Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants

Protocol

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Boston Children's Hospital
Until every child is well™

BabySeq2: Implementation of Genome Sequencing as Screening in a Diverse Cohort of Infants

Approved by the Boston Children's Hospital Institutional Review Board

(Protocol # IRB-P00041626, Activation date 4/15/2022, Latest approval date 11/29/2023)

A. Specific Aims/Objectives

There is growing societal interest in using genomic sequencing (GS) to identify genetic predispositions for disease early in life but there is insufficient evidence of its acceptability, psychosocial impact, and clinical utility. In order to begin to gather such evidence, over the past 5 years, our multi-disciplinary team launched the first randomized controlled trial (RCT) of GS in newborns: the BabySeq Project. We implemented a workflow for exome sequencing (ES), and curated 1514 disease-associated genes with favorable validity, age of onset, and penetrance. We randomized 325 families to a family history (FH) arm or a FH+GS arm, disclosed results and placed reports in each infant's medical record. Medically, we discovered and disclosed unanticipated monogenic disease risks (MDRs) in 11% of the infants randomized to GS, and we discovered previously unrecognized signs of underlying disease and relevant family history in over half of these. Behaviorally, we found no increased distress among parents or disruption to the parent-child relationship in response to receiving GS results. Economically, we found only modest increases in downstream health costs. The majority of healthcare providers (HCPs) felt there were health benefits associated with newborn GS.

The BabySeq Project demonstrated the feasibility of newborn GS, but the generalizability of our results was limited, as participant families were recruited as inpatients from one geographic region, predominantly White, and socio-economically privileged. We have now received NIH funding from the National Center for Advancing Translational Sciences (NCATS) for an entirely new RCT in ethnically/racially/socioeconomically diverse communities from Clinical and Translational Science Awards (CTSA) sites at Harvard University in Boston (Harvard Catalyst; sites BCH and Brigham and Women's Hospital [BWH]), Mount Sinai Medical Center in New York City, and the University of Alabama Medical Center in Birmingham to study how GS in infants can be implemented in diverse, resource-limited, "real-world" outpatient primary care settings. We will also improve the technical aspects of the GS offering by moving from ES to GS and adding interpretation of copy number variants (CNVs). Through this research we will develop, pilot, implement, and evaluate a practical, sustainable approach to GS early in childhood that leverages underserved community engagement to minimize distrust and maximize benefit.

In light of distrust of research among underrepresented minorities (URMs), we have established a **Stakeholder Board** with community representation from all 3 sites (see attached "Stakeholder Board Packet"). Under a separate IRB protocol (Protocol ID: IRB-P00038710), we are also soliciting parental input from the communities from which we will be enrolling to understand their concerns, especially within URM populations, towards GS research and how we can address those concerns as we develop our protocol, recruitment strategies, and disclosure methods.

Aim 1: With input from the stakeholder board, and interviews of parents from the 3 CTSA sites, we will develop a recruitment and retention strategy to enroll 500 ethnically and racially diverse infants (0-12 months) into an RCT of GS. Support will be provided for the HCPs through a structured genomics curriculum, and results will be returned to families and their HCP.

Aim 1a: We will enroll outpatient pediatric HCPs in the clinics from which we will enroll families (in Aim 1b), into a genomics education program modified from a successful program developed by HudsonAlpha SouthSeq that utilizes brief didactic videos and live training sessions. Patients seen in clinics where local HCPs have completed this program will be eligible to enroll in Aim 1b.

Aim 1b: We will enroll and randomize a cohort of families with infants 0-12 months of age, from clinics where HCPs have completed the education program in Aim 1a, from the 3 CTSA sites into a FH arm or a GS+FH arm. Results in both arms will be communicated by genetic counselors to the families and the participating HCPs.

Aim 2: To evaluate the impact of GS on a diverse group of infants, their families and their HCPs.

Aim 2a: To assess the psychosocial impact of infant GS on parent/guardians from varying ethnic and racial backgrounds, we will conduct longitudinal surveys and compare validated scales between arms of the RCT.

Aim 2b: To assess the medical impact of GS on infants and their families, we will review medical records and survey parents/guardians to track symptoms, laboratory or diagnostic results, new diagnoses, and medical actions attributed to the GS findings. Among infants with an MDR, we will determine whether the MDR: (a) reveals an unsuspected phenotype in the infant or family, (b) explains a family history of a condition, and/or (c) prompts surveillance in the infant or family.

Aim 2c: To assess the impact of GS in infants on clinical care, we will collect feedback from HCPs throughout the study by monitoring use of the "Genome Resource Center" and conducting interviews with HCPs towards the end of the study.

Aim 3: Exploratory Aim: To evaluate healthcare utilization and associated costs of GS. Using novel approaches, we will identify healthcare services motivated by the study in the two study arms and examine attributable healthcare costs accrued for the infants and other family members.

B. Background and Significance

The era of genomic sequencing (GS) in medicine has arrived,[1-3] and numerous laboratories are offering CLIA-certified exome (ES) or genome sequencing (GS) as a clinical service for characterization of rare disorders[4-6] and for individualized cancer treatments.[7-10] But many who envision a future of personalized and precision medicine have long considered GS to be equally or even more valuable for its potential to reveal predispositions to disease that would allow preventive measures,[11-13] and to have utility throughout the lifespan,[14] especially if performed early in life. Indeed, NIH director Francis Collins has said: "…whether you like it or not, a complete sequencing of newborns is not far away"[15] and former NICHD director, Alan Guttmacher, echoed this by stating: "One can imagine the day that 99% of newborns will have their genomes sequenced immediately at birth."[16] GS in the newborn period could reveal monogenic disease risks (MDR) that conventional newborn screening would miss, such as a pathogenic variant in *RB1* predisposing an infant to develop a retinoblastoma. As infants grow into their reproductive years, they would have access to the variants they carry for recessive conditions to use for family planning.[17-19] In adult life, sequenced individuals could benefit from knowing if they carry MDR variants in cancer predisposition genes like *BRCA1*,[20] Some of the arguments against GS early in life arise from our understanding of population-based screening tests, where screening large numbers of individuals for rare conditions with poorly understood penetrance could identify more individuals at risk than would actually develop the condition. There are also cost considerations, with some questioning whether genomic information will lead to increased healthcare expenditures.[21; 22] Finally, there is concern that the provider workforce may not be prepared to interpret and manage genomic results in their patients.[23-29]

<u>One of the major impediments to understanding the ultimate value of GS early in life is the absence of methodologically rigorous data on psychosocial impact and clinical utility</u>. While there are large-scale attempts to match genomic information to phenotype data such as the **E**lectronic **Me**dical **R**ecords and **Ge**nomics (eMERGE) Network, the Geisinger *MyCode* Program, the Alabama Genomic Health Initiative, and the Mount Sinai Bio*Me* Program, these programs are principally oriented toward adults and lack control populations against which to measure the clinical utility of GS. Over the past 5 years, our team has taken a rigorous approach to start to explore the psychosocial impact and clinical utility of GS in newborns as part of the **N**ewborn **S**equencing **I**n **G**enomic medicine and public **H**eal**T**h (NSIGHT) Consortium by conducting the

"*BabySeq Project*," the first pilot RCT of newborn GS.[30-33] The BabySeq Project demonstrated the feasibility of enrolling parents and their newborns in an RCT of GS, analyzing GS data to identify genetic findings that indicate risk of a disease, and returning results to parents and health care providers (HCPs). Importantly, there was no evidence for harm from returning the results.[34 35]

However, there were limitations to the BabySeq Project: parents were recruited in an inpatient setting immediately after giving birth, there was only a single site, and those who enrolled were predominantly White and of higher socioeconomic status. We now propose a new RCT to explore the implementation of GS in 3 diverse, resource-limited, "real-world" outpatient primary care settings across the country enriched for underrepresented minorities (URMs), focusing upon African-American (AA) and Hispanic (HA) families. AA and HA communities have not benefited from genomics research to the degree that White populations have,[36-39] in part because they tend not to participate in research. In the AA population, issues include mistrust, privacy concerns, fear of pain, and confusion around compensation,[40-43] which are reinforced by historical abuses, including the Tuskegee syphilis experiment and the development of the HeLa cell line from Henrietta Lacks.[44] Among HAs, lack of knowledge about research, lack of dissemination of results, fear of pain or harm, and distrust of the healthcare system are primary barriers to research participation.[45-48] It is critical to earn the trust of communities with robust engagement that involves welcoming patients/participants as essential and equal research partners before asking them to enroll in research studies.[49-51] The 3 CTSA sites in this project, in Boston, MA, New York City, NY, and Birmingham, AL, all have years of extensive experience in community engagement and in enrolling and retaining URMs in genomics research (see Preliminary Studies - Prior Work and Data). We will leverage this experience and take a systematic approach to community engagement to address the concerns of URMs towards research and GS by involving parents, HCPs, and a Stakeholder Board in a substantial way as we develop and implement our study. This study is significant in that it asks how GS of infants from ethnically and racially diverse populations can be ethically implemented.

C. Preliminary Studies

Here we demonstrate that (1) we have the infrastructure and experience to feasibly carry out the proposed research project, (2) we have expertise in engaging diverse populations in genetic research, and (3) we have experience in safely returning genetic results to HCPs.

Prior Work and Data: The BabySeq Project

Study Design: The first phase of the BabySeq Project (2015-2019) was a pilot RCT of two newborn cohorts, one healthy and one from neonatal and cardiac intensive care units (NICUs and CICUs). For all newborns, we obtained the state mandated newborn screening (NBS) report, a 3- to 4-generation pedigree by a genetic counselor (GC), and DNA samples on the newborn and both parents. Within each cohort, half were randomized for their parents to receive a report of the assessment of the family history and the NBS report only (FH arm) and half to additionally receive their ES report (FH+ES arm). Families in both arms returned for an in-person disclosure with a study GC and a final report was sent to the parents and to the infant's HCPs and placed in the medical record. Parental surveys were conducted at enrollment (baseline), disclosure, and at 3- and 10-months post-disclosure, and HCP surveys were conducted at baseline and after they received a report on an enrollee.[32; 33; 52]

Recruitment and enrollment: We had a 2-step approach to recruitment. We first approached families to assess interest in a genetics research study. For those who were interested in hearing about the study, we went over the details of the study and the consent form. Our study staff approached 5,022 inpatient families to assess their interest in a genetics research study and about 90% declined prior to hearing the details of the study, primarily due to lack of interest in "any research" during the stressful postnatal period. Of the families

who agreed to hear about the study, 67% enrolled, for a total of 325 families (257 healthy and 68 from the ICUs).[53]

Molecular Analysis and Reporting (Figure 1): We curated 1,514 genes associated with monogenic disease risk (MDR) based upon the ClinGen clinical validity classification framework criteria, age of disease onset, estimated penetrance, and mode of inheritance, through evaluation of published evidence.[31] Of these, 954 genes met our criteria for reporting; additional genes were included in the analysis as they arose through the pipeline comparisons with known and suspected genes and variants.[31; 32] Initially, only genes expected to cause disease in childhood were included in the reporting criteria, however this was later updated to include a select number of highly actionable adult-onset conditions as defined by the secondary findings list from the American College of Medical Genetics and Genomics (ACMG)[54,90]. Variant interpretation followed the ACMG/Association of Molecular Pathology (ACMG/AMP) guidelines for assessment of pathogenicity.[55] The Newborn Genomic Sequencing Report (NGSR)[30; 31] documented MDR, defined as pathogenic or likely pathogenic (P/LP) variants in the genes that met reporting criteria, recessive carrier variants, and pharmacogenomic (PGx) variants associated with medications used in pediatrics. The inheritance of the MDR allele/s (but not carrier status) were assessed by analysis of parental DNA. For infants with a condition suspected to have a genetic contribution, an additional Indication Based Analysis (IBA) was generated, which included variants of uncertain significance (VUSs) for the gene/s suggested by clinical features. This strategy was an attempt to maximize the lifelong value of GS for each infant by routinely searching for MDR in a large set of genes and also conducting an IBA for any illness where a genetic etiology was suspected and there were candidate genes.

