat useful (3)	Neutral (4)	Useful (5)	Very useful (6)	Extremely useful (7)

Help with my child's life planning							
Inform plans for my child's school or career							
Inform my child's decisions about having children							
Use for testing a future pregnancy, if appropriate							
Help me or our family mentally prepare for the future							
Help to better understand my child's health							
Contribute to my child's self-knowledge							
Help me cope with my child's health risks							
Help me feel more in control of my child's health							
Help me feel more in control of my child's life							
Simply to provide information							
Satisfy my curiosity about my child							
Help my child use social programs, like resources or services							
Improve communication with my family members							
Feel good about helping the medical community							
Feel good about having information for family members							

Feel good about taking responsibility for my child's health							

13.

a. **In general, would you say your health is:**

Excellent	Very Good	Good	Fair	Poor

14. **How well do you understand your child's test results?**

Not at all	A little bit	Moderately	Quite a bit	Extremely

15. **Please tell us about your experience receiving your child's genetic test results.**

	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree	Not Applicable
I was treated with sensitivity and respect.						
I felt listened to.						
The clinical team checked to make sure I understood the information						
I trust the clinical team						
The clinical team explained complicated topics well						
I got clear, understandable information.						
I received too much information to understand						

It was hard to make sense out of the information						
I felt I had the information and support available to me to answer any questions I had after receiving my child's genetic results						
I felt comfortable asking questions and voicing my concerns						
The clinical team helped me cope with any uncertainty or unknowns						
It was hard to ask questions about this information						
I felt comfortable talking about sensitive issues or embarrassing subjects with the clinical team						
The clinical team noticed when I had problems understanding						
I had questions about this information that I was unable to ask						

16. **Here are some questions about the support that is available to you**

a. About how many close friends and close relatives do you have (people you feel at ease with and can talk to about what is on your mind)?

Write in number of close friends and close relatives:_____

b. People sometimes look to others for companionship, assistance, or other types of support. How often is each of the following kinds of support available to YOU if you need it?

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
Someone to help you if you were confined to bed…					
Someone you can count on to listen to you when you need to talk…					
Someone to give you good advice about a crisis…					
Someone to take you to the doctor if you needed it…					
Someone who shows you love and affection…					
Someone to have a good time with…					
Someone to give you information to help you understand a situation…					
Someone to confide in or talk to about yourself or your problems…					
Someone who hugs you…					
Someone to get together with for relaxation…					
Someone to prepare your meals if you were unable to do it yourself…					
Someone whose advice you really want…					
Someone to do things with to help you get your mind off things…					
Someone to help with daily chores if you were sick…					
Someone to share your most private worries and fears with…					
Someone to turn to for suggestions about how to deal with a personal problem…					
Someone to do something enjoyable with…					
Someone who understands your problems…					
Someone to love and make you feel wanted…					

17. Which of the following sources, if any, did you use to find more information about the genetic test results you received at your last visit?
    Please rate the usefulness of the sources you used. (1-not useful at all, 5=very useful)

	Not useful at all (1)	2	3	4	Very useful (5)	N/A
Family or friends	o	o	o	o	o	o
Facebook	o	o	o	o	o	o
Support groups	o	o	o	o	o	o
My/my child's other doctors	o	o	o	o	o	o
Internet search (i.e. Google, PubMed, etc.)	o	o	o	o	o	o
Books and other print media	o	o	o	o	o	o
Information provided by the doctor who ordered my child's genetic test	o	o	o	o	o	o
Other (please specify): _____	o	o	o	o	o	o
None	o	o	o	o	o	o

Appendix 7.4 and 7.5

4-month and 4-mont plus post-ROR Survey

1. **Please identify the individual completing this survey.**
   - ○ Mother
   - ○ Father
   - ○ Other (please specify): _____

2. **In the past 3 months, has your marital status or employment changed?**
   - ○ Yes
   - ○ No

If you answered yes to question 2:

3. **Are you currently (please select one):**
   - ☐ Married
   - ☐ Living together but not married
   - ☐ Separated or Divorced
   - ☐ Widowed
   - ☐ Never married and currently not living together

If answered yes to question 2:

4. **What is your employment status from this past week?** (select all that apply)
   - ☐ No change
   - ☐ Working for pay at a job or business
   - ☐ With a job or business but not at work
   - ☐ Looking for work
   - ☐ Working, but not for pay, at a family-owned job or business
   - ☐ Not working at a job or business
   - ☐ Not looking for work
   - ☐ Taking care of house or family
   - ☐ Going to school
   - ☐ Retired
   - ☐ Disabled
   - ☐ Other: _____
   - ☐ Refused
   - ☐ Don't know

5. **In the past month, has your residential address changed?**
   - ☐ Yes
   - ☐ No

If you answered yes to question 5:

6. What is the address where you currently live?

   Street: _____

   _____

   City: _____ State: _____ Zip Code: _____

7. In the past month, has your child's residential address changed?
   - ☐ Yes
   - ☐ No

If you answered yes to question 7:

8. What is the address where your child currently lives?

   Street: _____

   _____

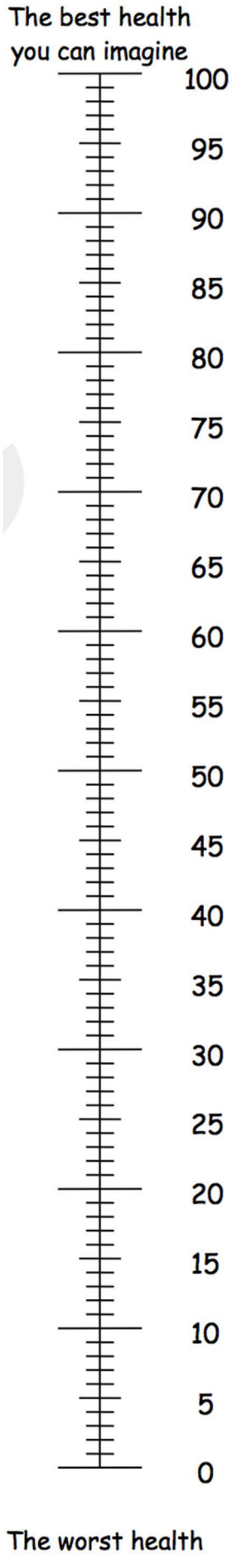
   City: _____ State: _____ Zip Code: _____

How good is your child's health TODAY?

- We would like know how good or bad your child's health is **TODAY**.
- This line is numbered **0** to **100**.
- **100** means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your child's health is TODAY
- Now please write the number you marked on the scale in the box below

YOUR CHILD'S HEALTH TODAY= _____

- **N/A**



9. **Considering your child's medical condition, please rank the degree to which you agree with the following statements:**

	Strongly Disagree	**Disagree**	**Somewhat Disagree**	**Neutral**	**Somewhat Agree**	**Agree**	**Strongly Agree**
I am clear in my own mind why my family has enrolled in SouthSeq.							
I can explain what the condition means to people in my family who may need to know.							
I understand the impact of the condition on my child(ren)/any child I may have.							
When I think about the condition in my family, I get upset.							
I don't know where to go to get the medical help I/my family need (s).							
I can see that good things have come from having this condition in my family.							
I can control how this condition affects my family.							
I feel positive about the future.							
I am able to cope with having this condition in my family.							
I don't know what could be gained from each of the options available to me.							
Having this condition in my family makes me feel anxious.							
I don't know if this condition could affect my other relatives (brothers, sisters, aunts, uncles, cousins).							

In relation to the condition in my family, nothing I decide will change the future for my children/any children I might have.							
I understand the reasons why my child's doctor referred my family to SouthSeq							
I know how to get the non-medical help I/my family need(s) (e.g. educational, financial, social support).							
I can explain what the condition means to people outside my family who may need to know (e.g. teachers, social workers).							
I don't know what I can do to change how this condition affects me/my children.							
I don't know who else in my family might be at risk for this condition.							
I am hopeful that my child(ren) can look forward to a rewarding family life.							
I am able to make plans for the future.							
I feel guilty because I (might have) passed this condition on to my children.							
I am powerless to do anything about this condition in my family.							

10. The following questions ask about how you, as a parent, felt after receiving your child's genetic test results. Please indicate how much you had each specific feeling in the past week by choosing the one answer for each question.

	Not at all	A little	Somewhat	A good deal	A great deal
How **upset** did you feel about your child's genetic test result?					
How **happy** did you feel about your child's genetic test result?					
How **anxious or nervous** did you feel about your child's genetic test result?					
How **relieved** did you feel about your child's genetic test result?					
How **sad** did you feel about your child's genetic test result?					
How **frustrated** did you feel about recommendations for your child's care based on the genetic test?					
How **uncertain** did you feel about what your child's genetic test result means for your child?					
How **uncertain** did you feel about what your child's genetic test result means for other family members' risk of disease?					
How much did you feel that **you understood clearly your child's choices** for care based on the genetic test result?					
How **concerned** did you feel that your child's genetic test result would affect his or her ability to get or keep health insurance?					
How **helpful** was the information you received from your genetic test result in planning for your child's future?					
How **concerned** did you feel that your child's genetic test result might make it hard for them to get or keep a job?					

