# Genome Sequence-Based Screening for Childhood Risk and Newborn Illness: The BabySeq Project

Study Protocol and Statistical Analysis Plan
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## BACKGROUND AND SIGNIFICANCE

### *Historical Background*

Laboratories around the country are now offering CLIA-certified whole exome (WES) or whole genome sequencing (WGS) as a clinical service[1-4] for molecular characterization of rare disorders[5,6] and individualized cancer treatments.[7,8] However, as costs come down and informatics advance, sequencing is likely to be applied much more broadly to pharmacogenomics, risk assessment in healthy adults, carrier screening, prenatal screening, and newborn screening.[9-13]

NIH leaders recognize that sequencing of newborns may not be far in the future. NIH director Dr. Francis Collins has said: "…whether you like it or not, a complete sequencing of newborns is not far away"[10] and NICHD director, Dr. Alan Guttmacher explicitly invoked genomic sequencing of newborns: "One can imagine the day that 99% of newborns will have their genomes sequenced immediately at birth."[9] As the President's Council on Bioethics concluded as early as 2008, it may soon "…prove impossible to hinder the logic of genomic medicine from assimilating the currently limited practice of newborn screening into its all-embracing paradigm."[14,15] As a result, the NIH, including the NICHD, NHGRI, and Office of Rare Diseases Research (ORDR) held a workshop in 2010 to "identify elements of a trans-NIH research agenda that could inform the possible application of new genomic concepts and technologies to newborn screening and child health". This led the NICHD and NHGRI to issue a Request for Applications (RFA) that was considered "an initial step along this path" with the purpose of exploring "opportunities to use genomic information for broadening our understanding of diseases identified in the newborn period". The NICHD and the NHGRI invited applications that "propose to explore the implications, challenges and opportunities associated with the possible use of genomic sequence information in the newborn period". The funding agencies recognized that the "new, sophisticated and increasingly cost-effective techniques for DNA-based sequencing and analysis may make it possible to expand newborn screening in the future and substantially expand its clinical and public health value". Our group applied for funding under this RFA and our proposal was funded through a cooperative agreement (U19). This IRB protocol presents the work to be undertaken.

The clinical use of genetic tools in the newborn period is currently being approached from two directions. First, as noted above, clinical sequencing is being increasingly used in ill children, including newborns, to more rapidly and accurately make a diagnosis and guide treatment. For example, Children's Mercy Hospital in Kansas City has pioneered rapid sequencing for infants in the NICU.[16] Secondly, most disorders screened in state-mandated dried blood spot newborn screening are genetic in origin. While the testing for these disorders is largely performed using a primary tier of biochemical and tandem mass spectrometry based assays, a few disorders currently incorporate DNA based genetic testing in a second testing tier (Cystic Fibrosis, Galactosemia, Medium Chain CoA Dehydrogenase Deficiency), and there is rapidly increasing potential for expanding this approach. In addition, state-mandated newborn hearing screening is increasingly benefiting from second tier genetic testing panels that identify sequence variants in genes associated with syndromic and nonsyndromic hearing impairment.[17-21] While the broad application of genomic sequencing as a primary approach in state-mandated newborn screening is likely far off due to costs and controversies surrounding its implementation in a public health program, the elective application of this technology as a primary screen or diagnostic tool for sick and well newborns may be increasingly imminent and is deserving of study.

### *Current Clinical Standards*

Diagnostic genetic testing (single gene, gene panel, or whole exome/genome sequencing) is currently accepted in clinical pediatric care under the following circumstances:

- Diagnosis of symptomatic children thought to have a genetic disorder[22-26]

- Follow-up or confirmatory testing of children identified on state-mandated biochemical newborn screening as at risk for having a genetic disorder[27-30]
- Selection of treatments in cancers, including childhood cancers[31-33]

Predictive or predispositional genetic testing of children with single gene assays is currently accepted in clinical pediatric care where there is a strong family history or identified familial mutation for a child onset disorder, or where identifying a genetic risk for an adult-onset disorder might lead to preventative interventions during childhood.

A major difference between whole exome or genome sequencing and targeted testing is the potential in the former for discovering incidental or secondary findings unrelated to the indication for the sequencing but of potential medical importance for clinical care. The American College of Medical Genetics (ACMG) has recommended that laboratories that perform whole exome or genome sequencing in the clinical setting search for and report on a targeted set of such incidental or secondary findings, i.e. pathogenic variants in a list of 56 genes for conditions where the individual may be asymptomatic for a long time and where intervention has been clearly demonstrated to be efficacious.[34] This list includes genes for a number of conditions that are of adult-onset, and the ACMG recommends return of these findings in children, regardless of age, as the findings in the child may have important implications for the health of the parent.