Table 1. BabySeq1 Monogenic Disease Risk Genes

ANKRD11^	ELN*	BTD*
G6PD+	GLMN*#	TTN$#
TTN$#	TTN$#	TTN$#
BRCA2$#	BRCA2$#	SLC7A9$#
KCNQ4$#	VCL$	CD46+
MYBPC3$	MSH2$#	CYP21A2$

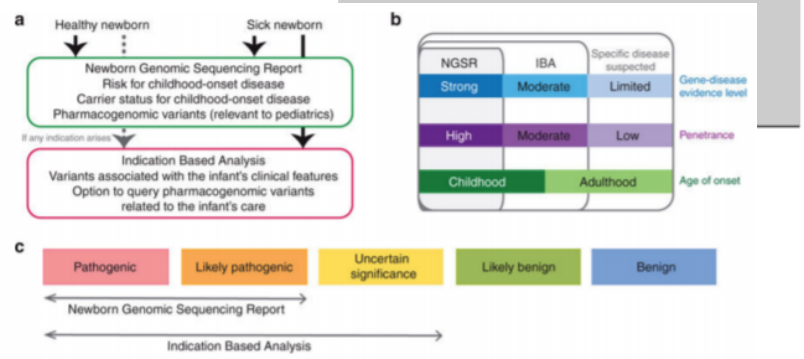


Figure 1. Return of results criteria in the BabySeq project

Medical Outcomes: Among the 159 infants who underwent GS, 18 (11%) had a MDR. As shown in Table 1, the findings in 3 cases prompted discovery of a related disease phenotype not previously recognized, in 2 cases identified vulnerability to future exposure, and in 1 case explained a previously unrecognized genetic etiology.[32] The remaining 12 cases offered future disease risk assessment for the infant and the parent carrying the variant. While surprisingly high, this is consistent with findings from an earlier GS study that we conducted in adults and is probably explained by the fact that few prior studies have comprehensively sequenced healthy individuals.[56] Carrier status was identified in 140 of the 159 (88%), with an average of 2 variants per infant (range 0-7).[57] Of the 7 genes identified most frequently, only CFTR is captured in conventional carrier screening, and most genes are not on expanded carrier screening panels.[58] Some parents used recessive carrier results to inform their reproductive planning, including one family that pursued preimplantation genetic testing after follow-up clinical carrier testing revealed that both parents carried pathogenic variants in the same gene.[59]

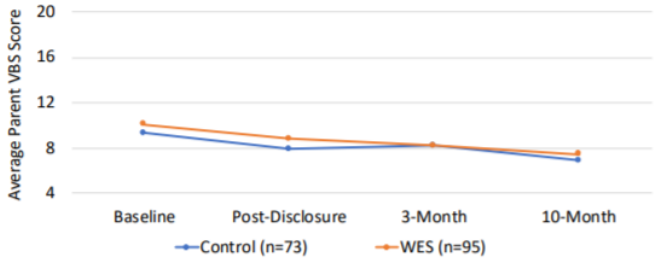


Figure 2. BabySeq1 average parent Vulnerable Baby Scale (VBS) score by study arm over time, showing no disruption to parent-child relationship

Behavioral Outcomes: We measured the impact of receiving GS information on the parent-child relationship using a modified version of the Vulnerable Baby Scale (VBS),[60] Mother-Infant Bonding Scale (MIBS),[61] and

Parenting Stress Index (PSI-4-SF).[62] We assessed parents' risk for depression and anxiety using validated scales. We found no parental distress that could be directly linked to study participation, and for all domains of parental distress and family impact we observed no effect between randomization arms, nor between parents whose infant did vs. did not have MDR findings in the GS arm (Figure 2). [139] These findings suggest that providing the parents with GS information about their newborn, including MDR, does not cause psychosocial distress or familial disruption.

Healthcare Utilization/Cost Outcomes: We explored healthcare utilization and costs using techniques developed and piloted in our prior projects.[21; 33; 63; 64] Data collected through the parental surveys and medical record reviews captured medical costs and parental time lost from work, and we reviewed the notes from the disclosure sessions. For those in the GS arm recommendations were frequently made for follow-up and testing for the newborn and a family member (Figure 3). Preliminary analyses of total healthcare spending in the 3-months following disclosure (Figure 4) showed that total costs per newborn were higher in the GS ($567) compared to control arm ($352).[65]

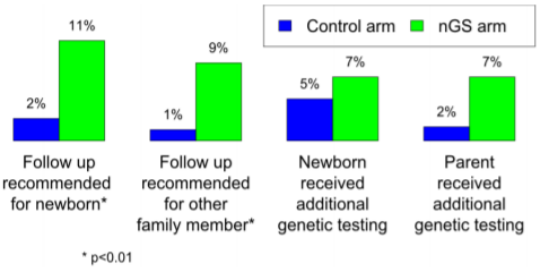


Figure 3. Percentage of BabySeq1 families who received recommendations for clinical follow-up at disclosure or genetic testing in the 10 months following disclosure

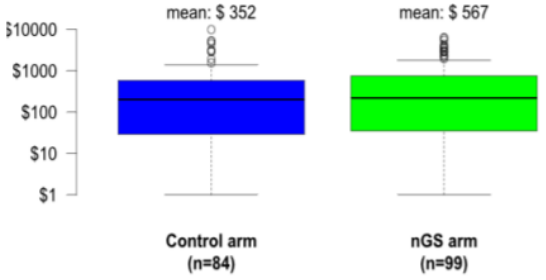


Figure 4. BabySeq1 total health sector expenditures in the 3 months following disclosure sessions.

Prior Work and Data: Engaging Diverse Populations in Genetic Research

All 3 of the sites bring extensive experience in engaging URMs in genomic research and in addressing mistrust, fear, stigma, and distress within URM communities, including through the All of Us Research Program (AoURP), the Clinical Sequencing Evidence-Generating Research (CSER) Consortium, and the **I**mplementing **G**e**N**omics **I**n prac**T**ic**E** (IGNITE) Network.

In Boston, Dr. Green has led NIH-funded collaborations that have explored URM issues related to genetic testing,[66-73] and consistently recruited 15-24% URM participants in some of the earliest trials disclosing genetic risk information.[74-77] Dr. Green also leads an NIH grant that is the first to systematically return genomic results to AA participants in the Jackson Heart Study, as presaged by these early data.[78]

In New York, Dr. Horowitz and her team have successfully recruited and retained thousands of AA and HA individuals in genomic clinical trials via robust community engagement.[79] Her local "genomic stakeholder board" of largely Black and Latino members is nationally known for community engagement and working with researchers on genomic discovery and translational research,[80] and has led engagement with URM groups in several ways, including the incorporation of novel tools for digital engagement and navigation.[81-83] Dr. Horowitz co-chaired the diversity-focused CSER II Consortium,[83] and chaired the IGNITE Consortium, forming and leading its Diversity Workgroup and engagement strategy.[85; 86] She has conducted mixed methods research to build, pilot, and revise a trial, similar to what we propose here,[87] testing over 2000 hypertensive AA patients at 16 clinical sites for *APOL1* variants that increase risk of kidney failure, retaining 93% at 3- and 88% at 12-months follow-up,[79] and demonstrating positive outcomes.

In Birmingham, University of Alabama (UAB) investigators are leading the Alabama Genomic Health Initiative and SouthSeq (part of the CSER II Consortium), and staff one of the leading recruitment sites for the entire national AoURP with an overall recruitment of 88.5% participants designated as URMs in biomedical

research, including 67.0% based on race/ethnicity. Each of these studies includes a highly functional community advisory board and conducts outreach to community groups to learn about concerns of the community regarding the research.[88; 89]

Prior Work and Data: Returning Unanticipated Genetic Results to HCPs

In addition to our experience in the BabySeq Project,[30-32; 34; 90] our group has extensive experience in the return of unanticipated genomic results to participants and HCPs and in studying the impact on both, which will inform our approach to return of results to HCPs. The NIH-funded MedSeq Project led by Dr. Green was the first to sequence healthy adults and report results directly to primary care HCPs,[56; 91; 92] demonstrating that after a minimal amount of education, HCPs returned the results to their patients without undue errors or distortion of the information.[56; 93] Dr. Holm is leading an NHGRI-funded study of the impact on HCPs of receiving unanticipated GS results in the eMERGE III Network. Interviews of HCPs prior to receiving GS showed concerns about workflow and lack of guidance on handling unanticipated genomic results.[94] The UAB group led by Dr. Korf is conducting a clinical trial of return of GS results to parents of newborns in the special care nursery. In addition, Dr. Korf's colleagues at HudsonAlpha, developed a curriculum of didactic lectures and simulation exercises to train non-genetics HCPs in the return of GS results, demonstrating clear improvement in provider confidence (see Figure 5 showing number of providers endorsing each category pre and post curriculum).[95]

Figure 5. Healthcare provider confidence managing patient care based on WGS results after HudsonAlpha genomics curriculum

D. Design and Methods

1. Study Design

This is a randomized clinical trial evaluating infant and family outcomes, as well as physician outcomes, after participation in one of the two arms. Figure 6 summarizes the proposed details of study participation for physicians. Overall design of the RCT is summarized in Figure 7. Figure 8 summarizes the proposed details of study participation for infants and parents/guardians. The study has been registered on clinicaltrials.gov. In light of distrust of research among underrepresented minorities (URMs), we have established a Stakeholder Board with community representation from all three sites. We are also soliciting parental input from the communities to understand the concerns, especially within URM populations, towards GS research and how we can address those concerns as we develop our protocol, recruitment strategies, and disclosure methods.