How **guilty** did you feel about your child's genetic test result?					
How **much loss of control** over your child's life did you feel because of your child's genetic test result?					

11. **Rate how certain you feel about the following aspects of your child's sequence**

a. **In general, would you say your health is:**

Excellent	Very Good	Good	Fair	Poor

12. **How well do you understand your child's test results?**

Not at all	A little bit	Moderately	Quite a bit	Extremely

13. **Please tell us about your experience receiving your child's genetic test results.**

	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree	Not Applicable
I was treated with sensitivity and respect.						
I felt listened to.						
The clinical team checked to make sure I understood the information						
I trust the clinical team						
The clinical team explained complicated topics well						
I got clear, understandable information.						

I received too much information to understand						
It was hard to make sense out of the information						
I felt I had the information and support available to me to answer any questions I had after receiving my child's genetic results						
I felt comfortable asking questions and voicing my concerns						
The clinical team helped me cope with any uncertainty or unknowns						
It was hard to ask questions about this information						
I felt comfortable talking about sensitive issues or embarrassing subjects with the clinical team						
The clinical team noticed when I had problems understanding						
I had questions about this information that I was unable to ask						

14. **Here are some questions about the support that is available to you**

a. About how many close friends and close relatives do you have (people you feel at ease with and can talk to about what is on your mind)?

Write in number of close friends and close relatives:_____

b. People sometimes look to others for companionship, assistance, or other types of support. How often is each of the following kinds of support available to YOU if you need it?

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
Someone to help you if you were confined to bed…					
Someone you can count on to listen to you when you need to talk…					
Someone to give you good advice about a crisis…					
Someone to take you to the doctor if you needed it…					
Someone who shows you love and affection…					
Someone to have a good time with…					
Someone to give you information to help you understand a situation…					
Someone to confide in or talk to about yourself or your problems…					
Someone who hugs you…					
Someone to get together with for relaxation…					
Someone to prepare your meals if you were unable to do it yourself…					
Someone whose advice you really want…					
Someone to do things with to help you get your mind off things…					
Someone to help with daily chores if you were sick…					
Someone to share your most private worries and fears with…					
Someone to turn to for suggestions about how to deal with a personal problem…					
Someone to do something enjoyable with…					
Someone who understands your problems…					
Someone to love and make you feel wanted…					

15. Which of the following sources, if any, did you use to find more information about the genetic test results you received at your last visit?
    Please rate the usefulness of the sources you used. (1-not useful at all, 5=very useful)

	Not useful at all (1)	2	3	4	Very useful (5)	N/A
Family or friends	o	o	o	o	o	o
Facebook	o	o	o	o	o	o
Support groups	o	o	o	o	o	o
My/my child's other doctors	o	o	o	o	o	o
Internet search (i.e. Google, PubMed, etc.)	o	o	o	o	o	o
Books and other print media	o	o	o	o	o	o
Information provided by the doctor who ordered my child's genetic test	o	o	o	o	o	o
Other (please specify): _____	o	o	o	o	o	o
None	o	o	o	o	o	o

16. Since receiving your child's study results, did you share the information with any biological family members (blood relatives)?
    - o Yes
    - o I didn't share this information with anyone **(if selected, skip to question 20)**
    - o I haven't shared this information yet, but plan to in the future **(if selected, skip to question 18)**
    - o I do not have blood relatives to share this information with **(if selected, skip all remaining questions)**

17. Since receiving your child's study results, have you shared the information with any of the following blood relatives?

	Yes	No	N/A
My child's other biologic parent	o	o	o
My other child(ren)	o	o	o
My siblings	o	o	o
My parents	o	o	o
My other biological family members **(If yes)** Please specify: _____	o	o	o

18. On a scale of 1 to 5, how important were each of the following reasons for sharing your child's genetic test results with blood relatives?

	Not at all important (1)	2	3	4	Very Important (5)
To give my blood relatives information about their genetic risk	o	o	o	o	o
To encourage my blood relatives to have genetic testing	o	o	o	o	o
The doctor/genetic counselor encouraged me to share the information with blood relatives	o	o	o	o	o
So my relatives could make family planning decisions	o	o	o	o	o
To share the information I learned because I thought it was interesting	o	o	o	o	o
To share my feelings about my genetic test results	o	o	o	o	o
So I could get help from blood relatives with coordinating and planning for things like appointments and other health-related responsibilities (for example, going to doctors' appointments, getting child care, getting transportation, etc.)	o	o	o	o	o

19. Are there any other reasons that influenced your decision to share the results with blood relatives? _____

20. (**SKIP IF ANSWERED YES or I haven't yet, but plan to TO QUESTION 16)** On a scale of 1 to 5, how important were each of the following reasons for not sharing your child's genetic test results with blood relatives?

	Not at all important (1)	2	3	4	Very Important (5)
I do not want to worry or upset them	o	o	o	o	o
I would have to talk to a blood relative I'm not close to/prefer not to talk to	o	o	o	o	o
I don't have contact information for my blood relatives	o	o	o	o	o

I have privacy concerns about sharing this information with my relatives	o	o	o	o	o
I do not know how to explain the genetic results to my relatives	o	o	o	o	o
I don't think this information is useful for my relatives	o	o	o	o	o
I'm having trouble coping with my child's results	o	o	o	o	o
I'm overwhelmed with my child's medication condition	o	o	o	o	o
I'm worried that my relatives will treat my child differently	o	o	o	o	o

21. (**SKIP IF ANSWERED YES OR I haven't Yet but plan to, TO QUESTION 16**) Are there any other reasons that influenced your decision not to share the results with blood relatives?

    _____

22. What type of information did you share with blood relatives? Please check all that apply.

    - ☐ General information about the study results
    - ☐ Detailed information about the genes they tested
    - ☐ My relative's risk of having a condition
    - ☐ Information about the possibility of being treated unfairly based on the study results
    - ☐ Recommendations of ways to prevent illness
    - ☐ Recommendations for more screening and testing
    - ☐ Feelings about the study results
    - ☐ Other, please specify: _____

23. How did you share information about your child's genetic test results with your blood relatives? Please check all that apply.
    - ☐ In person
    - ☐ By phone
    - ☐ By letter
    - ☐ By email
    - ☐ Through social Media
    - ☐ Other, please specify: _____

24. Did you discuss your child's genetic test results with your child's doctor(s) or health care provider(s)?
    - ○ Yes
    - ○ Not yet, but I plan to
    - ○ No and I don't plan to (**Skip to Question 26**)

25. **If you answered yes to question 24**. With whom did you discuss your child's results? Please indicate which doctor(s) or health care provider(s) you shared results with.
    - ○ Primary care doctor (pediatrician, family doctor) or nurse practitioner
    - ○ NICU doctor or nurse practitioner
    - ○ Neurologist
    - ○ Another specialist _____

26. If you answered "no and I don't plan to", why not? _____

27. **If you answered yes to question 26**. Did your child's doctor(s) or health care provider(s) make any recommendations based on the test result?
    - ○ Yes
    - ○ No
    - ○ I don't know / don't remember

28. **If you answered yes to question 27.** If yes, what were the recommendations (check all that apply)?
    a. Start a medicine
    b. Stop a medicine
    c. Change a medicine (change a dose of medicine)

    d. Start therapy (physical therapy, speech therapy, etc.)
    e. Stop therapy (physical therapy, speech therapy, etc.)
    f. Make changes to my child's therapy (physical therapy, speech therapy, etc.)

    g. Order a medical test (x-ray, CAT scan, heart test, etc.)
    h. Cancel a medical test (x-ray, CAT scan, heart test, etc.)

    i. Refer my child to another healthcare provider
    j. Cancel a referral to a healthcare provider

    k. Change my child's diet
    l. Start my child on vitamins or supplements

29. **If you checked j.** What kind of healthcare provider(s) did your child's doctor or nurse practitioner refer him/her to? (Check all that apply)
    a. Cardiologist (heart doctor)
    b. A neurologist (brain doctor)
    c. A geneticist (genetics doctor)
    d. A nephrologist (kidney doctor)
    e. A dermatologist (skin doctor)
    f. A pulmonologist (lung doctor)
    g. An immunologist (immune system doctor)
    h. A hematologist (blood doctor)
    i. An oncologist (cancer doctor)
    j. An audiologist (hearing doctor)
    k. A dentist
    l. A social worker

m. A hospice or palliative care program
n. Other _____

30. Sometimes children qualify for clinical trials because they have received certain genetic test results. Was your child's doctor able to find a clinical trial for your child?
    - ○ Yes
    - ○ No
    - ○ I don't remember
    - ○ I don't know

31. **If answered no to 30.** Sometimes families find out their child doesn't qualify for a certain clinical trial because they have received certain genetic test results. Did this happen to your child because of his/her genetic test results?
    - ○ Yes
    - ○ No
    - ○ I don't remember
    - ○ I don't know

The last few questions have been asking you about what your child's doctors or healthcare providers have recommended for your child. Now we want to know which of these things you've been able to do.