Most, if not all, commercial laboratories that perform clinical diagnostic testing using whole exome or genome sequencing report on the 59 genes recommended by the ACMG. For example, the molecular genetics laboratory at Baylor College of Medicine has sequenced well over 2000 cases, of whom 83% were children and 27% were under 5 years of age (personal communication, Dr. Christine Eng). The Baylor lab routinely reports pathogenic variants in the 59 genes recommended by the ACMG, recessive carrier variants and pharmacogenomic variants with an option for opt-out; and less than 10% of patients or parents elect not to receive these findings. At Baylor, physicians may also choose to order an “Expanded Report” that has an even wider array of genes screened for deleterious mutations, including treatable adult onset conditions, which has been ordered by 26% of the physicians using this service so far.[23,35] Partners Healthcare Laboratory for Molecular Medicine has issued over 25,000 genetic test reports in the past 10 years, and over 45 clinical whole genome sequencing reports in the past year that include carrier and pharmacogenomic variants and are being included in the Partners medical records. Thus, clinical laboratories across the country are already returning incidental or secondary genomic results in children related to highly actionable conditions, including adult-onset conditions. Our study is consistent with these practices. Our protocol is designed to apply current best medical practices in a randomized trial and study the clinical, behavioral, attitudinal and economic outcomes of the application of genomic sequencing in the practice of medicine. While genomic sequencing is a new technology, the results gleaned from genomic sequencing that will be returned in this protocol are conceptually similar to the types of medical information that are currently returned to parents in the clinical care of newborns. In addition, while caution has been advocated in providing predictive genetic testing in children due to concerns that it could damage the parent-child bond,[36] creating vulnerable “patients in waiting”,[37] there is little evidence to support any harm and this assessment of potential harms will be a focus of our study. In this project, we will collect medical, behavioral and economic outcomes related to the return of genomic sequencing information to the physicians and parents of newborns to better inform the imminent future when this technology will be widely available.

### *Prior Research/Preliminary Data*

*MedSeq Project*

The MedSeq Project (PI Dr. Green) is an NIH-funded U01 award that began in December, 2011. The MedSeq Project enrolls only adults, but is otherwise very similar to this Project in that patients with genetic disease (hereditary cardiomyopathy) and healthy middle aged adults are enrolled in a randomized trial to receive either standard of care, or standard of care plus genomic sequencing. As of this writing, the MedSeq Project has nearly completed its planned enrollment of 100 patients with cardiomyopathy and 100 healthy middle-aged adults. The LMM (led by co-PI Dr. Heidi Rehm) is generating clinical sequencing reports for the MedSeq Project and will do so as well for this Project. 44 sequencing reports have been processed and 24 returned thus far to cardiologists and primary care physicians caring for these individuals. The MedSeq Project has generated tremendous amount of preliminary data.[52,200-226] In the MedSeq Project, there has been careful monitoring of both psychological and medical outcomes and thus far, there have been no adverse events in the MedSeq Project.

In this Project, we will be using the same criteria for variant classification and reporting as is used in clinical analysis and reporting by the LMM, and in the MedSeq Project, except that variants will not be analyzed or reported in genes that are exclusively associated with adult-onset conditions.

*Pilot Survey*

In anticipation of our plan to recruit the parents of healthy newborns from the BWH Well Newborn Nursery, we conducted a survey of 514 parents within 48 hours after the birth of their child. These data indicate that the vast majority of parents (82.7%) reported being somewhat to extremely interested in genomic testing for their newborns. [227] None became confused about or refused standard NBS. We asked some of these parents, as well as other parents, the same questions 3-24 months after the birth of their infant and their answers were similar. In particular, less than 1% of parents who answered that they were very or extremely interested while in the hospital, answered that they were not at all interested at a later date indicating that parental choices made on the Newborn Unit appear to be stable.[228]

*Manton Center*

The Manton Center for Orphan Disease Research (Director Dr. Beggs) was established in 2008 with the goals of developing better diagnostic tests and treatments for rare diseases and discovering fundamental biological principles that can lead to advances in understanding of common diseases. The Gene Discovery Core (GDC), a human research protocol approved by the Boston Children's Hospital (BCH) IRB, was established to help accomplish these goals. Under the GDC (medical director, Pankaj Agrawal), patients are enrolled for exome sequencing and other molecular analysis, including gene expression assays, protein functional analysis and cell line creation, with the aim of identifying the underlying cause of the child's medical problems. To date, more than 2,000 individuals have been enrolled in the GDC, and many families with infants in the BCH NICU have been successfully approached and enrolled. Of the families approached, less than 7% declined participation in the study. As part of Dr. Holms' project "Returning Research Results in Children: Parental Preferences and Expert Oversight" (R01HG006615) her group interviewed 9 parents of 6 children who received a genetic diagnosis as a result of the GDC's work about their experience. All families reported having a positive experience with the project and the return of results (personal communication, Dr. Holm). Interestingly, the parents who expressed more negative feelings towards their child's diagnosis expected more actionable change after the molecular cause was identified. This highlights the need for additional projects to look at the outcomes of a genetic diagnosis in a child.

*Standards Development in Clinical Practice*

A number of investigators in this Project have been on the forefront of developing clinical and research standards in human sequencing. Drs. Green and Rehm have published recent summaries on the use of sequencing in clinical care.[4,25,229-231] Drs. Green, Rehm and McGuire, and

External Advisory Board members Drs. Biesecker and Korf, were all members of the ACMG Working Group on the return of incidental findings.[34,232-234] These findings advocated that a small set of incidental findings be returned to patients of any age, including conditions associated with the with highly actionable adult onset conditions. The Project team has elected to return genetic information relevant to childhood onset conditions in addition to the small subset highly actionable adult-onset conditions.