The Stakeholder Board

Building upon our prior experience,[96-99] our Stakeholder Board of parents, community leaders, and clinicians, with representatives from each site, consists of 10 members, all of whom are themselves AA or HA and a mix of academic experts and patient-participants. The Stakeholder Board has begun meeting quarterly via Zoom video conference. Drs. Horowitz and Holm are facilitating the Stakeholder Board meetings. We are using community-based participatory research (CBPR) approaches described by Dr. Horowitz to choose leaders and rules of engagement.[79; 100-102] In year 1, our Stakeholder Board is advising us on: (1) the perspectives of URMs and their HCPs towards genetics and research; (2) issues to address in parent interviews, who to include, and how best to structure them; and (3) integration of what we learn through the parent interviews to develop our protocol and materials. In years 2-4, our Stakeholder Board will review and suggest edits to study materials, discuss implementation challenges, and advise on all aspects of the study. Stakeholder Board members will receive a yearly stipend as compensation for their time.

Parent/caregiver interviews

Under a separate IRB protocol (IRB-P00038710), we are conducting up to 30 semi-structured interviews of parents split between each site who have a child 0-5 years of age. The interview guide includes

the following domains: (1) how parents prefer to be approached for research; (2) beliefs about genetics, prior experiences with genetic testing; (3) barriers to participation; (4) concerns about the study; (5) types of genetic information to disclose, e.g. monogenic risk, carrier status, adult-onset conditions, (6) how should genetic information be disclosed (in-person, phone, online); (7) what form results should be presented in, e.g., written, verbal, pictures, digitally; and (8) what outcomes and study results would be of interest. Interviews of Spanish-speaking parents will be conducted by a native Spanish-speaking Pediatric Genetics fellow.

Development of study procedures and materials

Study procedures and materials are in development and are being shaped by what we are learning through the parent interviews and our Stakeholder Board, our prior experiences in genomics research with diverse populations, and a literature review. The materials include recruitment strategies, informed consent, and results disclosure templates, and will accommodate low-literacy (less than or equal to 8th grade reading level) and non-English speaking participants. Stakeholder Board feedback has and will inform revisions.[83; 101; 104; 105] The final material will be submitted to the IRB before being implemented.

Piloting of study materials and procedures

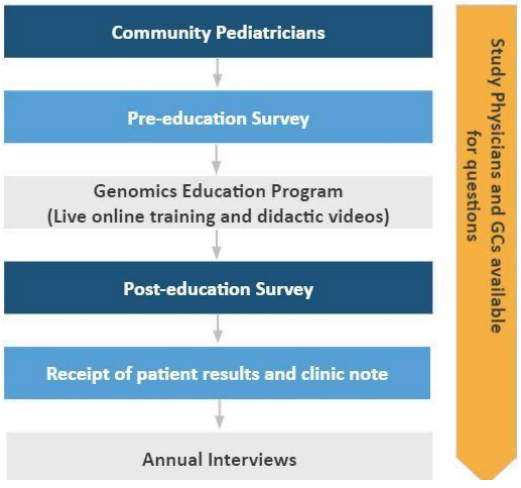
Stakeholder board members will pilot test participant surveys for content and length. We will also model enrollment and disclosure sessions with Stakeholder Board members. We will collect informal, open-ended feedback from initial participants regarding the enrollment approach, materials, and process. Additionally, we will collect informal, open-ended feedback from the first several participants at each site regarding their experience with the disclosure visit. What we learn will inform changes in our materials and process.

Aim 1: With input from a diverse stakeholder board and interviews of parents/guardians from the 3 CTSA sites, we will develop a recruitment and retention strategy to enroll 500 ethnically and racially diverse infants (0-12 months) into an RCT of GS. Support will be provided for the HCPs through a structured genomics curriculum, and results will be returned to families and their HCP.

Aim 1a: We will modify a successful HudsonAlpha SouthSeq genomics education program utilizing brief didactic videos and live online training sessions for the outpatient pediatric HCPs.

Although the study staff, not the HCPs, will be returning the results to the families, the HCPs will receive the results and follow the families, as in BabySeq. In order to provide education to the HCPs on GS and the results they may receive, an HCP education program and assessments will be developed by collaborators at the HudsonAlpha Institute for Biotechnology, built upon a similar curriculum they developed and used to train neonatology providers in the SouthSeq project. Initially, only the patients of HCPs who participate in the training will be recruited for the RCT. After initial clinic champions have been enrolled and completed the full training curriculum, the requirements may be modified, condensed, or removed as needed to increase access and enrollment.

Figure 6. Workflow for Physicians



1a.1 Recruitment of HCPs

Prior to initiating recruitment of families into the RCT, we will invite all HCPs who care for infants at each site to participate in the study. The research study will be introduced to pediatricians through word-of-mouth and presentations held during clinic staff meetings, hospital grand rounds and seminars (see attached “HCP Slides”). These

presentations will give pediatricians a background on the project and provide them with contact information for study staff. HCPs who decide to enroll will participate in the education intervention.

1a.2 HCP Genomics Education Program

The genomics education program will focus on helping HCPs understand GS, the contents of the Newborn Genomic Sequencing Report (NGSR), what to do next with the results, how to counsel parents/guardians about results, and resources available. The HCP curriculum will include brief, didactic videos as well as a live training at each site for facilitated small group discussion and simulation (see attached "HCP Curriculum Detailed Outline"). Fact sheets and other just-in-time resources will also be provided (see attached "Fact Sheets" and "Decision Trees").

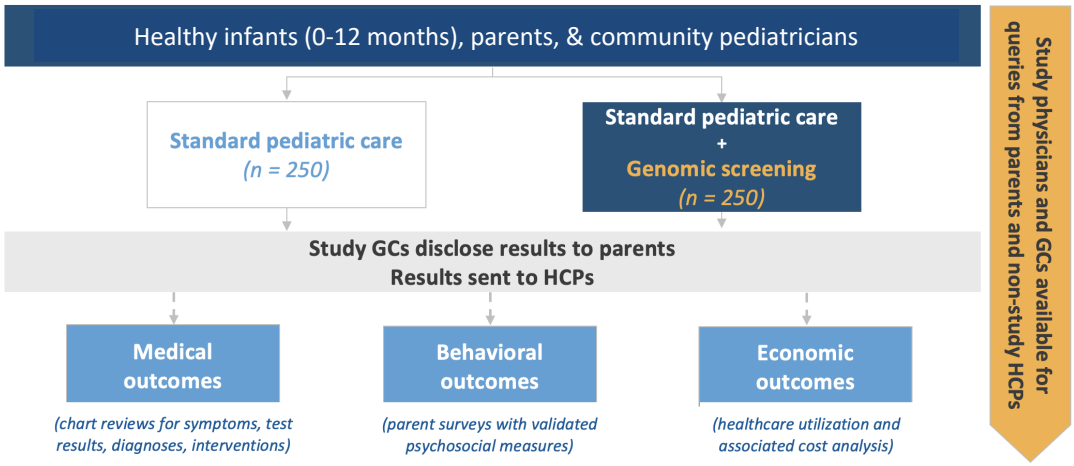
HCPs may complete brief, anonymous, pre- and post-training online surveys to assess their genetics background and perceived confidence reading and using GS results (see attached "HCP Pre- and Post-Ed Survey"). Consent to participate in the study will be implied by voluntary completion of the surveys and education intervention. HCPs may complete a brief self-reflection survey to engage with the study every 6 months and earn Maintenance of Certification Part IV credit (see attached "BabySeq2_Provider Survey_MOC"). Additionally, HCPs may compete an end-of-study survey at the conclusion of their participation (see attached "BabySeq2_Provider Survey_END OF STUDY"). In years 2-4, semi-structured feedback will be collected from HCPs through annual phone or video calls with a member of the HudsonAlpha education team. Future interview guides will be submitted for IRB review. Topics discussed may include their experiences receiving GS results, how often they engage in conversations with families about study results (all types), common patient questions, topics they feel more or less confident addressing, and whether gaps in education/training exist. Data from the assessments will be used to develop additional clinical decision support resources, as well as to provide data about HCP educational needs.

HCPs may receive either Maintenance of Certificate (MOC) Part IV credit or Continuing Medical Education (CME) credits for completion of the genomics education program. Additionally, HCPs may receive $50 as compensation for their time spent taking surveys and completing training. The format of compensation will depend on site-specific policies and may include gift cards, checks, or payroll additions.

After the initial clinic champions have been enrolled and trained at each site, the HCP training may be modified, condensed, or removed as needed to increase access and enrollment. Additionally, pediatricians in other clinics who are not familiar with BabySeq may be invited to compete optional surveys as a comparison group to assess the effects of training or the applicability of educational materials and genome reports to general pediatricians. Any modifications to training requirements or introductions of new surveys will be done in collaboration and with support of local clinics. Clinic champions who have completed the full training will be available as a local consultation resource for their colleagues. Additionally, "just in time" resources and educational materials including videos, fact sheets, and decision trees will be available on-demand for all pediatricians at each recruitment clinic, and live training sessions will be scheduled upon request. The study team and Genome Resource Center will be available for any pediatrician questions throughout the study. Genetic counselors will return study results to families and provide detailed chart notes for physician reference. In the case of a positive result, the study team will reach out directly to the physician with additional information and recommended next steps.

Aim 1b: We will enroll and randomize a cohort of families with infants 0-12 months of age from 3 CTSA sites with established expertise in engagement, diversity, and genomic clinical trials. Participants will be randomized into FH (Control) or GS+FH (Sequencing) arms, and results will be communicated by genetic counselors to the families and the participating HCPs.

Figure 7. Project Overview



1b.1 Enrollment Sites

In Boston, the ***Boston Children's Hospital (BCH) Primary Care Center (CHPCC)*** is the largest pediatric practice in Boston and serves about 16,000 children, most of whom live in low-income neighborhoods of Boston. Forty-five percent of patients are AA and 35% are Latino; 15% of families are exclusively non-English speaking. The ***Martha Eliot Health Center (MEHC)*** is owned and operated by BCH and is the second oldest community health center in the country. It cares for over 6,000 children, most living in local Boston neighborhoods. The patient population is diverse with 20% AA, 70% Latino.

In Birmingham, the ***Children's of Alabama Primary Care Clinic*** is part of the UAB Department of Pediatrics providing primary care for about 4,200 pediatric patients, with 8000-9000 clinical encounters per year. The clinic accepts 25 new infants each month, most of whom will have at least 5 visits in the first 6 months of life. The clinic population is 80% AA and 8% Hispanic. ***Children's of Alabama Over the Mountain Pediatrics*** provides comprehensive medical care to approximately 11,000 patients, from birth through adolescence, with over 29,500 visits per year, seeing over 80 infants per week who are 21% AA, 3% Hispanic/Latino.

In New York City, the ***Mount Sinai Pediatric Associates Practice*** provides comprehensive pediatric care to approximately 10,000 patients with over 23,000 visits per year with a patient population that is 40% HA and 34% AA.

1b.2 Recruitment in the postnatal period

Prior to initiating study recruitment, research assistants and other team members from each site will be trained on recruitment, enrollment, and consent procedures as well as data entry and follow-up. There will be standard operating procedures (SOPs) developed for all study processes. The coordinating site will lead live online trainings with mock sessions to promote uniform study conduct, and will be available for questions throughout the project.