32. **The following options are only presented if they were selected in the previous question (question 28).** Which of the following have you and your child been able to do so far as a result of your child's genetic results? (check all that apply)
    a. Start a medicine
    b. Stop a medicine
    c. Change a medicine

    d. Start a kind of therapy (physical therapy, speech therapy, etc.)
    e. Stop a kind of therapy (physical therapy, speech therapy, etc.)
    f. Make changes to a therapy (physical therapy, speech therapy, etc.)

    g. Get a medical test (x-ray, CAT scan, heart test, etc.)
    h. Avoid getting a medical test (x-ray, CAT scan, heart test, etc.)

    i. See another healthcare provider
    j. Avoid having to see another healthcare provider

    k. Change my child's diet
    l. Start my child on vitamins or another supplement

33. **If you checked g.** What kind of medical test(s) has your child had as a result of the genetic test results? (Check all that apply)
    a. Another genetic test
    b. Another type of blood test
    c. An X-ray
    d. An MRI

e. A CAT scan
f. A heart ultrasound or ECHO
g. An ultrasound of another part of the body
h. A test that required a surgery (such as a spinal tap or biopsy)
i. Another kind of surgery (getting a g-tube or trach)
j. A test of brain electricity (EEG)
k. A test of heart electricity (EKG)
l. A test of muscle electricity (EMG)
m. A test of nerve electricity (nerve conduction test)
n. Other _____

34. **If you checked i.** What kind of other healthcare provider(s) has your child seen as a result of his/her genetic test results? (Check all that apply)
    a. A cardiologist (heart doctor)
    b. A neurologist (brain doctor)
    c. A geneticist (genetics doctor)
    d. A nephrologist (kidney doctor)
    e. A dermatologist (skin doctor)
    f. A pulmonologist (lung doctor)
    g. An immunologist (immune system doctor)
    h. A hematologist (blood doctor)
    i. An oncologist (cancer doctor)
    j. An audiologist (hearing doctor)
    k. A dentist
    l. A social worker
    m. A hospice or palliative care program
    n. Other _____

35. **If at least one item was checked on 28, but no items were checked on 32.** It looks like your child's doctor or nurse practitioner recommended some things, but you haven't been able to do those things. Why is that?____

36. **If at least one item was checked on 28, but no items were checked on 32.** Do you still plan on doing some of these things?
    ○ Yes
    ○ No

37. **If you responded "no" on 36.** You said you don't plan to do the things your child's doctor(s) or health care provider(s) proposed. Why is that?____

38. Since you got your child's genetic test results, have you been told by a doctor or other healthcare provider that your child's diagnosis might affect future pregnancies in your family?
    ○ Yes
    ○ No
    ○ Not applicable (I wasn't planning on having more kids)

Appendix 8: DSMB Conflict of Interest Statement

DNA Sequencing for Newborn Nurseries in the South (SouthSeq)

Board Conflict of Interest and Confidentiality Statement

Members of the Data and Safety Monitoring Board (DSMB) are selected to reflect the disciplines and medical specialties necessary to interpret data from the study(ies) named above. All members of the DSMB are required to be completely independent of the studies being reviewed and all members are required to sign a DSMB Conflict of Interest and Confidentiality statement.

A conflict of interest exists when a DSMB member has a financial interest that could be affected by the study or a relationship with a study investigator that is likely to bias his or her review of it. An individual who has a financial conflict of interest with a study may not participate on its DSMB unless he or she receives a waiver from the NIH Institute or Center ethics official. Appearance of a conflict of interest should be avoided whenever possible; however, if it is established that there is no real conflict of interest and the ethics official determines that the integrity of the study would not be impaired, the individual in question may participate in the DSMB. Such actions by the ethics official shall be made in writing and become part of the DSMB record.

It is the responsibility of each DSMB member to notify the NIEHS ethics official of any conflict of interest situations that may pertain, whether real or apparent. Conflict of interest can include personal, professional, financial or proprietary interest. Potential conflicts that develop during the member's tenure on the DSMB must also be disclosed. Disclosure will serve to protect the integrity of the DSMB and its role in monitoring and oversight of clinical studies and will also help protect the DSMB member from allegations of inappropriate behavior. Failure to disclose a conflict of interest will lead to removal from the DSMB. The ethics official may independently determine that a particular situation involves a conflict of interest and consequently exclude the member from the DSMB.

The following should be considered in assessing whether or not there is a conflict of interest.

- **Employment:** Current or recent (within the past year) employment (e.g., full- or part-time salaried employee, consultant, or other recipient of honoraria; member of board of directors or advisory committee) with an institution or organization that is directly involved with conducting the research or that could receive financial benefit from the results of the study would generally be considered to be a conflict of interest.

- **Financial Benefit:** An individual who has received or could receive direct financial benefit, other than from employment, of any amount from an individual, institution or organization involved with the study, other than the NIH, may have a conflict of interest. Financial benefit may include stock ownership or prior research funding from an institution or organization involved in the study, whose product is being evaluated in the study or competes with a product being evaluated in the study, or which could otherwise

receive financial benefit from the results of the study. Regardless of the level of financial involvement, if the individual feels unable to provide objective advice, he/she must not serve on the DSMB.

- **Intellectual property:** Intellectual property ownership, such as copyrights, patents, trademarks, trade names, or trade secrets related to the study may be considered a conflict of interest.

- **Relatives or Associates:** A conflict of interest may exist if a close relative or professional associate of a member receives or could receive financial benefits from or provides financial benefits to the study or investigators. An apparent conflict of interest may also exist with a professional associate that includes any colleague, scientific mentor, or student with whom the DSMB member is currently conducting research or other professional activities or with whom the DSMB member has personally worked or published with within three years.

- **Longstanding Disagreements:** A conflict of interest may exist when a DSMB member has had longstanding scientific or personal differences with the study or its investigator(s) that may compromise objectivity.

Confidentiality and Non-Disclosure of Materials and Proceedings

Materials and information made available to the DSMB that are not in the public domain, as well as the discussions that take place during the meetings, are strictly confidential and must not be disclosed to or discussed with anyone who is not a member of the DSMB. Furthermore, confidential information obtained as a DSMB member may not be used by the member for personal benefit or for the benefit of the member's family, associates, or of organizations with which the individual is associated or has a financial involvement.

DSMB Certification Regarding Conflict of Interest, Confidentiality, and Non-Disclosure

NAME: _____

Primary employer: _____

[ ] I have read the attached DSMB Conflict of Interest and Confidentiality Form and hereby certify that I do not have a conflict of interest or have discussed and resolved with the ethics official any potential conflict of interest with the study reviewed by this DSMB.

[ ] I fully understand the confidential nature of the DSMB process and agree not to disclose or discuss the materials associated with the review or substance of any confidential discussions about the studies with any individual not a member of the DSMB or to use the information for my personal benefit or the benefit of others.

Signature: _____

Date: _____

Appendix 9: DSMB Plan and Charter

Data and Safety Monitoring Board (DSMB) Charter

This DSMB has been convened as a method for additional monitoring of study procedures. The safety of the study participants is the highest priority for this project. The ability to make appropriate, sound scientific decisions regarding the outcome of each participant, as early as possible, is the top priority. The DSMB will be comprised of three scientists/clinicians who are independent of the study.

DSMB Responsibilities

- Review the outcome instruments, informed consent documents and plans for data safety and monitoring
- Evaluate the progress of the clinical trial, including periodic assessments of data quality and timeliness, recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect study outcome
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial
- Review study performance, make recommendations and assist in the resolution of problems reported by the Principal Investigator(s) (Clinical Trial PIs)
- Protect the safety of the study participants and monitor the rate and scope of errors reported in the experimental arm of the clinical trial.
- Report on the safety and progress of the trial
- Make recommendations to the PIs concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the intervention under study
- The PIs will report findings of the DSMB to NGHRI in accordance with reporting guidelines
- Ensure the confidentiality of the study data and the results of monitoring
- Assist in commenting on any problems with study conduct, enrollment, sample size, and/or data collection.

The DSMB will discharge itself from its duties when the last participant completes the clinical trial.

DSMB Board Process

At the initial meeting the DSMB will discuss the protocol, suggest modifications, and establish guidelines to study monitoring by the Board. The DSMB Chairperson, in consultation with the Principal Investigator and the study team, will prepare the agenda to address the review of provider education materials, modifications to the study protocol and informed consent document, initiation of the trial, reporting of return of results errors, and statistical analysis plan. Meetings of the DSMB will be held annually or more frequently at the discretion of the DSMB, if necessary. The study investigators or their designees will attend the meetings. An emergency meeting of the DSMB may be called at any time by the Chairperson or by the PIs should safety questions or other unanticipated problems arise. The meetings are closed to the public because discussions may address confidential participant data. The meetings are attended by the Principal Investigators and members of their staff. Meetings may be convened as conference calls, as well as in-person.