Dr. Green was part of an ELSI grant that made recommendations for the return of genetic information in research biobanks,[235] and is currently part of a separate but similar team creating recommendations for the communication of genetic results to family members after the death of an individual whose DNA is sequenced as part of a research study.[236,237] Dr. Rehm is highly active in publishing standards for the utilization of clinical sequencing, [88,238-241] and is co-chair of the ACMG Working Group that has created new guidance on the clinical interpretation and reporting of sequence variants as presented at the ACMG annual conference in March 2014 and will be published shortly. Dr. Rehm is also one of nine principal investigators leading the new NHGRI-funded Clinical Genome Resource (ClinGen) program that will create standardized and shared resources to support the interpretation and use of DNA sequencing data for clinical care. This includes a centralized and public database, called ClinVar[95], for sharing clinically curated variants as well as additional resources provided through a new database called ClinGenDB to enable gene and variant curation as well as access to patient data for discovery. Over 85,000 clinically interpreted variants have already been shared through ClinVar (http://www.ncbi.nlm.nih.gov/clinvar).

Dr. Agrawal has been utilizing WES/WGS technologies in neonates and children whose diagnosis remains unknown despite extensive clinical work up as part of Gene Discovery Core. His team has successfully determined the genetic cause of disease for many such families.[129,199,242-244]

Dr. Parad introduced multi-mutation DNA testing into CF Newborn Screening, edited a supplement to Journal of Pediatrics summarizing the CDC workshop that proposed the implementation of CF newborn screening in the US,[116] and has co-authored the major implementation publications and guidelines for CF IRT/DNA newborn screening algorithms.[119,120]

***Rationale for this Research Project***

We believe genomic sequencing can provide substantive benefits to children and their parents in the newborn period. We have designed this pilot experiment to explore the impact of clinical sequencing in families that desire this information after genetic counseling. In our study, sequencing will be ordered by study physicians who will maintain a clinical relationship with the families.

*Rationale for Elective Sequencing of Healthy Newborns Born at BWH*

We believe that in rare cases, newborn sequencing will offer an opportunity to discover life-saving benefit if a pathogenic mutation associated with a treatable childhood condition is uncovered early. In addition, pre-symptomatic detection of an affected child or carrier detection will provide the possibility of an early warning for management of initial symptoms and future reproductive planning for that infant's family, even if related to childhood diseases that are not treatable. Genomic sequencing of healthy babies may become commercially available as the price of sequencing declines, and is already being implemented in various health systems.[245] Genomic sequencing of fetal DNA is also being discussed and may soon be implemented in limited situations (personal communication, Drs. Louise Laurent and Diana Bianchi). Thus, we believe that it is critically important to systematically study the behavioral, clinical and economic outcomes associated with elective sequencing of healthy newborns.

*Rationale for Elective Sequencing of Sick Newborns at BCH and the BWH NICU*

A significant portion of newborns in the Neonatal Intensive Care Unit (NICU) and other inpatient floors have undiagnosed genetic diseases. Currently, genetic tests are largely sent test by test as symptoms develop, delaying diagnosis and appropriate care. Whole exome or whole genome sequencing is already being ordered through commercial laboratories for some of these cases. For example, there have been at least 69 cases at Boston Children's Hospital so far where clinical whole exome sequencing (WES) has been ordered. Genomic sequencing immediately after birth offers an opportunity to make the appropriate diagnosis faster and offer appropriate care more quickly to these infants, potentially lowering hospitalization costs. As additional symptoms develop (e.g. an infant with liver abnormalities may later develop seizures) the existing sequence can be re-interrogated rapidly rather than ordering new tests that may take weeks to return.

*Utilizing Study Physicians to Deliver Consultations*

Throughout this protocol, the term "study physician" will be used to indicate physicians who will be providing medical consultations to the families at each study site based on the information provided in the two arms of the study. This will typically be Drs. Richard Parad and Joel Krier at BWH and Drs. Pankaj Agrawal, Ingrid Holm and Harvey Levy at BCH. The term "non-study physicians" is used in this protocol to indicate any physicians caring for the participating infants who are not part of the study staff.

## SPECIFIC AIMS/RESEARCH OBJECTIVES

The objective of this research protocol is to conduct a pilot randomized clinical trial to assess the benefits and risks of adding the information from a genomic sequencing report to physician-mediated medical care of newborns during their pediatric years.

***Aim 1: We will recruit, obtain parental consent and enroll 240 healthy neonates at BWH and 240 sick neonates at BCH or the BWH or MGH NICU and their parents, randomize them within each cohort to either standard-of-care (family history and standard newborn screening report) or to standard-of-care plus genomic sequencing. Samples for DNA analysis will be collected and forwarded to the clinical laboratory.***

***Aim 2: A study physician and genetic counselor will meet with each family for a medical consultation and physical exam of the infant as appropriate, including discussion of the family history and standard newborn screening report. For infants randomized to the genomic sequencing arm, the consultation will also incorporate a clinical genomic report of CLIA certified sequencing with Sanger confirmation of positive findings. Genomic reports will be included in the patient's chart and sent to physicians involved in the infant's care.***

***Aim 3: The research team will administer measures of clinical outcomes, behavioral responses and healthcare utilization to families enrolled in both arms, while providing careful monitoring for the safety of parents and newborns.***

***Aim 4: The research team will administer surveys to neonatal physicians and community physicians regardless of whether or not they are caring for infants whose families have enrolled in this study. In addition, physicians who receive genomic reports through the study will be surveyed about their understanding and utilization of the genomic reports.***

## INCLUSION/EXCLUSION CRITERIA

***Newborns and Parents at BWH:***

*Inclusion criteria*:

1) Infants born at BWH and admitted to the Well Newborn Nursery
2) At least one biological parent is physically available to have genetic counseling, donate DNA, and provide consent for testing the infant. If the second biological parent is known but not physically present, the second biological parent must be available to have genetic counseling by phone, return a signed consent form by mail, and donate DNA via a mailed saliva kit. If there is a "rearing parent" (an individual who is not biologically related to the infant, but who is dedicated to raising the child), that individual must also provide consent but will not be asked to submit a saliva sample.
3) Mother (either rearing or biological) carried the pregnancy

*Exclusion criteria:*

1) Parents are non-English speaking. (As the study progresses, we will explore the option of translating study materials into Spanish.)
2) Parents are unwilling to have genomic reports placed in the medical record or sent to their primary care pediatrician
3) Mother or father younger than 18 years of age
4) Mother or father with impaired decisional capacity

5) Age of infant is older than 90 days
6) One of a multiple gestation
7) Any infant in which clinical considerations preclude drawing 1.0 ml of blood
8) Missing consent of either biological parent (if known) or rearing parent (if applicable)

***Sick Newborns and Parents at BCH or the BWH or MGH NICU:***

*Inclusion criteria:*

1) Infants admitted to BCH or the BWH or MGH NICU
2) At least one biological parent is physically available to have genetic counseling, donate DNA, and provide consent for testing the infant. If the second biological parent is known but not physically present, the second biological parent must be available to have genetic counseling by phone, return a signed consent form by mail, and donate DNA via a mailed saliva kit. If there is a "rearing parent" (an individual who is not biologically related to the infant, but who is dedicated to raising the child), that individual must also provide consent but will not be asked to submit a saliva sample.
3) Mother (either biological or rearing) carried the pregnancy

*Exclusion criteria:*

1) Parents are non-English speaking. (As the study progresses, we will explore the option of translating study materials into Spanish.)
2) Parents are unwilling to have genomic reports in the medical record or sent to their primary care pediatrician
3) Mother or father younger than 18 years of age
4) Mother or father with impaired decisional capacity
5) Age of infant on admission is older than 90 days
6) One of a multiple gestation
7) Any infant in which clinical considerations preclude drawing 1.0 ml of blood
8) Hospital admission expected to be less than 72 hours
9) Missing consent of either biological parent (if known) or rearing parent (if applicable)
10) Previously performed exome/genome sequencing on patient

**RESEARCH DESIGN AND METHODS**

This is a randomized clinical trial evaluating infant and family outcomes, as well as physician outcomes, after participation in one of two types of medical consultation. Overall design is summarized in Figure 1. Figure 2 summarizes the proposed details of study participation for parents and infants. Figure 3 summarizes the proposed details of study participation for physicians. The study has been registered on clinicaltrials.gov.

Specific methods for each Aim are described below.

***Aim 1: We will recruit, obtain parental consent and enroll 240 healthy neonates at BWH and 240 sick neonates at BCH or the BWH or MGH NICU and their parents, randomize them within each cohort to either standard-of-care (family history and standard newborn screening report) or to standard-of-care plus genomic sequencing. Samples for DNA analysis will be collected and forwarded to the clinical laboratory.***

***1.1.1 Recruitment of Healthy Neonates and Families at BWH***

In an effort to provide potential participants the opportunity to learn about our study in the prenatal period, we have created an educational brochure that will be placed in obstetrics practices

and offices that traditionally have a significant number of patients deliver at BWH (please see the attached 'Genomic Sequencing for Childhood Risk and Newborn Illness Study Brochure'). This brochure will include an overview of the study along with the contact information of a study team member who will be available to answer any questions potential participants may have about the study. We may also present at prenatal classes at BWH to provide families planning to deliver at BWH with more information before their hospital stay. We will track which of our participants received the educational materials prenatally via questions incorporated into the consent discussion. The research study will be introduced to obstetricians through presentations by Dr. Richard Parad (see attached "OB Presentation Slides"). These presentations will give obstetricians a background on the project and provide them with contact information for study staff.

The Department of Pediatric Newborn Medicine at BWH recently hired a Nursery Recruitment Research Assistant (RA) to coordinate recruitment in the Well Newborn Nursery across multiple research studies, ensuring that parents are only approached about participation in appropriate studies and are not overwhelmed by competing offers of enrollment. The Nursery Recruitment RA will be trained on our study's eligibility requirements. After obtaining permission to approach parents from the mothers' Well Newborn Nursery care team, the Nursery Recruitment RA will share with parents our Study Brochure (see attached study brochure) and will notify our study RA of any parents who express interest in learning more about our study. Our study RA and/or genetic counselor will then visit these families in the BWH Well Newborn Nursery and provide more information, as detailed below in the Enrollment and Consent section. Preliminary data to support the feasibility of recruiting parents while they are inpatients in the immediate post-natal period were provided in the previous section on Prior Research/ Preliminary Findings.

### *1.1.2 Recruitment of Sick Neonates and Families from BCH, BWH and MGH*

Study staff will check in daily with floor clinical staff at each respective hospital to identify neonates who were admitted in the past 24-48 hours and who meet the enrollment criteria for the study. For the most part, we will be enrolling all-comers to the BCH inpatient floors and BWH and MGH NICU, however we will enrich for a wide-variety of admission reasons and for neonates who will spend a longer period of time at BCH/BWH/MGH. We are excluding neonates if they are expected to be admitted for less than 72 hours to better fit with our recruitment plan. The goal is to give parents ample time to consider participation.