Recruitment may be initiated in person or remotely by an RA, or by patient self-referral.

Prior to clinic visit: Study RA will pre-screen patients for eligibility prior to scheduled clinic appointments. A letter to assess study interest may be sent to eligible families by mail, secure email, or patient portal (see "Initial Recruitment Letter") ahead of a regularly scheduled clinic visit. This letter may be sent by the study team directly, or by the recruitment clinic with a "Clinic Cover Letter". The letter will introduce the study and provide contact information as well as include a study flyer (see "Peds Intro Flyer"). If the family is interested in learning more or would like to opt-out of additional contact, they will be directed to a study phone number and/or email. If a response is not received within 2 weeks of the mailing/email/message, study staff may reach out to the parent by phone to introduce the study ahead of their next visit, or meet with the

family at the next visit. Those who opt-out will be noted in the recruitment screening log and not approached at future visits.

In Person: In light of the COVID-19 pandemic, where possible and with permission of clinic management, we will embed an RA in each pediatric clinic and will take advantage of the frequent well baby visits, at 1-, 2-, and 4-months. Each week the RA will have access to the clinic schedule to pre-screen patients for study eligibility by reviewing the patients of HCPs who are enrolled in the study. A member of the patient's clinical staff will ask if they are interested in speaking with someone from the research team. If permission is granted, the RA will approach families while they are in the clinic to assess interest and provide parents/guardians with study materials, in English or Spanish, to take home. The RA will be Spanish-speaking in clinics with a large Spanish-speaking population or will otherwise utilize hospital approved interpreter services (in-person or remote interpreters). We will strive to hire RAs from the same communities as our participants. They will be trained using techniques proven effective in recruiting URM patients, interviewing mock patients, and receiving feedback.[106-113]

Remote: Study RAs will have access to the clinic schedule to pre-screen patients for eligibility and provide clinical providers with a list of patients. Clinical providers will approach families while they are in the clinic to briefly assess interest and provide parents/guardians with study materials. With permission from the clinical provider and patient, an RA will contact families who express an interest in the study by their preferred method of contact (i.e., phone or email) to continue the consenting and enrollment process.

Patient Self-referral: Flyers and study handouts will be available in recruiting pediatric clinics, including contact information for the study team (see attached "Peds Intro Flyer," "Peds Detailed Flyer," and "Peds FAQ Sheet"). Parents/guardians who are interested in the study may contact a study team member about their eligibility and any other questions they may have about the study. If the participants HCP is not presently enrolled in the study, they will be notified of their patient interest and re-sent information on enrolling/completing the HCP education.

Final enrollment notification: As the infant approaches their first birthday, if parents are still considering participation (have not enrolled nor declined) they will be sent a "Final Recruitment Letter". This will remind parents that they are eligible to enroll up until their child turns one year old.

Participants who are approached for enrollment and then decline to participate will be asked by the RA to provide an open-ended reason for decline. The reasons will be tracked along with demographics and minimum necessary identifying information so that the family is not re-contacted.

1b.3 Enrollment session

An enrollment session will be scheduled with the parents/guardians of newborns who express interest in participating in the study. A research assistant will meet with the parent/guardian, verify their interest in participating in the study, and initiate the consent process. This session may take place in person, by video, or by phone.

During the enrollment session, parents/guardians will learn about genetics and genomic sequencing, the study protocol, the benefits and risks of participation, and will have opportunities to ask any questions. The research assistant will verbally review the informed consent form, including discussing all of the study procedures.

After completing the enrollment session, if parents/guardians are unsure and prefer additional time to decide about participation, a follow-up conversation will be scheduled if requested.

It should be noted that if there are multiples (i.e., twins), only one would be enrolled, at the parent/guardian discretion.

1.b.4 Consent

For parents/guardians who decide to enroll, informed consent will be obtained through a paper consent form or REDCap eConsent (see attached "Primary ICF"). The eConsent platform will be hosted by the coordinating institution at BWH and a copy of the consent forms will be stored there. The consent will include the following:

Infant's participation includes demographic collect, randomization, review medical records from all medical providers of the infant, sample collection if in the GS arm, return of results to the parent/guardian and their HCP, placement of results in EHR, access of billing information from state and institutional databases, and the potential for long-term follow-up, including consent at age 18 years, if the study is still in progress..

Parent/guardian participation includes consent to complete surveys and for review of the mother's prenatal records, if applicable. **After detailed conversations with the study team and our Stakeholder Board, the decision was made to only require the consent of one parent/guardian for participation.** This is in contrast to the original BabySeq Project I which there was a requirement that both parents enroll. The rationale for this decision is as follows: 1) *Requiring two parents to consent may exclude a significant proportion of families.* Our stakeholder board and team members experienced in working with our target population felt strongly that this requirement would counteract the goals of equitable access. We saw this in BabySeq, where the requirement for both parents to enroll played a significant role in the biased recruitment of a non-racially/economically diverse population. Here we want to avoid restricting access to those with only one actively involved parent and continuing to propagate the existing disparities in genomic research. 2) *One of the goals of this study is to study the use of genomic screening in a way that would be as closely applicable to real world implementation as possible, with a focus on the infant*. In newborn screening, or any other screening scenario, only the individual undergoes GS, not family members.

A corollary of the decision to not require both parents to enroll was the decision to not collect samples for DNA on the parent/guardian. If an MDR is found in the infant, we will offer the parent/s and sibling/s the option for cascade testing, and consent/assent will be obtained separately for these individuals for their own testing (see attached "Cascade ICF). If a relative consents, a saliva collection kit will be mailed for them to provide their own sample for targeted testing of only the variant identified in the infant. If only one parent chooses to get testing, the study team realizes this may lead to potentially revealing the other parent's status by exclusion - although not with certainty as with each genetic variant there is always a possibility that it may be *de novo* in the child.

It should be noted that if we become aware that a second parent/guardian opposes their infant's participation in the study, the family will not be enrolled.

We will collect informal, open-ended feedback from initial participants regarding the enrollment approach, materials, and process for quality improvement.

1b.5. Data collected at enrollment

Demographics and other study intake information will be recorded in a secure REDCap database accessible only to the clinical study team.

A 3-generation family history will be obtained by the research assistant at this stage of enrollment using a standardized template with scripted questions. The family history will be utilized later by the laboratory and the consultation team in the interpretation and contextualization of the sequencing report as well as to create a family history report (FHR) for the family (see attached "Sample FHR"). In the event that the family history suggests that a more targeted form of genetic testing should be pursued (such as a family history suggestive of Lynch syndrome in the parents), the family will receive additional genetic counseling and may be referred for clinical genetic counseling and/or additional targeted genetic testing for this indication.

Baseline survey. All surveys (i.e., baseline, post-disclosure, and 6-months post-disclosure) may be completed in person, over the phone, or online (via REDCap). Participants will be offered the option to have an RA read the survey questions and to respond verbally.

1b.6. Randomization

After completion of the baseline survey, infants will be randomized (1:1) to either standard-of-care (family history) or to standard-of-care plus genomic sequencing, divided approximately equally between the 3 sites. Parents will be notified which group their child is part of and whether a sample needs to be collected.

1b.7. Sample collection

Infants randomized to the sequencing group will have a sample collected for GS. Infants randomized to the control group will not have a sample taken. Sample collection will take place in the clinic by clinical staff or trained research personnel. A blood sample (through a heel stick, finger stick, or venipuncture) of less than 1.0 ml will be obtained from all infants randomized to the genomic sequencing arm. Alternatively, and when possible, leftover blood and/or cord blood samples already obtained may be retrieved, a saliva or buccal swab may be collected. In the case that the sample for an infant does not yield enough DNA for sequencing, we would offer a second sample collection should they agree to this. These samples will be shipped to the Laboratory for Molecular Medicine (LMM) or other CLIA compliant clinical diagnostic facility.

The decision to only collect a sample from those in the FH+GS arm was based on insight from our Stakeholder Board and study team member experienced in recruiting in diverse population, who felt that having a blood sample obtained from an infant who ultimately did not undergo GS would be a significant deterrent to enrollment in our populations. After a long discussion with the full study team, we decided that since we will collect the baseline survey and data PRIOR to randomization, we did not feel that not obtaining a sample for DNA in those in the FH only arm will compromise our study outcomes.

1b.8 Genomic Sequencing and Reporting

Genomic sequencing of infants randomized to the sequencing arm will be conducted in a CLIA certified sequencing laboratory at the Broad Institute Additional genetic testing may be used to help with data interpretation and confirmation (for example, chromosomal microarray or Sanger sequencing). Data interpretation will be performed at the LMM. Variant classification will be based upon current medical practice standards in the laboratory for targeted gene panels and other clinical sequencing.[114] The genomic reporting framework for this protocol is shown in Appendix 1 below. A CLIA-compliant newborn genomic sequencing report (NGSR) will be issued for each case and uploaded to the infant's medical record after their disclosure session.

1b.8.1 Gene and Variant Reporting Criteria

To help establish which results will be returned, the following reporting criteria will be used to determine whether a result should be included on the NGSR.

1) Monogenic Disease Risk and Carrier Status for Childhood-Onset Disorders

Gene-level criteria

Validity of gene-disease association: Gene-disease pairs will be evaluated using the ClinGen framework for determining the strength of a gene-disease association.[115] In this method, the validity of a gene–disease association is evaluated by reviewing the evidence reported in the literature, such as the number of families with pathogenic variants in the gene and functional studies, and classified into the following categories: conflicting evidence, no reported evidence, limited evidence, moderate evidence, strong evidence, and definitive evidence. For the NGSR, we will only be returning results in genes that have a definitive or strong level of evidence.

Penetrance: Estimated penetrance will be curated based on the phenotype information for reported individuals in the literature. For the NGSR, we will return results associated with genetic conditions with high or moderate penetrance.. Results in genes with lower than moderate penetrance will be discussed with the team to review available evidence around actionability, severity of the associated condition, burden of available

interventions, and other clinical factors. Reporting decisions for these results will be made based on clinical judgment.

Age of Onset: The youngest age at which individuals with pathogenic variants in the gene presented with disease will be recorded based on available information in the literature. Results will be returned in genes where the earliest reported onset of disease or actionability is in pediatric patients (<18 years old).

Mode of Inheritance: The most common inheritance pattern for the gene will be determined using the GenCC database and relevant literature. This will determine whether the variant indicates that the individual is at risk for the disease or is a carrier.

In addition to the resources mentioned above, online databases that will be used to determine gene level criteria include: Medline Plus (formerly Genetics Home Reference; GHR), Orphanet, ClinVar, HGMD, gnomAD, OMIM, and Gene Reviews.

Variant-level criteria

Sequence Variants: Variant calls will be made using the Genomic Analysis Tool Kit (GATK). Variant interpretation will follow the American College of Medical Genetics and Genomics/ Association of Molecular Pathology (ACMG/AMP) guidelines for assessment of pathogenicity, with additional incorporation of all new modifications set forth by ClinGen's Sequence Variant Interpretation working group, including the PVS1 criterion for predicted loss-of-function (pLOF) variants,[116] and rule adaptations specific to certain genes, as determined by ClinGen expert panels. Any variant that meets criteria to be likely pathogenic or pathogenic will be reported on the NGSR.