DSMB Meeting Format

DSMB meetings will consist of open and closed sessions. Discussion held in all sessions is confidential. The PI and key members of the study team attend the open sessions. Discussion will focus on the

conduct and progress of the study, including participant accrual, protocol compliance, and problems encountered.

Each meeting must include a recommendation to continue or to terminate the study and whether the DSMB has any concerns about participant safety made by a formal DSMB majority or unanimous vote. Should the DSMB decide to issue a termination recommendation, the full vote of the DSMB is required. In the event of a split vote, majority vote will rule and a minority report will be appended. The DSMB Chair provides the tiebreaking vote in the event of a 50-50 split vote. A recommendation to terminate the study may be made by the DSMB at any time by majority vote. The Chair should provide such a recommendation to the PIs immediately by telephone and email.

Meeting Materials

A DSMB interim report template will be prepared by the study staff, typically by the study statistician, and will be reviewed by the DSMB members at the first meeting. The format and the content of the reports for, and the plans for, interim analyses will be finalized and approved at the initial DSMB meeting, although changes throughout the trial may be requested by the Board. The reports will list and summarize safety data and describe the status of the study. All meeting materials will be sent to PIs who will forward the materials to the DSMB between 7 to 14 days prior to the meeting. The reports will be numbered and provided in sealed envelopes and can be returned within an express mailing package or by secure email, as the DSMB prefers. In select cases, PIs may approve direct mailing of the reports from the study to the DSMB.

DSMB Reports

Reports generally include administrative reports by site that describe participants screened, enrolled, completed, and discontinued, as well as baseline characteristics of the study population, and interim error statistics from HudsonAlpha obtained through review of the ROR sessions (i.e. errors tracking). Other general information on study status may also be presented. The DSMB may direct additions and other modifications to the reports on a one-time or continuing basis. The reports may also contain data on study outcomes, including safety data, and perhaps efficacy data.

A formal report containing the recommendations for continuation of, or modification to the study will be prepared by the DSMB Chairperson, PIs, or designee. The draft report will be sent to the DSMB members for review and approval. It is the responsibility of the PIs to distribute the DSMB recommendation to all co-investigators and to ensure that copies are submitted to the IRBs. As previously stated, the formal DSMB report must include a recommendation to continue or to terminate the study. This recommendation should be made by formal majority vote. A termination recommendation may be made by the DSMB at any time by majority vote. In the event of a split vote in favor of continuation, a minority report will be contained within the regular DSMB report.

DSMB Confidentiality

All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.

Appendix 10: Training Log

Training Log

Sponsor:	NHGRI
Protocol:	DNA Sequencing for Newborn Nurseries in the South (SouthSeq)
Site/PI Name:	
Training Date:	
Trainer/Affiliation	
Subject:	

Meeting Participants

Name	Signature	Study Role/Responsibility

Appendix 11: Screening Log

Study: SouthSeq

Principal Investigators: Bruce Korf, MD, PhD (University of Alabama at Birmingham); Greg Cooper, PhD (HudsonAlpha); Greg Barsh, MD (HudsonAlpha)

Procedure: Whole Genome Sequencing (WGS)

Protocol Version: TBN

Target Goal: 800 families with proband sequenced

Screening ID	Proband Demographics			Date of Screening	Date of Consent MM/DD/YYYY	SouthSeq ID	Eligible for Enrollment (Yes/No)	If not enrolled, provide a reason	If other, describe	Eligible but declined						
	Gender	Ethnicity	Race							Completed decliner survey (Yes/No)	Enrolled in Clinical Trial Yes/No	Completed W9 Yes/No	Genome Gateway Account Created? (Yes/No)	Consent version (Approval Date)	Awaiting RoR	Additional Notes

Appendix 12: Communication Log

Communication Log

Sponsor:	NHGRI
Protocol:	DNA Sequencing for Newborn Nurseries in the South (SouthSeq)
Site/PI Name:	

Calls/Meetings

Name	Recipient	Subject	Notes

Appendix 13: Return of Results (ROR) Audio Recording

Audio Recording Process in SouthSeq

Audio recorder supplies:

- Recorder, something like https://www.amazon.com/Sony-ICDPX370-Digital-Recorder-Built/dp/B06XFTWCBJ/ref=sr_1_4?ie=UTF8&qid=1547149909&sr=8-4&keywords=digital+recorder+built+in+usb
- Phone adapter https://www.amazon.com/gp/product/B000KL0XA6/ref=oh_aui_detailpage_o08_s00?ie=UTF8&psc=1
- Batteries

Protocol:

1. Make sure recorder is charged/has power (prior to result appointment)

2. At beginning of RoR session, prior to starting recording, say the following:

"I want to remind you that as part of the SouthSeq study, we are audio-recording conversations about test results. The reason we are recording our meeting today is so that study researchers can learn more about how healthcare providers talk about genetics and describe test results. Only the study team will have access to the recording. Is it OK that I turn on the audio recorder now?"

If yes → Turn on audio recorder and proceed with #5
If no → Read this fallback text:

"The study requests recording of the conversations when participants receive results. The reason for this request is that is important for the study to learn from our experiences and how we describe results to you. Is there anything else I can explain to make you more comfortable about it?"

If yes → Answer questions and ask again for permission to turn on audio recorder
If no → Is the participant in the standard of care arm (randomized to disclosure by genetics provider)?

If yes (disclosure by genetics provider) → Proceed with #3
If no (disclosure by non-genetics provider) → Proceed with #4

3. The participant can opt-out of audio recording and still receive results at the current time. Put away the audio recorder and proceed with the disclosure of results. Following the disclosure, message the HudsonAlpha genetic counselor assigned to your site* to say that the participant (give study ID#) declined audio recording. Do not proceed with any further steps.

4. The participant can opt-out of audio recording but unfortunately cannot receive results from a non-genetics provider without audio recording permission. Tell the family:

   "Unfortunately, because of our research plan and for your safety, I cannot discuss the results with you right now without using audio recording. If you choose to opt out of having this conversation recorded, we can have a genetic counselor for the study discuss the results with you at another time. Is that what you would like to do?"

   If yes → Apologize for the inconvenience, tell them a study genetic counselor will be in touch soon, and that the results will be placed into the child's medical record once the results have been discussed with the family. Notify the study coordinator at the site and the HudsonAlpha genetic counselor assigned to your site of status.*

   If no (would like to proceed with audio recording) → Proceed to step 5

5. State the proband's study ID# clearly on the recording, along with the date and the name of the provider doing the result return.

6. Disclose the results to the participant family. Elicit and answer questions from the family.

7. Once the result disclosure conversation is concluded, end the recording.

8. Give audio recorder back to site coordinator/research nurse.

9. Study Coordinator: Save the audio file to a secure, HIPAA compliant computer or storage drive using the study ID number as the file name, and upload the file within Genome Gateway to the HudsonAlpha genetic counselor assigned to your particular site.* This is done by selecting files on the left side menu, clicking on the person you want to send the file to from the list of people, and then clicking the "add file" button in the top right corner of the screen. This will allow you to select a file from your computer to send.

10. Study Coordinator: Maintain an electronic, backup copy of all audio files on a computer prior to deleting the files from the recording device.

11. HudsonAlpha genetic counselors: review the audio recording for disclosures in the experimental arm of the trial (disclosure by non-genetics provider). This review will occur within a week for negative results, within 72 business hours for positive and uncertain results and any errors will be tracked (minor errors, major errors, safety errors). All errors will be tracked for future aggregate analysis. Only major/safety errors will trigger real-time feedback to the disclosing provider from the genetic counselor. Store all audio files in a centralized, electronic location that is HIPAA compliant, organized by site, randomization arm, and study ID.

***HudsonAlpha Genetic Counselor contacts by site:**

Alabama: Meagan Cochran
Mississippi: Whitley Kelley
Louisiana: Veronica Greve

Appendix 14: Certified Letter Template

[Date]

Guardian of **[Patient Name]**

Patient: **[Patient Name]**
Date of Birth: **[Patient DOB]**

Dear family of **[Patient Name]**:

Multiple attempts to reach you via phone have been unsuccessful. See enclosed your child's results from the SouthSeq research study that you enrolled in on **[Enrollment Date]**. Upon review of these results, please call **[Provider Name]**, **[Recruitment Site, Provider Title]** for SouthSeq at **[Provider Phone Number]**. Thank you.