After obtaining permission to approach parents from the attending clinical staff, a research assistant and/or genetic counselor will approach the parents with the clinical staff to provide a copy of the Study Brochure and consent form and answer any initial questions the parents may have. Parents who speak to a study staff member and decline participation will be asked if they are willing to complete our "decliner form" and/or our "decliner survey" to better understand parents' reasons for decline.

### *1.2 Pre-enrollment Informational Session and Consent at BWH, MGH, and BCH*

An informational session will be scheduled with the parents of both healthy and sick newborns who express interest in participating in the study. The genetic counselor (Ms. Genetti, Mr. Fayer, or Ms. VanNoy) will meet with the parents, verify their interest in participating in the study and initiate the consent process.

In the Pre-enrollment Informational Session, parents will learn from the genetic counselor about genetics and genomic sequencing, the study protocol, and the benefits and risks of participation, and will have opportunities to ask any questions that they may have. The study genetic counselor will discuss the following topics in detail with parents:

- Each infant will be randomly assigned to receive a medical consultation with a study physician, in which their infant will be evaluated. Based upon the randomization, this consultation will utilize the family history and standard newborn screening report, with or without genomic sequencing. There is a 50% chance for each infant to be assigned to the

group that receives genomic sequencing.

- Genomic sequencing will be limited to one infant per family; parents and other relatives will not be sequenced (although parent DNA will be collected in the form of a saliva and/or blood sample to be available if needed for targeted confirmation to interpret the infant's results).
- Brief overview of genetic principles, sequencing and sequence variants/mutations
- Genome-scale sequencing is a new technology and the interpretation of genomic sequence results is an evolving science. Therefore, interpretations made by the clinical team are not certain to be accurate or complete
- Sequencing is not a substitute for all types of genetic testing and is not guaranteed to find all genetic abnormalities, including known genetic conditions in the family
- The genome reports generated as part of this protocol may provide 5 types of information:
    - Mutations in genes that are associated with childhood-onset recessive diseases, for which the newborn is likely a carrier and therefore disease is not expected unless a second mutation was missed or not interpretable
    - Mutations for disease predisposition that could be of medical importance during childhood for the infant
    - Variants that provide pharmacogenomic information about a selected number of agents that are used in the childhood period for treatment
    - ABO and D blood types, plus clinically relevant antigen typing
    - Mutations in genes that are associated with highly actionable adult-onset conditions.
        - Highly actionable adult-onset genetic conditions are defined as those that are likely to be asymptomatic in the childhood period (***with onset at the age of 18 years and older***) for which screening and surveillance are available and for which treatment or prophylactic measures may be offered.
        - Guidelines for determining reportable highly actionable adult-onset conditions will be based on the American College of Medical Genetics and Genomics recommendations regarding reporting of secondary findings in clinical sequencing. This ACMG list currently includes 59 genes, 6 of which are exclusively adult-onset, and we will adhere to these principles of high actionability in selecting genes for return.
- At least one parent must complete the baseline survey within 14 days of enrollment in order for the family to continue participating in the study
- The newborn will be followed by a study physician/genetic counselor team who will interpret the findings for the parents, and who will provide a clinical report that will be placed in the medical record and sent to the newborn's non-study physician(s)
- Results may have medical implications for other members of the family
- Non-paternity will not be specifically tested for, and if inadvertently discovered, will not be disclosed to the family unless considered of medical importance to the health of the family
- Parents and children have legal protections against employment and health insurance discrimination under the Genetic Information Non-Discrimination Act (GINA), but GINA does not cover life, long-term care, and disability insurance. However, in Massachusetts, there is a law (175 §120E) which extends protections to address life, long-term care, and disability insurance. If a family were to move out of the state, to another state without a similar law, these same protections may not be available. Further, we cannot predict how these laws may change before the infant reaches the age of maturity
- In some cases, a finding may prompt follow-up physician visits or testing, some of which could incur out-of-pocket expenses that would not be covered by the study
- The raw sequence data will not be returned to study participants or placed in the medical record at the time of disclosure
- 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

- If parents 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 at BCH, BWH or MGH will have become part of clinical care, and cannot be deleted or withdrawn. Any sequences or data that have been uploaded to shared databases such as the Database of Genotypes and Phenotypes (dbGaP) cannot be withdrawn.
- Outcome measures will assess parental depression and anxiety. If any participants' scores exceed pre-defined cut-offs, a study physician, genetic counselor, or study psychologist may reach out to them. We may alternatively, or in addition to, be discussing their survey answers with appropriate clinicians involved in their care.

After completing the Pre-enrollment Session, if parents are unsure and prefer additional time to decide about participation, a follow-up conversation will be scheduled. If parents decide that they are ready to participate, they will both be asked to answer questions that assess their understanding of the information that the genetic counselor has discussed with them focused on the topics of 1) the purpose of the study, 2) what is involved in participation; 3) expected outcomes and 4) possible risks and benefits (please see attached 'Consent Understanding Questions'). The genetic counselor will review any incorrect responses with parents to ensure that they understand all critical aspects of study participation; then parents will be asked again to respond to any questions that they originally answered incorrectly. Once parents are able to answer all questions correctly, they will have the option of enrolling in the study.