Copy Number Variants: We will employ GATK for structural variants (GATK-SV) to analyze the WGS to identify copy number variants (CNVs). CNVs known to confer risk for childhood-onset disorders will be reported on the NGSR. We will make use of deeply analyzed benchmark datasets generated by the Genome in a Bottle Consortium and the Human Genome Structural Variation Consortium. We will only return pathogenic or likely pathogenic variants (not variants of uncertain significance). All variants will be interpreted using the ACMG/ClinGen CNV classification criteria.[117] Regulatory (noncoding) variants will not be returned unless previously classified as disease-causing (e.g., in ClinVar or HGMD), in which case they will be evaluated according to the ACMG guidelines for predicting pathogenicity. The criteria for disease validity, age of onset, and penetrance will be similar to the reporting criteria for childhood-onset monogenic disease risks.

2) Monogenic Disease Risk for Highly Actionable Adult-Onset Disorders

Gene-level criteria

The NGSR will also include monogenic disease risk for highly actionable adult-onset disorders per the current version of the ACMG secondary findings gene list at the time the report is generated (see Appendix 2 below for version 3.2, updated June 2023[140]). This list will be updated as new clinical guidelines are published, approximately on an annual basis. [140] The most updated version of the list will be used to determine which results to return, consistent with clinical practice.

Variant-level criteria

The same criteria will used as above (see “Monogenic Disease Risk and Carrier Status for Childhood-Onset Disorders”).

1b.8.2 The Genomic Newborn Sequencing Report

For infants randomized to the GS arm, a “Newborn Genomic Sequencing Report” (NGSR) will be generated that will follow a format already being utilized clinically by the LMM, and in the MedSeq Project[92] but with modifications to include only genes associated with childhood onset conditions and a small subset of highly actionable adult-onset conditions (see attached “Sample NGSR”). Separate sections on the NGSR will indicate results under the following headings:

Monogenic Disease Risk: We will report pathogenic or likely pathogenic variants that meet reporting criteria that are in heterozygous state and are associated with autosomal dominant or X-linked disorders; in homozygous or compound heterozygous state and are associated with autosomal recessive disorders; or in hemizygous state and are associated with X-linked recessive disorders. These variants may be caused by alterations in the DNA sequence (i.e., missense, nonsense variants) or alterations in gene dosing and genome structure (i.e. microdeletions, copy number variants).

Highly Actionable Adult-Onset Only Monogenic Disease Risk: We will report pathogenic or likely pathogenic variants in highly actionable adult-onset conditions as characterized by the ACMG recommendations. Of note, although this was not the initial plan in the initial BabySeq study, this category was added in agreement with (and under the advice of) the IRB. Currently this includes hereditary breast and ovarian cancer genes (BRCA1, BRCA2) and Lynch syndrome genes (MLH1, MSH2, MSH6, PMS2) that are autosomal dominant.[118] If the ACMG recommendations are updated and other genes are added that are of adult-onset only, we will add these.

Carrier Risk: In the case of autosomal recessive or X-linked recessive disorders, we will report pathogenic or likely pathogenic variants that meet reporting criteria that are in heterozygous state (recessive) or in a female (X-linked recessive) and thus the infant is a carrier and not affected.

1b.8.3 The Indication-Based Analysis

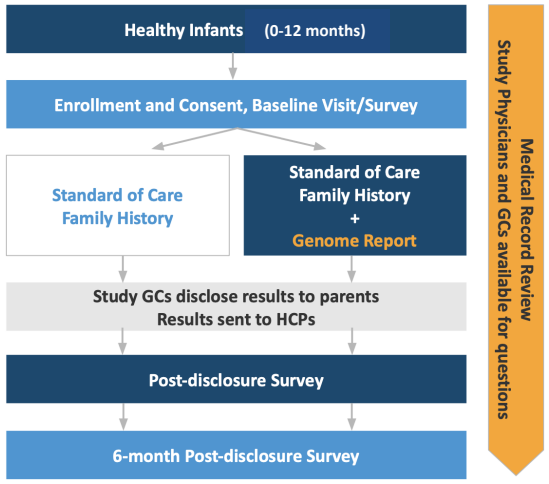
In the event that one of the babies becomes ill with symptoms where a genomic analysis may be helpful for diagnosis or treatment of a particular presentation, an "Indication-Based Analysis" (IBA) will be generated in response to requests by the baby's physicians in consultation with the study team, or by the study team physicians. The IBA will include interrogation of genes associated with the syndrome or clinical features in question, as currently practiced in medical genetics. In addition, upon request, an IBA may additionally include Evidence Class I and II variants from PharmGKB[119] for specific indications (e.g., anti-epileptic medication in neonates with seizures). For every situation in which an IBA is requested, the study physician will be in communication with the clinical team or physician ordering the IBA and will make sure that a re-query of the genomic sequence is not ordered in lieu of a targeted genetic test or panel that would be more appropriate for a specific presentation. Gene-disease criteria for the IBA will include results in genes that have a moderate level of evidence (using the ClinGen framework). Penetrance will not be considered in reporting as these individuals will be exhibiting symptoms. The IBA will include variants that are considered Variants of Uncertain Significance (VUSs) relevant to the condition, according to the ACMG/AMP criteria in addition to pathogenic and likely pathogenic variants.

1b.9 Consultation and Disclosure of Reports

A study physician and/or genetic counselor will disclose study results during a consultation with each family held either in-person, by video, or by phone. The study physician/genetic counselor will provide the consultation to families utilizing all available medical information. For Spanish-speaking families, the session will be completed in Spanish with a professional interpreter and the reports will be in Spanish.

Both arms: The review of the family history report will be returned. If the family history obtained during the baseline visit suggests that targeted genetic testing for a Mendelian condition should be pursued, the family will receive additional genetic counseling, and may be referred for clinical genetic counseling and/or targeted testing for this indication. For the FH arm, this is the only result that will be returned

Figure 8. Workflow for Infants and Parents



FH+GS arm: In addition to the family history report, the sequencing report(s) will be returned. If an MDR is identified in the infant, cascade screening will be offered to all first-degree relatives (biological parents and siblings).

We will collect informal, open-ended feedback from the first several participants at each site regarding their experience with the disclosure visit. What we learn will inform changes in our materials and process.

It should be noted that the raw sequence data will not be returned to participants or placed in the medical record at the time of disclosure. This data will be available to parents/guardians and/or physicians upon request and consent for release.

1b.10 Generating a Clinical Note

The team of study physician and genetic counselor will generate a clinical note following the results disclosure visit summarizing the findings of the reports, what was discussed in the consultation, and what recommendations were made. This note will be included in the patient's chart and forwarded to physicians involved in the infant's care.

1b.11 Return of Results and Follow-up

Genetics Resource Center (GRC): Oversight of the return of reports to HCPs will be supported through the GRC, which will be available to the HCPs and families throughout the study. The GRC will be designed as a two-tier e-consult service managed by the GCs and genetics specialists from each site: Dr. Holm (BCH) and Dr. Korf (UAB), both pediatricians and medical geneticists; Dr. Green (BWH), a medical geneticist; and Dr. Gelb (Mount Sinai), a pediatric cardiologist and Professor of Genetics and Genomic Sciences. Tier 1 involves the management of HCP and family inquiries by each individual site, including clinical referrals. Tier 2 involves the escalation of study-based inquiries and de-identified clinical questions to a central study resource managed by the coordinating site (BWH). The GCs and genetics specialists will be available to discuss the reports and other issues with HCPs, and to answer questions for families throughout the study.

Providing Genomic Reports to HCPs: The FHR +/- the NGSR will be provided to the HCP via EMR upload, fax, and/or secure email. If there is a MDR finding on the NGSR, the GRC genetics specialist at the site will contact the HCP by phone or in person, discuss the report, and provide advice, if needed, on interpretation and clinical management. HCPs can use the results to guide care, make needed referrals, etc., informed by the educational activities (Aim 1a). In addition, the GRC geneticist and GC will be available at all times for HCP questions about the study, a FHR, or a NGSR.

1b.12 Follow-up Surveys

Once the results have been returned, there will be a post-disclosure and 6-months post-disclosure survey. These may be completed in person, over the phone, or online (via REDCap). Participants will be offered the option to have an RA read the survey questions and to respond verbally.

1b.13 Retention

We will leverage methods implemented in the AoURP at UAB and BWH to encourage relationship-building and retention of participants: 1) RAs will be paired with families to coordinate participation and follow-up. 2) We will collect multiple contact methods at enrollment, including preferred method. Texting via hospital-approved methods will be an option. Participants my opt-in to texting and non-secure email during consent and these methods of communication may be used for follow-up such as survey and appointment reminders. 3) We will keep track of when our participants return for a clinic visit, using that as an opportunity to connect with them, answer questions, and encourage continued involvement. 4) We will mail/email birthday cards to the child (see attached "Sample Birthday Card"). 5) Newsletters, reviewed by the Stakeholder Board, will be shared via email and regular mail, and be available in print at follow-up visits, so families can stay updated on study progress and findings (see attached "Sample Newsletter"). 6) Participating families will be contacted multiple times and through a variety of contact methods to schedule study visits and complete surveys. Contact

methods may include phone, email, text, electronic medical record messaging, physical mail, and/or direct contact from pediatricians or other clinic staff.

Families will be contacted at least annually throughout the funded period of the study by birthday card, newsletter, and/or additional survey or interview requests. All communication will:

1) Provide a link to updated scientific papers publishing results of the study
2) Remind families that study staff will continue to have access to the child's medical record for long-term data collection
3) Provide study contact information for questions or to opt-out of further participation

We will monitor retention closely throughout the study and discuss additional strategies and troubleshooting with the Stakeholder Board.

1b.14 Long term follow-up

We plan to access medical records and may conduct annual surveys or interviews until the infant reaches age 18 to best capture the effects of genomic sequencing on the entire pediatric period (if the study is still ongoing). Parents will consent to continued involvement throughout the funded study period, potentially up to age 18. Given the long-term nature of the project, if the study remains active, we will contact the family after the child's 18th birthday to obtain consent from the participant. No study procedures (i.e. medical record review) will take place after the child turns 18 until consent is obtained. If we are unable to reach the family and obtain consent from the participant, we will withdraw them from further participation in the study. In some cases, the participant may not be cognitively able to provide assent or consent, in which case we will discuss continued participation with the parent(s)/legal guardian(s), document the child's cognitive ability and obtain documentation of the parent's/legal guardian's legal health care proxy status (in the instance that the child turns 18 years).

1b.15 Study withdrawal

If parents/guardians ask to withdraw their family's samples and infant's genomic data from the study, any genomic reports on their infant that have already been placed in the electronic medical record will have become part of clinical care and cannot be deleted or withdrawn. Any de-identified sequences or data that have been uploaded to shared databases such as the Database of Genotypes and Phenotypes (dbGaP) cannot be withdrawn.