Sincerely,

[Provider Name]
[Provider Title]

Appendix 15:
Return of Results Workflow

SouthSeq Result Return Workflow
for Site Coordinators

Return of Results for Cases randomized to Standard of Care Arm (GC disclosure)

Preparation

1. Receive message within Genome Gateway from HA genetic counselor that a case has results ready to be returned and has been randomized to GC disclosure. Message will include participant ID. Site GC will also receive this message.
2. Review result report, attached to the message sent in Genome Gateway. Reach out to HA genetic counselor with any questions or concerns.
3. Return of result visit gets scheduled with primary parent contact. Depending on site-specific procedures this could be done by the GC, site coordinator, or administrative support. Encourage in-person disclosure if possible. At this time, confirm that the participant's address has not changed. If it has, please update it in the demographics section of Genome Gateway and have them complete a new W9 form. The new W9 should be uploaded to the participants account and to the "Clinical Trial" account in Genome Gateway.

Disclosure (via phone)

1. Site genetic counselor will call the primary parent contact at the scheduled time.
2. RESULTS ARE DISCLOSED by the site genetic counselor.
3. Site genetic counselor will be in communication with you during the disclosure to let you know if they successfully connected with the family and when the conversation is finished.
4. Once result disclosure is in process, log into Genome Gateway and assign the "In-clinic Survey" and "At-Home Survey" to the participant.
5. Site genetic counselor will transfer the call to you when disclosure is over, if you are available. If you are not available at that time, call the primary parent contact back within the next 72 hours. Attempt to reach multiple times if no answer.
6. Over the phone, have primary parent contact complete the "In-clinic survey" by asking the questions and marking their response on a paper version of the survey. The paper survey should then be scanned and uploaded to the participant's account and to the Clinical Trial account. If the participants decide not to do the survey over the phone, please remind them to log into Genome Gateway to complete them and remind them that compensation will be provided for completed surveys.
7. Discuss next steps in SouthSeq for family to expect (see below "Next Steps" list).
8. Find out if they remember their Genome Gateway username/password and website? If not, give it to them. If they don't remember their password there is a link on the GG website they can click to re-set. (participants.southseq.org)

Disclosure (in-person)

1. RESULTS ARE DISCLOSED by the site genetic counselor.

2. Site genetic counselor will be in communication with you to let you know if the family showed up and when the conversation is finished.
3. Once result disclosure is in process, log into Genome Gateway and assign the "In-Clinic Survey" and "At-Home Survey" to the participant.
4. Site genetic counselor will let you know when the result disclosure is finished and the family is ready to complete the in-clinic survey.
5. Go into room with study iPad and have family log into their Genome Gateway account (participants.southseq.org). If they do not remember their password there is a link on the website to re-set it via email.
    a. If participants cannot get into their email to reset a forgotten password, you can contact your HA genetic counselor to have it manually reset.
    b. If technology fails completely, have a paper version of the surveys available as a last resort. However, it is critical to get families into Genome Gateway and familiar with it to increase future questionnaire completion.
6. Discuss next steps in SouthSeq for family to expect (see attached "Next Steps" list).

Follow-up

1. Site genetic counselor is responsible for completing "Result Return" provider survey, uploading audio file, and mailing copies of results for phone disclosures.
2. Ensure copy of result report gets in the patient's medical record.

Return Results for Cases randomized to Experimental Arm (NICU disclosure)

Preparation

1. Receive message within Genome Gateway from HA genetic counselor that a case has results ready to be returned and has been randomized to NICU non-genetic professional disclosure. Message will include participant ID.
2. Review result report, attached to the message sent in Genome Gateway. Reach out to HA genetic counselor with any questions or concerns.
3. Return of result visit gets scheduled with primary parent contact. Depending on site specific procedures this could be done by the GC, site coordinator, or administrative support. Encourage in-person disclosure if possible. At this time, confirm that the participant's address has not changed. If it has, please update it in the demographics section of Genome Gateway and have them complete a new W9 form. The new W9 should be uploaded to the participants account and to the "Clinical Trial" account in Genome Gateway.
4. Within NICU determine which provider will be doing the disclosure. Communicate this name to your HA genetic counselor when it is known. (This process will be site specific, once you have an established process, please send a description of that process to Candice Finnila.)

Disclosure (via phone)

9. Disclosing NICU provider will call the primary parent contact at the scheduled time.
10. RESULTS ARE DISCLOSED by the NICU provider.

11. NICU provider will be in communication with you to let you know if they successfully connected with the family and when the conversation is finished.
12. Once result disclosure is in process, log into Genome Gateway and assign the "In-clinic Survey" and "At-Home Survey" to the participant.
13. NICU provider will transfer the call to you when disclosure is over, if you are available. If you are not available at that time, call the primary parent contact back within the next 72 hours. Attempt to reach multiple times if no answer.
14. Over the phone, have primary parent contact complete the "In-clinic survey" by asking the questions and marking their response on a paper version of the survey.
15. Discuss next steps in SouthSeq for family to expect (see below "Next Steps" list).
16. Find out if they remember their Genome Gateway username/password and website? If not, give it to them. If they don't remember their password there is a link on the GG website they can click to re-set. (participants.southseq.org)

Disclosure (in-person)

7. Make sure disclosing provider has audio recording equipment (recorder with charge/batteries/available storage).
8. Make sure disclosing provider has a printed copy of the report to give to the family.
9. RESULTS ARE DISCLOSED by the NICU provider.
10. NICU provider will be in communication with you during the disclosure to let you know if the family showed up and when the conversation is finished.
11. Once result disclosure is in process, log into Genome Gateway and assign the "In-Clinic Survey" and "At-Home Survey" to the participant.
12. NICU provider will let you know when the result disclosure is finished and the family is ready to complete the in-clinic survey.
13. Go into room with study iPad and have family log into their Genome Gateway account (participants.southseq.org). If they do not remember their password there is a link on the website to re-set it via email.
    a. If participants cannot get into their email to reset a forgotten password, you can contact your HA genetic counselor to have it manually reset.
    b. If technology fails completely, have a paper version of the surveys available as a last resort. However, it is critical to get families into Genome Gateway and familiar with it to increase future questionnaire completion.
14. Discuss next steps in SouthSeq for family to expect (see attached "Next Steps" list).

Follow-up

1. Get audio recorder back from NICU provider.
2. Upload audio recording to computer. Keep copy stored locally on computer. Send file to HA genetic counselor in Genome Gateway. Do NOT upload recording to participant's account, should be uploaded directly to the HA genetic counselor.
3. (If result return was done by phone) Mail hard copy of result letter to participant.
4. Ensure copy of result report gets in the patient's medical record.

<u>Certified Letters (if needed)</u>

1. Certified letter disclosure should be triggered if you cannot reach family after 2 attempts to primary phone plus one attempt at non-household contact
2. Alert site genetic counselor when a case reaches this threshold and a certified letter should be sent.
3. Certified letters will be sent by the site genetic counselor.

Re-analysis/Amended Reports (if new information leads to change in result)

1. Receive a message from HA GC that an amended report is available, amended report will be uploaded in Genome Gateway.
2. Review result report, attached to the message sent in Genome Gateway. Reach out to HA genetic counselor with any questions or concerns.
3. Amended result will be returned by same type of provider (same study arm) that returned the initial result (genetic counselor or NICU provider). Does not have to be the same exact provider.
4. For NICU provider disclosures, determine which provider will be doing the disclosure. Communicate this name to your HA genetic counselor when it is known via Genome Gateway.
5. Amended result is communicated by appropriate provider (likely by phone, but any mode of communication is fine). Utilize audio recorder as described elsewhere.
6. Follow-up the same as for initial disclosure (audio recordings sent to HA, copy of results mailed to participant, copy of results into EMR, update the child's clinical team, if possible).

Next Steps (what participants can expect):

- Surveys:
  - Encourage survey completion!
  - There is financial compensation for completion of surveys ($25/completed survey).
  - There are two brief surveys we will ask you to do on Genome Gateway right away after our conversation.
  - At several points over the next several months there will be new surveys to complete in Genome Gateway (family will receive message/email/text when it is time).
- Result Report:
  - A copy of the result report will be available to view/download in Genome Gateway within next couple of days.
  - A paper copy will also be mailed (if phone disclosure).
  - A copy will also be put in child's medical record.
- Education:
  - Some additional educational information about genetics and the result will be available in Genome Gateway a couple of days post-RoR (family will receive a message/email/text when they are available).
  - Educational materials can be accessed at any time in the future using Genome Gateway.

- Clinical Follow-up:
    - If in-patient disclosing provider will discuss result with [relevant doc] and they will make decisions about management. If out-patient, encourage patient to do whatever is needed to get looped into genetics.
    - Encourage patients to take copies of results reports to future appointments.

Audio Recording Protocol in SouthSeq

1. Make sure recorder is charged/has power (prior to result appointment)

2. At beginning of RoR session, prior to starting recording, say the following:

"I want to remind you that as part of the SouthSeq study, we are audio-recording conversations about test results. The reason we are recording our meeting today is so that study researchers can learn more about how healthcare providers talk about genetics and describe test results. Only the study team will have access to the recording. Is it OK that I turn on the audio recorder now?"