Parents who decide to enroll will sign the consent form for the infant's participation and to allow the study team to review medical records from all medical providers of the infant (including the mother's prenatal records). We will also be accessing billing information from state and institutional databases. Parents will also be asked to sign the consent form for their own enrollment (i.e. consent to complete surveys and saliva/blood samples for DNA collection). If both biological parents are known we will obtain consent from both parents for their infant's participation, and will obtain saliva and/or blood samples from both. We will attempt to consent both parents at the same time, however if after exploring several time options, only one parent is available for a consent session prior to discharge, we may collect samples from an infant before obtaining consent from the second parent. We will then follow up with the second parent to obtain consent. If they choose not to enroll, or if a consent session cannot be organized in a reasonable amount of time, the family will be removed from our study. No samples will be sent for analysis until verbal and written consent is obtained from both parents (if applicable). If a non-biologically related parent will be rearing the child (e.g. if the biological mother has committed to raising the child with someone other than the child's biological father) that individual will also be asked to provide consent for the child's participation but will not provide a DNA sample. Rearing parents will also be asked to complete study surveys.

For families at both BWH, MGH, and BCH, while we will attempt to complete all consent sessions and sample collection prior to discharge of the infant/mother, in some cases, this is prohibited by time constraints. If a family has been approached by our study RA and/or genetic counselor and has expressed interest in completing the Pre-enrollment session, but a session cannot be scheduled prior to discharge, they will be given the option of returning to either BWH or BCH, to complete enrollment at a later date. If they are willing to return, they will participate in the Pre-Enrollment Informational Session and sample collection process as detailed above.

We plan to access medical records and send annual surveys 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). Given the long-term nature of the project, if the study remains active, we will contact the family after the child's 13$^{th}$ birthday to obtain assent, and after the child's 18$^{th}$ birthday to obtain consent from the participant. If we are unable to reach the family and obtain assent/consent from

the participant, we will withdraw them from 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 parents, document the child's cognitive ability and obtain documentation of the parent's legal health care proxy status (in the instance that the child turns 18 years).

A detailed family history will be obtained by the genetic counselor at this stage of enrollment. The family history will be utilized later by the laboratory and the consultation team in the interpretation and contextualization of the sequencing report, and 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.

**For families who consented to the study prior to the addition of adult-onset findings, and are part of the sequencing arm:

A mailing will be sent out to those families who have already completed their disclosure with a cover letter and addendum consent form (see attached). The letter will request that families interested in learning more about the actionable adult onset disclosure call study staff to set up a verbal consent call. The letter also contains language that states if we do not hear from them with in 2 weeks, a member of the study staff will call to assess interest. Uninterested families may also notify the study staff by phone or email.

Families who have not yet returned for disclosure will either receive a letter prior to disclosure or will be introduced to the addendum consent option at their disclosure session, depending on time allowance. Written consent will be obtained for families who choose to receive these results. We will require one consent form to be signed by both parents as well as the investigator (genetic counselor) who obtains the verbal consent. Verbal consent may be obtained via phone or in person.

As is required for the study in general, both parents must agree to consent to this new class of findings. If there is disagreement between the parents the default will be to NOT consent. If a parent feels strongly that they want this information for themselves, the study team is happy to refer them for clinical evaluation where they can obtain genomic screening through clinical consent. This discussion with and among the couple will be mediated by a study genetic counselor who is trained to facilitate these types of genetic testing decisions.

A specific script will not be utilized for the verbal consent. However it will be completed by a genetic counselor and will touch on the following points:

- Study now allows for the return of a subset of adult onset conditions that are known to be highly actionable through treatment and screening.
- Examples of these conditions include a significantly increased lifetime risk for breast or colon cancer or certain types of highly heritable heart disease. These do not include classes of conditions like Alzheimer's disease and other adult onset neurodegenerative disorders, since there is little clinical actionability for these conditions in terms of screening, prevention and treatment.
- As with the previous consent, both parents must agree
- They may learn this information about themselves as well as their infant. Results must first be found in the infant. Parental results will be reported on the infant's GNSR and will not be placed by study staff into the parent's medical record.
- Review of the risks discussed in the original consent
- Parents are permitted to change their mind at anytime
- Results disclosed reflect our current knowledge of these conditions at the time of disclosure, it is possible that new genes or disorders in this category will be discovered in

the future and will not be reflected in the report. We will not regularly be reviewing an infant's data to account for such discoveries outside the context of an Indication Based Analysis ordered for the infant.

Disclosures for positive results will be completed in person with project genetic counselor and physician. Negative results can be done over the phone or in person.

### *1.3 Sample Collection*

After receiving permission from the inpatient clinical staff to draw blood, a blood sample (through a venipuncture or heel stick) of no more than 1.0 ml may be obtained from each enrolled infant. Alternatively, when possible, blood and/or cord blood samples already obtained for clinical reasons may be retrieved. In the case that the blood collection for an infant does not yield enough DNA for sequencing, we would offer to bring the family back in for a second blood draw should they agree to one. This second blood draw will again be approximately 1.0 ml and will be performed by clinicians specialized in blood drawing in newborns. We will only draw an additional sample if the infant is in the sequencing arm, so that infants in the control arm are not exposed to unnecessary risk. These samples will be shipped to the Laboratory for Molecular Medicine (LMM) or other CLIA compliant clinical diagnostic facility. Buccal swab samples from the infant, and saliva and/or blood samples (approximately 7.0 ml of blood) from both biological parents (if available), will be collected and stored at the LMM. Saliva samples or an additional sample (blood, cord blood, or other samples already obtained for clinical reasons) will be used if needed for quality control or Sanger confirmation of sequence results, or to facilitate the interpretation of results in the newborn (via metabolic, biochemical or other analytical testing). Discarded samples, if available and anonymized, may be used for other research studies.