Aim 2: To evaluate the impact of GS on a diverse group of infants, their families and their HCPs.

Aim 2a: To assess the psychosocial impact of infant GS on parents/guardians from varying ethnic and racial backgrounds, we will conduct longitudinal surveys and compare validated scales between arms of the RCT.

The psychosocial impact of GS on families will be evaluated in three domains: 1) parent-child relationship, 2) partner relationship, and 3) personal impact (see Table 2). In order to thoroughly assess the impact of GS on families, we will use the Parenting Stress Index Short Form (PSI-4-SF),[121] a well-accepted measure of parent-child relationships that has been previously used to examine the impact of expanded NBS,[121-123] as our primary outcome, and the Child Vulnerability Scale[124] as a secondary outcome. To study relationship conflict and satisfaction, and partner blame, we will measure marital satisfaction with the Kansas Marital Satisfaction scale[121-123; 125] as our primary outcome, and partner blame using a novel measure developed for BabySeq as a secondary outcome. Given that a significant proportion of our parents may be single, relationship status will be important to factor into the analyses. Our primary outcome measure of personal distress will be anxiety, using the 7-item General Anxiety Index (GAD-7).[126] Secondary measures of distress will be depression, as assessed with the 9-item Patient Health Questionnaire (PHQ-9),[126] and self-blame using a novel measure created for BabySeq. The study staff will follow-up and offer clinical support

services to any parent who scores above a predetermined threshold for anxiety or distress on the measures, as we did in BabySeq.

Table 2. Psychosocial Outcome Domains

Domain	Construct	Measure
H1. Parent-child relationship	Parenting stress, relationship dysfunction	†Parenting Stress Index, 4th Edition Short Form
	Child vulnerability	Child Vulnerability Scale
H2. Partner relationship	Relationship satisfaction	†Kansas Marital Satisfaction Scale
	Partner blame	Novel, developed for BabySeq
H3. Personal distress	Anxiety	†GAD-7
	Depression	PHQ-9
	Self blame	Novel, developed for BabySeq
†denotes primary outcome for hypothesis		

Surveys at baseline (enrollment) and immediately and 6-months post-disclosure will be brief (20-30 minutes) and completed by the one parent enrolled in the study (see attached "Baseline Survey," "PD Survey," and "6mth PD Survey"). Parents/guardians will complete the surveys online (RedCap) via email or text message (if that is an option), on paper, a tablet computer, or verbally with an RA at the HCP office or over the phone. We will make all study materials available in Spanish, which will be submitted to the IRB following initial approval of the English-language materials. Several of our outcome measures have been validated in Spanish-speaking populations, including the PSI-4-SF,[127] the Kansas Marital Satisfaction scale,[128] and the GAD-7.[127] Measures that are novel or do not have a Spanish language version will be translated by native Spanish speakers using forward and back translation procedures.

Parents/guardians participating in this study will be compensated for each visit and survey completed, with remuneration as follows: $50 for the baseline visit and survey; $50 for the disclosure visit and post-disclosure survey; and $50 for the 6-month post-disclosure survey. Thus, each household will receive $150 if they finish the study and complete all of the study surveys from the baseline through the 6-month post-disclosure survey. Parents/guardians will receive this remuneration in the form of electronic gift cards, checks, physical gift cards, or reloadable ClinCards. If a parent withdraws from the study, they will be compensated for the surveys completed up until the time of withdrawal.

If we can obtain long-term funding, we may also contact families for an annual survey or interview until the infants turn 18 years to assess how participation in the study affected their family or thought process. At this time, we do not have the funding to provide remuneration for the completion of these surveys/interviews; however, if funding were to become available, we plan to offer a small payment.

Aim 2b: To assess the medical impact of GS on infants and their families, we will review medical records and survey parents/guardians to track symptoms, laboratory or diagnostic results, new diagnoses, and medical actions attributed to the GS findings. Among infants with an MDR, we will determine whether the MDR: (a) reveals an unsuspected phenotype in the infant or family, (b) explains a family history of a condition, and/or (c) prompts surveillance in the infant or family.

Data on medical outcomes will provide insight into the impact of the FHR and NGSR on diagnostic thinking and intermediate clinical outcomes.[129] On a yearly basis, information collected from parents/guardians via surveys and/or from the medical records will include: contact information for the child's HCPs, outpatient visits, hospitalizations and surgeries, parent medical visits and/or testing (due to study information), and parental records relevant to reproductive decision-making. Using methods developed for BabySeq,[33] we will create outcome forms specific to each MDR and condition of note on the FHR that list associated diseases, diagnostic and screening tests, and treatments. We will query the infants' medical record to determine if (a) the MDR was a new or known diagnosis, (b) family histories for the MDR diseases had been recorded, and (c) related diagnostic or screening tests were ordered for an MDR or a condition noted on the FHR. If the information collected is incomplete, a study GC or RA may contact the parent for follow-up details. Any future interview guide will be reviewed by the study Stakeholder Board and submitted for IRB review. We will keep track of emerging signs and symptoms in children with an MDR and will collect the impact on medical outcomes.

Aim 2c: To assess the impact of GS in infants on clinical care, we will collect feedback from HCPs throughout the study by monitoring use of the "Genome Resource Center" and conducting interviews with HCPs towards the end of the study.

HCPs providing care for our participants are well positioned to identify the benefits and challenges of implementing GS in their healthy patients and more broadly in the populations enrolled. We will conduct semi-structured interviews of HCPs who received a NGSR. Interviews will be as efficient as possible (target 30 minutes) and we will offer an incentive to participate. We will interview HCPs of infants randomized to the FH+GS arm until we reach thematic saturation, when additional interviews no longer yield novel information.[130] Our goal is to ensure that a broad range of experiences are represented to capture benefits and challenges that may be unique to the different sites, as well as obtain sufficient information power.[131] At each site a trained RA, with oversight by an investigator, will conduct the interviews by phone, videoconference (e.g., Zoom), or in person. HudsonAlpha will lead the development of a future interview guide that will be submitted for IRB review. The semi-structured format allows us to guide the HCP to topics we want all interviewees to address, while allowing them to share experiences and introduce relevant issues we did not anticipate. Interviews will be audio-recorded, transcribed, and the data uploaded to Dedoose for analysis.

It should be noted that we currently do not have an interview guide for these interviews. Once we have developed a guide, we will submit to the IRB for approval before implementing.

Aim 3: Exploratory Aim: To evaluate healthcare utilization and associated costs of GS. Using novel approaches, we will identify healthcare services motivated by the study in the two study arms and examine attributable healthcare costs accrued for the infants and other family members.

This project provides a unique opportunity to gather exploratory trials-based economic data about the impact of GS in diverse populations of healthy infants. Data will inform analyses from the health sector and societal perspectives.[132] We will expand on approaches we developed for previous studies and use multiple strategies to identify services and costs associated with the care of infants, their parents, and family members.[21; 63; 64] Approaches are summarized in Table 3.

Table 3. Healthcare Utilization Analysis Strategy

Approach	Overview of Services Included	Population of Focus
Attributable services	Services that were recommended during disclosure sessions and services patients reported as motivated by BabySeq disclosure	Child and parents
Genomic services	Any genetic or genomic test	Child and parents
All costs	All healthcare, out-of-pocket, and informal health sector costs	Child only

Primary analyses of healthcare utilization and costs will expand an "attributable services" approach implemented in related work we have conducted.[56; 63] We will use the notes from disclosure sessions to identify services that were recommended for infants or parents/guardians, and then verify whether the services occurred. By including only services that we can link directly to this study, this approach will produce data with the greatest measurement precision. To identify efficiencies where genetic tests were avoided by having GS, and to identify instances of cascade genetic testing, we will also focus on genetic services that infants and parents/guardians received after disclosure sessions. Finally, we will conduct "all costs" analyses where we summarize all health sector costs observed in medical records and supplemented by survey items that ask about hospitalizations, health care visits, genetic services, and familial out-of-pocket expenses. Due to the expansiveness of this approach, "all costs" analyses will focus on costs for the care of the child only.

Data about health care utilization will be obtained from infants' medical records, primarily from each institution's corporate data warehouse, and supplemented with participant-reported data from interviews and surveys. Costs for services will be assigned to services based on actual costs, where data is available, or by assigning cost weights using reimbursement rates per the Centers for Medicare and Medicaid Studies.

2. Patient Selection and Inclusion/Exclusion Criteria

Inclusion criteria:

HCP participants

a. Age 18 years of age or older
b. Pediatric health care provider providing primary care to infants in the clinics from which we will enroll (physician, nurse practitioner, physician assistant).

Infant participants

a. Age 0-12 months
b. Seen for pediatric care at participating clinic where local clinic champions have completed the GS education program
c. One parent or guardian meeting the parent/legal guardian inclusion criteria

Parent/Guardian participants

c. Biological parent or legal guardian of an infant participating in the study
d. Age 18 years of age or older
e. Has unimpaired decisional capacity
f. English or Spanish speaking
g. Available to have genetic counseling and provide consent for testing the infant
h. Available to complete 3 surveys over 9 - 12 months

Exclusion criteria:

a. Infant has previously undergone ES or GS
b. Parent(s)/guardian(s) are unwilling to have genomic reports placed in the infant's medical record or sent to their primary care pediatrician
c. Any infant in which clinical considerations preclude drawing up to 1.0 ml of blood

3. Description of Study Treatments or Exposures/Predictors

The intervention in this research study is GS.