If yes → Turn on audio recorder and proceed with #5
If no → Read this fallback text:

"The study requests recording of the conversations when participants receive results. The reason for this request is that is important for the study to learn from our experiences and how we describe results to you. Is there anything else I can explain to make you more comfortable about it?"

If yes → Answer questions and ask again for permission to turn on audio recorder
If no → Is the participant in the standard of care arm (randomized to disclosure by genetics provider)?

If yes (disclosure by genetics provider) → Proceed with #3
If no (disclosure by non-genetics provider) → Proceed with #4

3. The participant can opt-out of audio recording and still receive results at the current time. Put away the audio recorder and proceed with the disclosure of results. Following the disclosure, message the HudsonAlpha genetic counselor assigned to your site* to say that the participant (give study ID#) declined audio recording. Do not proceed with any further steps.

4. The participant can opt-out of audio recording but unfortunately cannot receive results from a non-genetics provider without audio recording permission. Tell the family:

   "Unfortunately, because of our research plan and for your safety, I cannot discuss the results with you right now without using audio recording. If you choose to opt out of having this conversation recorded, we can have a genetic counselor for the study discuss the results with you at another time. Is that what you would like to do?"

If yes → Apologize for the inconvenience, tell them a study genetic counselor will be in touch soon, and that the results will be placed into the child's medical record once the results have been discussed with the family. Notify the study coordinator at the site and the HudsonAlpha genetic counselor assigned to your site of status.*

If no (would like to proceed with audio recording) → Proceed to step 5

5. State the proband's study ID# clearly on the recording, along with the date and the name of the provider doing the result return.

6. Disclose the results to the participant family. Elicit and answer questions from the family.

7. Once the result disclosure conversation is concluded, end the recording.

8. Give audio recorder back to site coordinator/research nurse.

9. Study Coordinator: Save the audio file to a secure, HIPAA compliant computer or storage drive using the study ID number as the file name, and upload the file within Genome Gateway to the HudsonAlpha genetic counselor assigned to your particular site.* This is done by selecting files on the left side menu, clicking on the person you want to send the file to from the list of people, and then clicking the "add file" button in the top right corner of the screen. This will allow you to select a file from your computer to send.

10. Study Coordinator: Maintain an electronic, backup copy of all audio files on a computer prior to deleting the files from the recording device.

11. HudsonAlpha genetic counselors: review the audio recording for disclosures in the experimental arm of the trial (disclosure by non-genetics provider). This review will occur within a week for negative results, within 72 business hours for positive and uncertain results and any errors will be tracked (minor errors, major errors, safety errors). All errors will be tracked for future aggregate analysis. Only major/safety errors will trigger real-time feedback to the disclosing provider from the genetic counselor. Store all audio files in a centralized, electronic location that is HIPAA compliant, organized by site, randomization arm, and study ID.

***HudsonAlpha Genetic Counselor contacts by site:**

Alabama: Meagan Cochran
Mississippi: Whitley Kelley
Louisiana: Veronica Greve

SouthSeq Result Return Workflow
for Site Genetic Counselors

Variant Review for Cases with WGS findings

1. Receive notification via email that a case has findings and is ready for review in Freedcamp (SouthSeq-VRC Reports)
2. Review case/findings in Freedcamp and provide comments as appropriate (within 24-48 business hours)

Return Results for Cases randomized to Clinical Trial Standard of Care Arm

Preparation

1. Receive message within Genome Gateway from HA genetic counselor that a case has results ready to be returned (and has been randomized to GC disclosure). Message will include participant ID.
2. Review result report, attached to the message sent in Genome Gateway. Reach out to HA genetic counselor with any questions or concerns.
3. Return of result visit gets scheduled with primary parent contact. Depending on site specific procedures this could be done by the GC or by administrative support. Encourage in-person disclosure if possible.

Disclosure (via phone)

1. Connect recording equipment to phone (phone adapter and recorder).
2. At the scheduled time, call the primary parent contact. Confirm it is a good time to discuss SouthSeq results. Document who (all) is on the phone listening and their relationship to proband.
3. Read script from recording procedure and obtain permission to turn on recorder (see attached "Audio Recording Protocol").
4. Turn on recorder and state on the recording the participant study ID#.
5. DISCLOSE RESULTS TO FAMILY. Answer questions specific to result disclosure discussion, being careful not to extend discussion into initiating additional care management plans (management examples may still be discussed, just not *initiated* during this encounter).
6. Discuss next steps in SouthSeq for family to expect (see below "Next Steps" list).
7. Find out if they remember their Genome Gateway username/password and website? If not, give it to them. If they don't remember their password there is a link on the GG website they can click to re-set. (participants.southseq.org)
8. Wrap up conversation. End Recording.
9. Notify site study coordinator disclosure is finished, transfer call to study coordinator if available for post result surveys.

Disclosure (in-person)

1. Make sure recording equipment is available and ready.
2. Have printed copy of result report to give to family.
3. Document who (all) attends disclosure and their relationship to proband.

4. Read script from recording procedure and obtain permission to turn on recorder (see attached "Audio Recording Protocol").
5. Turn on recorder and state on the recording the participant study ID#.
6. DISCLOSE RESULTS TO FAMILY. Answer questions specific to result disclosure discussion, being careful not to extend discussion into initiating additional care management plans (management examples may still be discussed, just not *initiated* during this visit).
7. Discuss next steps in SouthSeq for family to expect (see attached "Next Steps" list).
8. Find out if they remember their Genome Gateway username/password and website? If not, give it to them. If they don't remember their password there is a link on the GG website they can click to re-set. (participants.southseq.org)
9. Wrap up disclosure. End Recording.
10. Notify site study coordinator disclosure is finished, study coordinator will come into the room to facilitate post result surveys.

Certified Letters (if needed)

1. Certified letter disclosure should be triggered if you cannot reach family after 2 attempts to primary phone plus one attempt at non-household contact.
2. Use certified mail to send result letter and SouthSeq cover letter. Depending on the site, this task could be done by the site coordinator or administrative support.
3. Complete "Result Return" questionnaire at time letter is sent.
4. If contact is made with the family, or if the letter is returned undeliverable, add this information to the "Result Return" survey (in the open text box) and submit it again.
5. Send HudsonAlpha GC message in Gateway to inform of that an update has been made.

Follow-up

1. Complete "Result Return" questionnaire in Genome Gateway (assigned to you by HA genetic counselor).
2. Upload audio recording to computer. Keep copy stored locally on computer. Send file to HA genetic counselor in Genome Gateway. Do NOT upload recording to participant's account, should be uploaded directly to the HA genetic counselor.
3. (If result return was done by phone) Mail hard copy of result letter to participant. Remember do not include any additional letters/notes/information.
4. Document results/disclosure clinically at institution. Pass result off to clinical team.

Re-analysis/Amended Reports (if new information leads to change in result)

1. Receive a message from HA GC that an amended report is available, amended report will be uploaded in Genome Gateway.
2. Contact the patient with the new information (likely by phone, but any mode of communication is fine). Utilize audio recorder as described elsewhere.
3. Complete "Amended Result Return" questionnaire in Genome Gateway (assigned to you by HA genetic counselor).
4. Upload audio recording to computer. Keep copy stored locally on computer. Send file to HA genetic counselor in Genome Gateway. Do NOT upload recording under participant's

account, label the audio file using the SouthSeq study ID instead and upload it to the HA GC only.

5. (If RoR by phone) Mail hard copy of result letter to participant. Remember do not include any additional letters/notes/information.
6. Document results/disclosure clinically at institution. Pass result off to clinical team.

Next Steps (what participants can expect):

- Surveys:
  - Encourage survey completion!
  - There is financial compensation for completion of surveys ($25/completed survey).
  - There are two brief surveys we will ask you to do on Genome Gateway right away after our conversation.
  - At several points over the next several months there will be new surveys to complete in Genome Gateway (family will receive message/email/text when it is time).
- Result Report:
  - A copy of the result report will be available to view/download in Genome Gateway within next couple of days.
  - A paper copy will also be mailed (if phone disclosure).
  - A copy will also be put in child's medical record.
- Education:
  - Some additional educational information about genetics and the result will be available in Genome Gateway a couple of days post-RoR (family will receive a message/email/text when they are available).
  - Educational materials can be accessed at any time in the future using Genome Gateway.
- Clinical Follow-up:
  - If in-patient still can say that you will discuss result with [relevant doc] and they will make decisions about management. If out-patient, encourage patient to do whatever is needed to get looped into genetics. Avoid doing clinical care during the research result disclosure.
  - Regardless, encourage patients to take copies of results reports to future appointments.

Audio Recording Protocol in SouthSeq

1. Make sure recorder is charged/has power (prior to result appointment)

2. At beginning of RoR session, prior to starting recording, say the following:

"I want to remind you that as part of the SouthSeq study, we are audio-recording conversations about test results. The reason we are recording our meeting today is so that study researchers can learn more about how healthcare providers talk about genetics and describe test results. Only the study team will have access to the recording. Is it OK that I turn on the audio recorder now?"