Samples will be collected from all infants and parents enrolled, regardless of the arm to which they are assigned, in order to follow the same protocol for all subjects prior to randomization.

### *1.4 Randomization*

Infants within each cohort will be randomized (1:1) to either standard-of-care (family history and standard newborn screening report) or to standard-of-care plus genomic sequencing.

***Aim 2: A study physician and genetic counselor will meet with each family for a medical consultation and physical exam of the infant as appropriate, including discussion of the family history and standard newborn screening report. For infants randomized to the genomic sequencing arm, the consultation will also incorporate a clinical genomic report of CLIA certified sequencing with Sanger confirmation of positive findings. Genomic reports will be included in the patient's chart and sent to physicians involved in the infant's care.***

### *2.1 Genomic Sequencing and Reporting*

Genomic sequencing of infants randomized to the sequencing arms will be conducted in a CLIA approved sequencing laboratory. Additional genetic testing may be used to help with data interpretation and confirmation (for example, chromosomal microarray or Sanger sequencing). Data interpretation and individual variant confirmation with Sanger sequencing 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.[88]

#### *2.1.1 Genes to be Interrogated and Reported*

When conducting clinical sequencing, the LMM software interrogates approximately 5,000 disease-associated genes across panels, exomes and genomes. In this protocol, we will restrict our

analysis and reporting to approximately 1,751 genes that have been linked to childhood-onset diseases (hereafter referred to as Childhood Onset Gene List and see Appendix 1), in addition to a small subset of genes (including but not limited to: BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, and EPCAM) that meet ACMG criteria for highly actionable adult-onset conditions**.** We will **not** be reporting on genes that are only associated with adult-onset conditions that are not considered to be highly actionable such as those for neurodegenerative conditions that have no options for prevention or amelioration.

Before reporting, all genetic variant findings will be confirmed by Sanger sequencing, as per standard clinical practice, prior to being included on a report and returned to clinicians and families. We may test the parental DNA to confirm/ determine inheritance of a result found in a child. These results will be reported on the child's GNSR. We will not test parental DNA for findings that were not first identified in the child.

Results disclosed will reflect current knowledge of these conditions at the time of disclosure, it is possible that new genes or disorders will be discovered in the future and will not be reflected in the report. We will not regularly be reviewing an infant's data to account for such discoveries outside the context of an Indication Based Analysis ordered for the infant.

### *2.1.2 The Genomic Newborn Sequencing Report*

For both sick and healthy infants, a "Genomic Newborn Sequencing Report" (GNSR) will be generated that will follow a format already being utilized clinically by the LMM, and in the MedSeq Project[52] but with modifications to include only genes associated with childhood onset conditions and a small subset of highly actionable adult-onset conditions (see example in Appendix 2). Separate sections on the GNSR will indicate results under the following headings:

*Monogenic Disease Risk*: After Sanger confirmation, we will report pathogenic or likely pathogenic variants in conditions from the Childhood Onset Disease Gene List (see Appendix 1) 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.

*Highly Actionable Adult-Onset Monogenic Disease Risk*: After Sanger confirmation, we will report pathogenic or likely pathogenic variants in highly actionable adult-onset conditions as characterized by the ACMG recommendations 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.

*Carrier Risk*: After Sanger confirmation, we will report pathogenic or likely pathogenic variants in conditions from the Childhood Onset Disease Gene List (see Appendix 1) that are in heterozygous state and are associated with recessive disorders.

*Pharmacogenomic Associations*: After Sanger confirmation, we will report pathogenic variants in two genes associated with potentially severe complications from specific medications: Glucose-6 Phosphate Dehydrogenase Deficiency (*G6PD* gene) and Malignant Hyperthermia (*RYR1* gene). As more is known about pharmacogenomics, additional genes may be reported on, but only if they are related to medications which may reasonably be given in childhood and if the variants are in the PharmGKB Class I or II categories.

*Blood and Platelet Antigen Types:* After confirmation by conventional serological testing, we may return ABO and D blood types, plus clinically relevant platelet antigen typing detected through sequencing and confirmed on an FDA-approved chip.

### *2.1.3 The Indication-Based Analysis*

For sick babies who have clinical presentations where a genomic analysis may be helpful for diagnosis or treatment of a particular presentation, and in the event that one of the healthy babies becomes ill with symptoms that warrant such analysis, an "Indication-Based Analysis" (IBA) will be generated in response to requests by the baby's physicians in consultation with the study physicians, or by the study physicians. The IBA will include interrogation of disease-associated 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[246] for specific indications (e.g. anti-epileptic medication in neonates with seizures). Examples of the IBA are shown in Appendices 3 and 4. 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.

### *2.2 Obtaining the Standard Newborn Screening Report*

The standard NBS report, by state mandated regulation, is returned to the birth hospital of each newborn. For the BWH Well Newborn cohort, the study physician will obtain this standard NBS at BWH. Standard NBS is typically repeated on infants admitted to BCH/the BWH or MGH NICU and is part of the active chart for sick babies. The study physician will obtain the NBS reports for the BCH/BWH/MGH NICU subjects. In both sick and healthy infants, if reports are not available in the subject's hospital chart, they may be requested from the New England Newborn Screening Program Laboratory by a study physician. For all infants who were born outside of Massachusetts and transferred to BCH, NBS is performed at the time of admission, and a report is issued to BCH. Reporting of NBS results to families will occur through their pediatrician, as part of their normal clinical care. For the purposes of our study, we will be obtaining the reports and reviewing them with families at the time of result disclosure, which will happen after any positive results have been disclosed to families by their clinician (see next section).