4. Definition of Primary and Secondary Outcomes/Endpoints

Primary Outcome Measures:

1. *Monogenic disease risks (MDRs)*: Pathogenic (P) and likely pathogenic (LP) variants identified relevant to infant's health (dominant or biallelic recessive disease risks) [Time Frame: 3 months after enrollment]
2. *Carrier status variants*: P and LP variants identified as recessive carrier status in infant [Time Frame: 3 months after enrollment]
3. *MDR-associated phenotype*: Signs or symptoms of monogenic disease risk identified by genome sequencing [Time Frame: 3 months after enrollment and 1-year post-disclosure (15 months after enrollment)]
4. *Parent-Child Relationship*: Parenting Stress Index, 4th Edition Short Form; Vulnerable Baby Scale [Time Frame: Baseline, post-disclosure (3 months after enrollment), 6 months post-disclosure (9 months after enrollment)]
5. *Partner Relationshi*p: Kansas Marital Satisfaction Scale; Partner Blame [Time Frame: Baseline, post-disclosure (3 months after enrollment), 6 months post-disclosure (9 months after enrollment)]
6. *Personal Distress*: General Anxiety Disorder-7, Patient Health Questionnaire (PHQ)-9 , Self-Blame [Time Frame: Baseline, post-disclosure (3 months after enrollment), 6 months post-disclosure (9 months after enrollment)]

Secondary Outcome Measures:

7. *MDR-associated family history*: Signs or symptoms of monogenic disease risk or recessive condition present in infant's biological family [Time Frame: 3 months after enrollment and 1-year post-disclosure (15 months after enrollment)]
8. *Feelings about genomic testing*: Feelings About genomiC Testing Results (FACToR) Questionnaire [Time Frame: Baseline, post-disclosure (3 months after enrollment), 6 months post-disclosure (9 months after enrollment)]

   Other Pre-specified Outcome Measures:

   MDR-associated intervention: Healthcare intervention prompted by monogenic disease risk or recessive carrier variant [Time Frame: 1-year post-disclosure (15 months after enrollment)]
9. *Suspected genetic condition*: Any phenotype that develops in an infant suspected to have a genetic cause, or any genetic testing ordered as part of clinical care [Time Frame: 1-year post-disclosure (15 months after enrollment)]
10. *Cost of attributable services*: Cost of healthcare services that were recommended for infants and parents/guardians as part of study disclosure session [Time Frame: 1-year post-disclosure (15 months after enrollment)]
11. *Cost of genomic services*: Cost of genetic services infants and parents/guardians received after study disclosure session [Time Frame: 1-year post-disclosure (15 months after enrollment)]
12. *All healthcare costs*: All health sector costs observed in medical records and survey questions regarding family out-of-pocket expenses [Time Frame: 1-year post-disclosure (15 months after enrollment)]

5. Data Collection Methods, Assessments, Interventions and Schedule (what assessments performed, how often)

Visit 1 (may occur in multiple parts, remote or in person): Eligibility, consent, demographics, medical history (diagnoses, visits, tests, procedures, medications, hospitalizations, surgeries), family history, baseline parent survey, sample collection

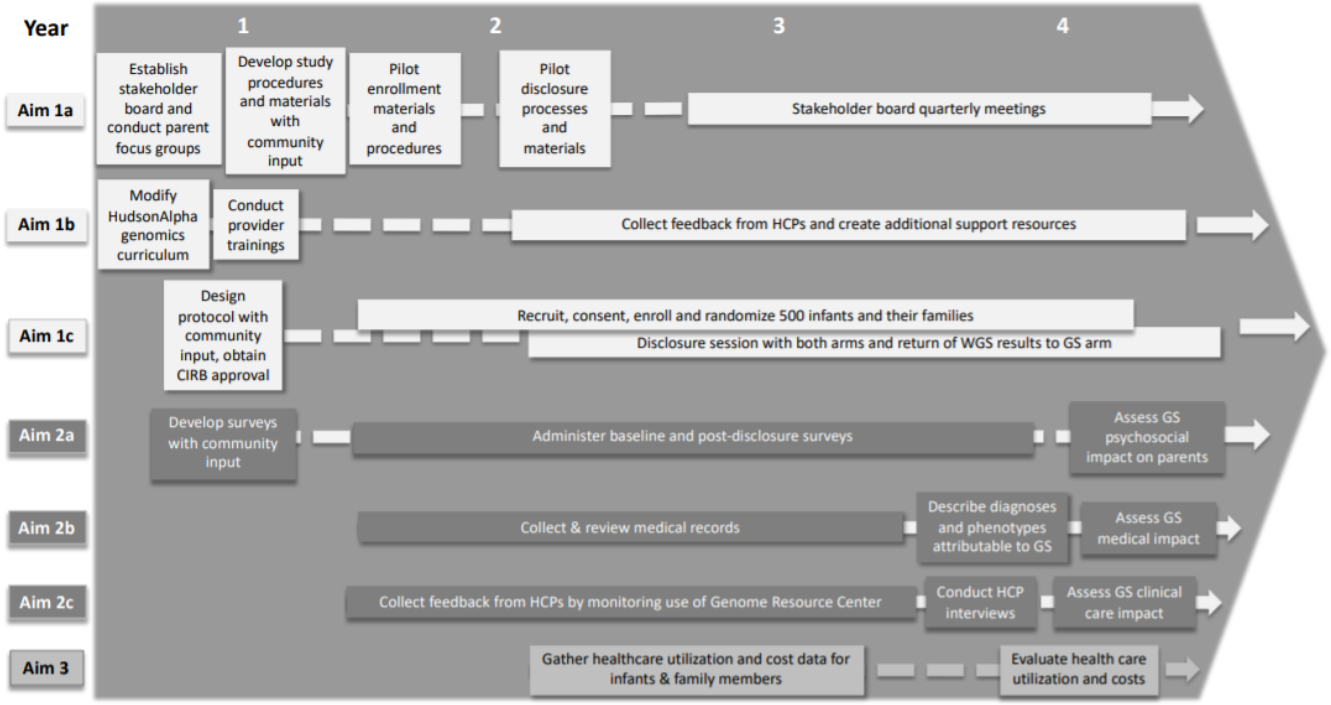
Visit 2 (*3-4 months after Visit 1- remote or in person*): Genome results (for sequencing intervention group), updated medical history, updated medical history, physical exam, post-disclosure parent surveys. Log clinical disclosure note as PDF.

Visit 3 (*6 months after Visit 2- remote*): 6-month post-disclosure parent survey.

Visit 4 (*1 year after Visit 2- remote*): Updated participant medical history. Parent(s) medical visits and/or testing (due to study information), and parental records relevant to reproductive decision-making. Document whether each data point is related to genome findings and estimate any associated costs.

Repeat Visit 4 procedures on an annual basis throughout the study period.

6. Study Timeline (as applicable)



E. Adverse Event Criteria and Reporting Procedures

If a participant expresses emotional distress related to study participation or provides survey responses suggesting impaired family bonding or emotional distress, they will be referred to a study physician or study psychologist for further psychosocial assessment as described above. All serious such cases, including those requiring a referral to mental health professional or other therapeutic intervention, will be reported to the IRB as per the current IRB reporting guidelines and at the annual continuing review for the protocol

F. Data Management Methods

Participant and outcomes data collected as part of this research study will be entered into REDCap: a secure, HIPAA-compliant software hosted inside the coordinating institution firewall (BWH). An experienced data manager will build this database. Each recruitment site will enter identifiable data about participants that cannot be viewed by other recruitment sites. Participant surveys will also be administered through REDCap. Study team members at the coordinating site will have access to all data entered, as needed for recruitment coordination, data monitoring and quality assurance.

Any identifiable data exports from REDCap will be kept in locked cabinets, or in password protected computer files stored securely on institutional HIPAA-compliant platforms. Identifiable data will be kept to the minimum necessary and only included if required for specific analyses. Recruitment sites will never have access to identifiable data from other sites. Teams involved with analysis of psychosocial survey data will not have access to identifiable data unless needed to coordinate interviews. Teams involved with analysis of medical and economic data will have access to identifiable data for analysis of medical records and healthcare claims.

The Laboratory for Molecular Medicine will receive biological samples and store data according to their secure HIPAA-compliant procedures.

All reports placed in the medical records of participating infants will be subject to all privacy protections afforded clinical information.

When genomic data are uploaded to dbGaP and/or other databases for sharing with qualified research investigators, no PHI information will be uploaded that could lead to the identification of these research participants. However, since genome data is a unique dataset (like fingerprints or retinal scans), and since advanced computational techniques may allow deductions with other publically available datasets, it is unlikely but may be possible in the future for individuals to identify research participants through these datasets. This possibility will be discussed in the Pre-enrollment Sessions and in the consent process. We will obtain a Certificate of Confidentiality as another layer of confidentiality protection for participants in this study.

G. Quality Control Method

Research assistants at each site will be trained on data entry methods prior to beginning recruitment. At each recruitment site, one study team member will enter data, and another will cross-check each record until they are confident in accuracy and consistency. After this time, records will be cross-checked as needed. The coordinating site will have access to all data entry and will review regularly and raise queries as needed.

Laboratory quality control will be implemented according to current CLIA- approved methods.

H. Data Analysis Plan

Aim 2a: To assess the psychosocial impact of infant GS on parents/guardians from varying ethnic and racial backgrounds, we will conduct longitudinal surveys and compare validated scales between arms of the RCT.

We will view the GS arm as non-inferior if upper bounds of confidence intervals for the differences in means on these outcomes (FH+GS arm minus FH arm) are less than the differences in scores on each scale that are considered clinically meaningful. We will conduct per-protocol analyses in which all families who attended disclosure sessions are analyzed. We will use generalized linear models fit with generalized estimating equations to conduct repeated measures analyses and use contrasts to compare means in the two randomization arms. For analyses of personal distress and parent-child relationships per GAD-7 and PSI-4 scores, we will use a log link, given the right-skewed distributions, while analyses of marital satisfaction per the Kansas Marital Satisfaction scale will use an identity link. Missing data will be imputed using fully conditional specification. Models will include terms for time as a categorical variable, interaction between time and randomization arm, and the corresponding baseline measure, where applicable.

Aim 2b: To assess the medical impact of GS on infants and their families, we will review medical records and survey parents/guardians to track symptoms, laboratory or diagnostic results, new diagnoses, and medical actions attributed to the GS findings. Among infants with an MDR, we will determine whether the MDR: (a) reveals an unsuspected phenotype in the infant or family, (b) explains a family history of a condition, and/or (c) prompts surveillance in the infant or family.

The analysis of these data will largely be descriptive, due in part to the nature of the data with heterogeneous diagnoses.

Aim 2c: To assess the impact of GS in infants on clinical care, we will collect feedback from HCPs throughout the study by monitoring use of the “Genome Resource Center” and conducting interviews with HCPs towards the end of the study.

Once at least 5 interviews have been transcribed, Drs. Holm and Pereira will work with the project coordinator at BWH to develop a coding scheme utilizing thematic content analysis.[134] Inductive codes will be added to the coding scheme as new themes emerge. Using the coding scheme, we will use standard methods for team-based qualitative analysis with consensus coding[135] conducting interviews with HCPs towards the end of the study.

Aim 3: Exploratory Aim: To evaluate healthcare utilization and associated costs of GS. Using novel approaches, we will identify healthcare services motivated by the study in the two study arms and examine attributable healthcare costs accrued for the infants and other family members.

Since standards have not been established about what to report from GS, we will collect data to conduct one-way scenario analyses that provide insight about reporting strategies that vary the following:

- *Definition of attributable services*. To provide a high side estimate of care that may have been prompted, we will use genomic references, including GeneReviews, OMIM, and primary literature,[136; 137] to identify all possible follow-up services that may be used to screen for conditions identified on the FHR or NGSR.
- *Classes of findings reported* (e.g., reporting only findings from an IBA, or only MDR).
- *Conditions reported* (e.g., if we reported findings associated only with pediatric-onset conditions, or conditions on the ACMG SF v3.0 list[118]).
- *Classification criteria* (e.g., if we reported only variants classified as pathogenic)

Intervention costs will include pre-analytics, such as DNA extraction, GS variant classification, and disclosure of results. Post-disclosure costs will use actual cost data when available, updated to the year of analysis using the medical care component of the Consumer Price Index (CPI).[137; 138] Costs will be assigned to other downstream healthcare services by multiplying utilization by cost weights derived from the Centers for Medicare and Medicaid Studies fee schedules.[63] To facilitate analyses from the societal perspective, we will collect data about family out-of-pocket expenses using survey items.[63; 132] We will use generalized linear models with a log link and gamma family error to compare randomization arms on attributable costs for infants and their parents/guardians. We will also run regression models that include terms for ethnicity and ethnicity-randomization arm interactions to determine whether costs overall and/or incremental cost of GS varies by ethnicity.