If yes → Turn on audio recorder and proceed with #5
If no → Read this fallback text:

"The study requests recording of the conversations when participants receive results. The reason for this request is that is important for the study to learn from our experiences and how we describe results to you. Is there anything else I can explain to make you more comfortable about it?"

If yes → Answer questions and ask again for permission to turn on audio recorder
If no → Is the participant in the standard of care arm (randomized to disclosure by genetics provider)?

If yes (disclosure by genetics provider) → Proceed with #3
If no (disclosure by non-genetics provider) → Proceed with #4

3. The participant can opt-out of audio recording and still receive results at the current time. Put away the audio recorder and proceed with the disclosure of results. Following the disclosure, message the HudsonAlpha genetic counselor assigned to your site* to say that the participant (give study ID#) declined audio recording. Do not proceed with any further steps.

4. The participant can opt-out of audio recording but unfortunately cannot receive results from a non-genetics provider without audio recording permission. Tell the family:

   "Unfortunately, because of our research plan and for your safety, I cannot discuss the results with you right now without using audio recording. If you choose to opt out of having this conversation recorded, we can have a genetic counselor for the study discuss the results with you at another time. Is that what you would like to do?"

If yes → Apologize for the inconvenience, tell them a study genetic counselor will be in touch soon, and that the results will be placed into the child's medical record once the results have been discussed with the family. Notify the study coordinator at the site and the HudsonAlpha genetic counselor assigned to your site of status.*

If no (would like to proceed with audio recording) → Proceed to step 5

5. State the proband's study ID# clearly on the recording, along with the date and the name of the provider doing the result return.

6. Disclose the results to the participant family. Elicit and answer questions from the family.

7. Once the result disclosure conversation is concluded, end the recording.

8. Give audio recorder back to site coordinator/research nurse.

9. Study Coordinator: Save the audio file to a secure, HIPAA compliant computer or storage drive using the study ID number as the file name, and upload the file within Genome Gateway to the HudsonAlpha genetic counselor assigned to your particular site.* This is done by selecting files on the left side menu, clicking on the person you want to send the file to from the list of people, and then clicking the "add file" button in the top right corner of the screen. This will allow you to select a file from your computer to send.

10. Study Coordinator: Maintain an electronic, backup copy of all audio files on a computer prior to deleting the files from the recording device.

11. HudsonAlpha genetic counselors: review the audio recording for disclosures in the experimental arm of the trial (disclosure by non-genetics provider). This review will occur within a week for negative results, within 72 business hours for positive and uncertain results and any errors will be tracked (minor errors, major errors, safety errors). All errors will be tracked for future aggregate analysis. Only major/safety errors will trigger real-time feedback to the disclosing provider from the genetic counselor. Store all audio files in a centralized, electronic location that is HIPAA compliant, organized by site, randomization arm, and study ID.

***HudsonAlpha Genetic Counselor contacts by site:**

Alabama: Meagan Cochran
Mississippi: Whitley Kelley
Louisiana: Veronica Greve

SouthSeq Result Return Workflow
for Site NICU Providers (non-genetic providers)

Variant Review for Cases with WGS findings

1. Receive notification via email that a case has findings and is ready for review in Freedcamp (SouthSeq-VRC Reports)
2. Review case/findings in Freedcamp and provide comments as appropriate (within 24-48 business hours)

Return Results for Cases randomized to Clinical Trial Experimental Arm

Preparation

1. Your SouthSeq site coordinator will receive a message within Genome Gateway from the HA genetic counselor that a case has results ready to be returned by a NICU provider. The result report will be uploaded in Genome Gateway to the coordinator.
2. Within NICU team it will be decided which NICU provider will do disclosure. Care should be taken to avoid having provider currently doing care of child do disclosure if possible.
3. Site coordinator will send you a copy of any result reports that you will be responsible for disclosing. This will be sent as a file in Genome Gateway.
4. Review result report. Reach out to HA genetic counselor* (via Genome Gateway) with any questions or concerns.
5. Site coordinator will work with you to schedule return of result visit with primary parent contact. Encourage in-person disclosure if possible.

Disclosure (via phone)

1. Connect recording equipment to phone (phone adapter and recorder).
2. At the scheduled time, call the primary parent contact. Confirm it is a good time to discuss SouthSeq results. Document who (all) is on the phone listening and their relationship to proband.
3. Read script from recording procedure and obtain permission to turn on recorder (see attached "Audio Recording Protocol").
4. Turn on recorder and state on the recording the participant study ID#.
5. DISCLOSE RESULTS TO FAMILY. Answer questions specific to result disclosure discussion, being careful not to extend discussion into initiating additional care management plans (management examples may still be discussed, just not *initiated* during this encounter).
6. Discuss next steps in SouthSeq for family to expect (see below "Next Steps" list).
7. Find out if they remember their Genome Gateway username/password and website? If not, give it to them. If they don't remember their password there is a link on the GG website they can click to re-set. (participants.southseq.org)
8. Wrap up conversation. End Recording.
9. Notify site study coordinator disclosure is finished, transfer call to study coordinator if available for post result surveys.

Disclosure (in-person)

1. Make sure recording equipment is available and ready.
2. Document who (all) attends disclosure and their relationship to proband.
3. Read script from recording procedure and obtain permission to turn on recorder (see attached "Audio Recording Protocol").
4. Turn on recorder and state on the recording the participant study ID#.
5. DISCLOSE RESULTS TO FAMILY. Answer questions specific to result disclosure discussion, being careful not to extend discussion into initiating additional care management plans (management examples may still be discussed, just not *initiated* during this visit).
6. Discuss next steps in SouthSeq for family to expect (see attached "Next Steps" list).
7. Find out if they remember their Genome Gateway username/password and website? If not, give it to them. If they don't remember their password there is a link on the GG website they can click to re-set. (participants.southseq.org)
8. Wrap up disclosure. End Recording.
9. Notify site study coordinator disclosure is finished, study coordinator to come into the room to facilitate post result surveys.

Follow-up

1. Complete "Result Return" questionnaire in Genome Gateway (assigned to you by HA genetic counselor). If the questionnaire has not yet been assigned with the correct participant ID send a message to the HA genetic counselor to have it assigned.
2. Give audio recorder back to site coordinator for audio file upload to HA
3. Document results/disclosure clinically at institution. Pass result off to clinical team.

Re-analysis/Amended Reports (if new information leads to change in result)

1. Site coordinator will receive a message from HA GC that an amended report is available, with a copy of the amended report.
2. Patient should be contacted with the new information (likely by phone, but any mode of communication is fine). Utilize audio recorder as described above. This re-contact does not have to be done by the same provider who did initial return, however the participant needs to remain the same study arm.
3. Complete "Amended Result Return" questionnaire in Genome Gateway (assigned to you by HA genetic counselor). If the questionnaire has not yet been assigned to you with the correct participant ID send a message to the HA genetic counselor to have it assigned.
4. Give audio recorder back to site coordinator for audio file upload to HA.
5. Document results/disclosure clinically at institution (i.e note encounter in the EMR, upload result letter, etc.). Pass result off to clinical team.

Next Steps (what participants can expect):

- Surveys:
  - Encourage survey completion!
  - There is financial compensation for completion of surveys ($25/completed survey).
  - There are two brief surveys we will ask you to do on Genome Gateway right away after our conversation.

    - At several points over the next several months there will be new surveys to complete in Genome Gateway (family will receive message/email/text when it is time).
- Result Report:
    - A copy of the result report will be available to view/download in Genome Gateway within next couple of days.
    - A paper copy will also be mailed (if phone disclosure).
    - A copy will also be put in child's medical record.
- Education:
    - Some additional educational information about genetics and the result will be available in Genome Gateway a couple of days post-RoR (family will receive a message/email/text when they are available).
    - Educational materials can be accessed at any time in the future using Genome Gateway.
- Clinical Follow-up:
    - If in-patient still can say that you will discuss result with [relevant doc] and they will make decisions about management. If out-patient, encourage patient to do whatever is needed to get looped into genetics/etc. Avoid doing clinical care during the research result disclosure.
    - Encourage patients to take copies of results reports to future appointments.

Audio Recording Protocol in SouthSeq

1. Make sure recorder is charged/has power (prior to result appointment)

2. At beginning of RoR session, prior to starting recording, say the following:

"I want to remind you that as part of the SouthSeq study, we are audio-recording conversations about test results. The reason we are recording our meeting today is so that study researchers can learn more about how healthcare providers talk about genetics and describe test results. Only the study team will have access to the recording. Is it OK that I turn on the audio recorder now?"

If yes → Turn on audio recorder and proceed with #5
If no → Read this fallback text:

"The study requests recording of the conversations when participants receive results. The reason for this request is that is important for the study to learn from our experiences and how we describe results to you. Is there anything else I can explain to make you more comfortable about it?"

If yes → Answer questions and ask again for permission to turn on audio recorder
If no → Is the participant in the standard of care arm (randomized to disclosure by genetics provider)?

If yes (disclosure by genetics provider) → Proceed with #3
If no (disclosure by non-genetics provider) → Proceed with #4

3. The participant can opt-out of audio recording and still receive results at the current time. Put away the audio recorder and proceed with the disclosure of results. Following the disclosure, message the HudsonAlpha genetic counselor assigned to your site* to say that the participant (give study ID#) declined audio recording. Do not proceed with any further steps.

4. The participant can opt-out of audio recording but unfortunately cannot receive results from a non-genetics provider without audio recording permission. Tell the family:

   "Unfortunately, because of our research plan and for your safety, I cannot discuss the results with you right now without using audio recording. If you choose to opt out of having this conversation recorded, we can have a genetic counselor for the study discuss the results with you at another time. Is that what you would like to do?"

If yes → Apologize for the inconvenience, tell them a study genetic counselor will be in touch soon, and that the results will be placed into the child's medical record once the results have been discussed with the family. Notify the study coordinator at the site and the HudsonAlpha genetic counselor assigned to your site of status.*

If no (would like to proceed with audio recording) → Proceed to step 5

5. State the proband's study ID# clearly on the recording, along with the date and the name of the provider doing the result return.

6. Disclose the results to the participant family. Elicit and answer questions from the family.

7. Once the result disclosure conversation is concluded, end the recording.

8. Give audio recorder back to site coordinator/research nurse.

9. Study Coordinator: Save the audio file to a secure, HIPAA compliant computer or storage drive using the study ID number as the file name, and upload the file within Genome Gateway to the HudsonAlpha genetic counselor assigned to your particular site.* This is done by selecting files on the left side menu, clicking on the person you want to send the file to from the list of people, and then clicking the "add file" button in the top right corner of the screen. This will allow you to select a file from your computer to send.

10. Study Coordinator: Maintain an electronic, backup copy of all audio files on a computer prior to deleting the files from the recording device.

11. HudsonAlpha genetic counselors: review the audio recording for disclosures in the experimental arm of the trial (disclosure by non-genetics provider). This review will occur within a week for negative results, within 72 business hours for positive and uncertain results and any errors will be tracked (minor errors, major errors, safety errors). All errors will be tracked for future aggregate analysis. Only major/safety errors will trigger real-time feedback to the disclosing provider from the genetic counselor. Store all audio files in a centralized, electronic location that is HIPAA compliant, organized by site, randomization arm, and study ID.

***HudsonAlpha Genetic Counselor contacts by site:**

Alabama: Meagan Cochran
Mississippi: Whitley Kelley
Louisiana: Veronica Greve

Statistical Analysis Plan

Statistical Analysis: Descriptive statistics were calculated by randomized group. Specifically, for continuous demographic variables, sample means and standard deviations were calculated. For categorical demographic variables, counts and sample proportions were calculated. To test for differences between the randomized groups regarding demographics, two-sample tests were conducted for continuous variables and Chi-square analyses categorical outcomes. Sample means and standard deviations were calculated by randomization group for the primary outcome (GCOS) and secondary outcomes (PUGS, PRU). For all the outcomes, sample means and standard deviations were calculated by genetic testing results (none, variant of unknown significant, pathogenic) within each randomized group. Margin of noninferiority was set per outcome. To test non-inferiority, a one-tailed two-sample test comparing the difference of means, calculated as mean score outcome score of mother's randomized to receive genetic results from genetic counselors minus the mean score outcome score of mother's randomized to receive genetic results from non-genetic providers, to the non-inferiority margin was conducted. The normality assumption was examined using normal-probability plots and histograms. The same testing strategy was used for stratified analyses to determine if non-inferiority could be declared by genetic result types. All tests utilized a Type I error rate of 0.025 and were conducted in SAS 9.4.

Primary outcome

Results of the non-inferiority analysis for the primary outcome of GCOS are first presented by all genetic results combined for each group and then stratified by genetic result type. To conduct a non-inferiority analysis, one must declare a difference between group means, called a non-inferiority margin, such that if the data provides statistically significant evidence that the difference of means is below that margin, then study can declare one group is non-inferior to the other. Non-inferiority designs are by design one-tailed hypothesis tests. Within our study, we sought to demonstrate that the Nongenetic providers are non-inferior to Genetic Counselors. We calculated the difference of means as the Genetic Counselor mean minus the NonGenetic Provider mean and based upon consultation with NIH, a non-inferiority margin of 10 points. We have chosen to conduct the test using a Type I error rate of 0.025. As can be seen in the Results Section, the mean and standard deviation of the Genetic Counselor group is 117.94 ± 13.85 and the mean and standard deviation of the Nongenetic Provider group is 117.19 ± 14.86. The observed difference between mean is less than 1 point. The test generates a p-value of <0.0001 when using a non-inferiority margin of 10. Using a Type I error rate of 0.025, we can conclude that nongenetic providers are non-inferior to genetic counselors when compared on the GCOS. Because some clinicians may prefer to consider different non-inferiority margins, we have provided a one-tailed 97.5% confidence interval. For the combined genetic results, we are 97.5% confident that the true mean difference is less than 4.83 points. Therefore, the noninferiority margin can be reduced to 4.83 and significance would still be declared. However, if one insists on a margin of non-inferiority less than 4.83 points, our data would not provide sufficient evidence to declare non-inferiority. As can be seen from the stratified analysis, non-inferiority can be declared for the genetic result strata of none and VUS. However, the data does not provide sufficient evidence to declare nongenetic providers noninferior to genetic counselors when the genetic results are pathogenic.

Secondary outcomes

For secondary outcome of PUGS results are first presented by all genetic results combined for each group and then stratified by genetic result type. To conduct a non-inferiority analysis, one must declare a difference between group means, called a non-inferiority margin, such that if the data provides statistically significant evidence that the difference of means is below that margin, then study can declare one group is non-inferior to the other. Non-inferiority designs are by design one-tailed hypothesis tests. As mentioned above we sought to demonstrate that the Nongenetic providers are non-inferior to Genetic

Counselors. We calculated the difference of means as the Genetic Counselor mean minus the NonGenetic Provider mean and based upon consultation with NIH, a non-inferiority margin of 3.5 points. We have chosen to conduct the test using a Type I error rate of 0.025. As can be seen from the table, the mean and standard deviation of the Genetic Counselor group is 29.11 ± 7.31and the mean and standard deviation of the Nongenetic Provider group is 29.74 ± 5.87. The observed difference between mean is less than 1 point in favor of the nongenetic providers. The test generates a p-value of <0.0001 when using a non-inferiority margin of 3.5. Using a Type I error rate of 0.025, we can conclude that nongenetic providers are non-inferior to genetic counselors when compared on the PUGS. Because some clinicians may prefer to consider different non-inferiority margins, we have provided a one-tailed 97.5% confidence interval. For the combined genetic results, we are 97.5% confident that the true mean difference is less than 1.22 points. Therefore, the noninferiority margin can be reduced to 1.22 points and significance would still be declared. However, if one insists on a margin of non-inferiority less than 1.22 points, our data would not provide sufficient evidence to declare non-inferiority. As can be seen from the stratified analysis, non-inferiority can be declared for the all genetic result strata of none, VUS, and pathogenic.

The results of the non-inferiority analysis for the secondary outcome of PRU are also first presented by all genetic results combined for each group and then stratified by genetic result type. To conduct a non-inferiority analysis, one must declare a difference between group means, called a non-inferiority margin, such that if the data provides statistically significant evidence that the difference of means is below that margin, then study can declare one group is non-inferior to the other. Non-inferiority designs are by design one-tailed hypothesis tests. Within our study, we seek to demonstrate that the Nongenetic providers are non-inferior to Genetic Counselors. We calculated the difference of means as the Genetic Counselor mean minus the NonGenetic Provider mean and based upon consultation with NIH, a non-inferiority margin of 10 points. We have chosen to conduct the test using a Type I error rate of 0.025. As can be seen in the Results Section, the mean and standard deviation of the Genetic Counselor group is 78.40 ± 20.51 and the mean and standard deviation of the Nongenetic Provider group is 73.93 ± 19.86. The observed difference between mean is 4.47 points in favor of the genetic providers. The test generates a p-value of 0.0277 when using a non-inferiority margin of 10. Using a Type I error rate of 0.025, we cannot conclude that nongenetic providers are non-inferior to genetic counselors when compared on the PRU. Because some clinicians may prefer to consider different non-inferiority margins, we have provided a one-tailed 97.5% confidence interval. For the combined genetic results, we are 97.5% confident that the true mean difference is less than 10.13 points. Therefore, the noninferiority margin would need to be increased to 10.13 points for significance to be declared. As can be seen from the stratified analysis, non-inferiority can be declared for pathogenic strata.