I. Statistical Power and Sample Considerations

Aim 2a:

Based on 1-sided t-tests and non-inferiority bounds of 5 points for the GAD-7, 9 points for the PSI-4 (0.5 sd), and 1.1 points for the Kansas Marital Satisfaction scale (0.5 sd) and assuming complete data from at least 200 (an 80% completion rate) families in each randomization arm, we estimate over 99% power to confirm noninferiority of GS on each measure at $\alpha = 0.016$ (after Bonferroni correction for three outcomes). Actual analyses will probably be even more precise due to the use of repeated measures and imputation of missing data. Also, for a correlation of about 0.5 among repeated observations in the same subject (as observed on multiple outcomes during BabySeq), we find that the sample size needed with 3 observations, compared to a single observation, is about 65% for the same power and alpha levels. We will also run separate regression models that include terms for ethnicity and ethnicity-randomization arm interactions to determine whether outcomes vary by ethnicity and whether any impact of GS varied by ethnicity. Our Stakeholder Board will be encouraged to pose additional questions for analysis, review and present results, and co-author publications.

Aim 3:

We will use generalized linear models with a log link and gamma family error to compare randomization arms on attributable costs for infants. Cost analyses will be exploratory, but we anticipate that we will have 93% power at $\alpha=0.05$ (two-tailed) to detect a standardized effect size of $d=0.31$, which is roughly equivalent to attributable costs in the GS arm being approximately 61% greater than attributable costs in the control arm.

J. Study Organization

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Alan Beggs, PhD (Co-I)
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Robert C. Green, MD, MPH (Contact PI and mPI)

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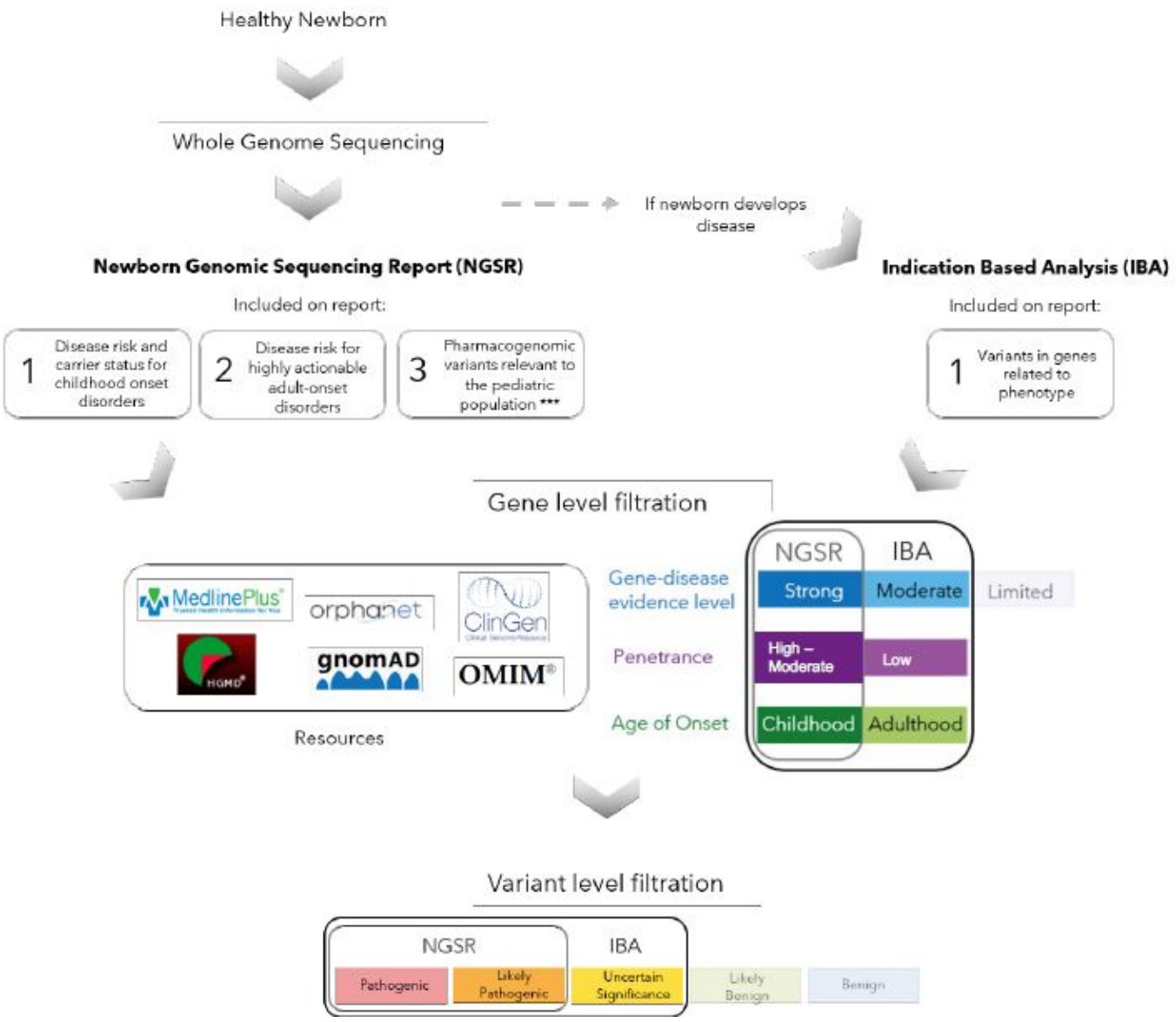
Appendix 1: Genomic Reporting Framework



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Appendix 2: ACMG SF v3.2 gene and associated phenotypes recommended for return as secondary findings from clinical exome and genome sequencing (adapted from Miller et al., 2023, PMID: 37347242)

Genes related to cancer phenotypes

	Gene	Inheritance	Variants to report	Notes
Familial adenomatous polyposis	*APC*	AD	All P and LP	
Familial medullary thyroid cancer	*RET*	AD	All P and LP	RET is also associated with multiple endocrine neoplasia type 2
Hereditary breast and/or ovarian cancer	*BRCA1*	AD	All P and LP	
	BRCA2			
	PALB2			
Hereditary paraganglioma–pheochromocytoma syndrome	*SDHD*	AD	All P and LP	
	SDHAF2			
	SDHC			
	SDHB			
	MAX			
	TMEM127			
Juvenile polyposis syndrome	*BMPR1A*	AD	All P and LP	
	SMAD4			SMAD4 is also associated with hereditary hemorrhagic telangiectasia.
Li–Fraumeni syndrome	*TP53*	AD	All P and LP	
Lynch syndrome	*MLH1*	AD	All P and LP	
	MSH2			
	MSH6			
	PMS2			
Multiple endocrine neoplasia type 1	*MEN1*	AD	All P and LP	
MUTYH-associated polyposis	*MUTYH*	AR	P and LP (2 variants)	
Neurofibromatosis type 2	*NF2*	AD	All P and LP	
Peutz–Jeghers syndrome	*STK11*	AD	All P and LP	
PTEN hamartoma tumor syndrome	*PTEN*	AD	All P and LP	
Retinoblastoma	*RB1*	AD	All P and LP	
Tuberous sclerosis complex	*TSC1*	AD	All P and LP	
	TSC2			

von Hippel–Lindau syndrome	*VHL*	AD	All P and LP	
WT1-related Wilms tumor	*WT1*	AD	All P and LP	

Genes related to cardiovascular phenotypes

	Gene	**Inheritance**	**Variants to report**	**Notes**
Aortopathies	*FBN1*	AD	All P and LP	
	TGFBR1			
	TGFBR2			
	SMAD3			
	ACTA2			
	MYH11			
Arrhythmogenic right ventricular cardiomyopathy	*PKP2*	AD	All P and LP	
	DSP			DSP is also associated with dilated cardiomyopathy (DCM) as a primary disease
	DSC2			
	TMEM43			
	DSG2			
Catecholaminergic polymorphic ventricular tachycardia	*RYR2*	AD	All P and LP	
	CASQ2	AR	P and LP (2 variants)	
	TRDN			TRDN is also associated with long QT syndrome
Dilated cardiomyopathy	*TNNT2*	AD	All P and LP	TNNT2 is also associated with hypertrophic cardiomyopathy (HCM)
	LMNA			
	FLNC			
	TTN			
	BAG3			
	DES			
	RBM20			

	TNNC1			
Ehlers–Danlos syndrome, vascular type	*COL3A1*	AD	All P and LP	
Familial hypercholesterolemia	*LDLR*	AD	All P and LP	
	APOB			
	PCSK9			
Hypertrophic cardiomyopathy	*MYH7*	AD	All P and LP	MYH7 is also associated with dilated cardiomyopathy (DCM) as a primary disease
	MYBPC3			
	TNNI3			
	TPM1			
	MYL3			
	ACTC1			
	PRKAG2			Pathogenic variants in PRKAG2 are associated with metabolic storage disease that mimics a HCM, but also can involve skeletal muscle.
	MYL2			
Long QT syndrome types 1 and 2	*KCNQ1*	AD	All P and LP	
	KCNH2			
Long QT syndrome 3; Brugada syndrome	*SCN5A*	AD	All P and LP	SCN5A is also associated with dilated cardiomyopathy (DCM) as a primary disease
Long QT syndrome types 14-16	*CALM1*	AD	All P and LP	
	CALM2	AD		
	CALM3	AD		

Genes related to inborn errors of metabolism phenotype

	Gene	Inheritance	Variants to report	Notes
Biotinidase deficiency	*BTD*	AR	P and LP (2 variants)	
Fabry disease	*GLA*	XL	All hemi, het, homozygous P and LP	GLA also applies to the cardiovascular category
Ornithine transcarbamylase deficiency	*OTC*	XL	All hemi, het, homozygous P and LP	
Pompe disease	*GAA*	AR	P and LP (2 variants)	

Genes related to miscellaneous phenotypes

	Gene	Inheritance	Variants to report
Hereditary hemochromatosis	*HFE*	AR	HFE p.Cys282Tyr homozygotes only (NM_000410.3)
Hereditary hemorrhagic telangiectasia	*ACVRL1* *ENG*	AD	All P and LP
Malignant hyperthermia	*RYR1* *CACNA1S*	AD	All P and LP
Maturity-onset diabetes of the young	*HNF1A*	AD	All P and LP
RPE65-related retinopathy	*RPE65*	AR	P and LP (2 variants)
Wilson disease	*ATP7B*	AR	P and LP (2 variants)
Hereditary TTR amyloidosis	*TTR*	AD	All P and LP