### *2.3 Consultation and Disclosure of Randomization Status and Reports*

A study physician and genetic counselor will disclose the infant's randomization assignment and study results during an in-person consultation with each family. The study physician and genetic counselor will provide the consultation to families utilizing all available medical information. In the sequencing arm of the study, this will include the medical history and examination, family history, standard NBS report and sequencing report(s). In the non-sequencing arm of the study, this will include the medical history and examination, family history and standard NBS report.

If an infant dies after enrollment, but before result disclosure, a study genetic counselor will call the family and disclose what their randomization arm was. If they were in the sequencing arm, the family will be given the option to receive results as scheduled, postpose the disclosure date to a time of their choosing, or decline receiving results. The study genetic counselor will discuss with them the possible benefits of receiving results for risk assessment of future pregnancies and other family members. Families of deceased infants will also be given the choice to return to the hospital for result disclosure or to receive results over the phone. For families who receive results, they will be asked to complete modified surveys about the results impact.

### *2.4 Generating a Clinical Note*

The team of study physician and genetic counselor will generate a clinical note following the consultation 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.

***Aim 3: The research team will administer measures of clinical outcomes, behavioral responses and healthcare utilization to families enrolled in both arms, while providing careful monitoring for the safety of parents and newborns.***

### *3.1 Administration of Outcome Measures*

The study team will collect outcome measures from parents in the domains indicated and at the times specified in Table 1. For raw data and adult onset result interviews: Parents who request their child's raw data from the BabySeq project will be invited to participate in an interview. We expect that we will conduct up to 30 interviews with parents on this topic.

Each parent who participates in this study will be compensated for each visit and survey completed, with remuneration as follows: $15 for the disclosure visit and completing the post-disclosure survey; $20 for completing the 3-month follow-up survey; and $40 for the 10-month follow-up and completing the 10-month follow-up survey. Thus, a parent will receive $75 if he/she finishes the study and completes all study surveys from the baseline through the 10-month post-disclosure survey. If both parents complete all study procedures and surveys, each parent will receive $75, for a total of $150 for the family. Parents will receive this remuneration in the form of a check. In addition, parking for study visits will be covered by the study. Remuneration will be provided at the end of the study. 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 (or our younger colleagues) may also send annual surveys to families until the babies turn 18 years to assess for how participation in the study affected their family or thought process. These surveys will be similar to the 3-month follow up survey. At this time, we do not have the funding to provide remuneration for the completion of these surveys; however, if funding were to become available we plan to offer a small payment. Parents who participate in the raw data, adult onset, or genetic risk interviews will receive $50 per family, per interview (we will not compensate each parent separately) to compensate them for their time.

The family will be randomized (and samples sent for sequencing from infants in the genomic sequencing arm) after at least one parent has completed the baseline survey. Completion of the baseline survey must occur within 14 days after enrollment; otherwise the family's participation in the study will be discontinued. This requirement will be covered in detail in the Pre-enrollment Genetic Counseling Session. If a family is to be withdrawn from the study in this way, we will follow up with them to collect voluntary withdrawal information, as we do from those who decline to enroll during approaches. This information would include demographics, reason for withdrawal, attitudes on testing in the newborn period, and some questions similar to our baseline survey (see appendix for survey). Parents who request their child's raw data will be required to undergo a genetic counseling session with genetic counselors at the parent site (BWH/BCH, covered by their IRB protocol). After the genetic counseling session, parents will be asked if they would be willing to participate in a 30 minute telephone interview. Parents who 1) parents who received an adult-onset result, 2) parents who agreed to receive such results, but did not, and 3) parents who did not agree to receive such results will be invited to participate in an interview that will last from 30 minutes to 1 hour. Additionally, parents who received general genetic risk results will be invited to participate in an interview. If they agree to be contacted for interview, we will reach out to set up a time to speak. Interviews will be recorded with participants' permission, and parents will be informed that participation in the interview is not required in order to receive their child's raw data or for continued participation, that they may skip any question they prefer not to answer, and that they may end the interview at any time for any reason. See appendix for the consent statement and interview guide.

### *3.2 Safety Monitoring of Parents and Newborns*

The study physician and genetic counselor will provide clinical consultation to the family and will have multiple clinical opportunities to respond to parents' questions and provide clinical advice, including responding to distress, confusion or parental requests for additional information or

additional medical services. For example, if after the disclosure session, it is the clinical judgment of the study physician or genetic counselor that the parents seem particularly anxious or distressed, the study physician and/or genetic counselor may consult with study psychologist Dr. Susan Waisbren, who is also an expert on parent-child bonding and parental stress. The study physician or Dr. Waisbren will make referrals to the parent's primary care physician and/or a mental health professional if it is determined that such a referral is clinically indicated or if the patient requests a referral.

In addition to this clinical monitoring, outcome measures outlined in Table 1 will also serve to monitor the safety of parents. If any participants exceed pre-defined cut-off scores for depression or anxiety, the genetic counselor will be alerted and will review the case with the study physician. The study physician, genetic counselor or Dr. Waisbren may contact the parents by phone for further psychosocial assessment, and referrals to the parent's primary care physician and/or a mental health professional will be made if it is determined that such a referral is clinically indicated or if the patient requests a referral. When appropriate, if there is a social worker or clinical mental health provider already involved with a family (as is the case for all families in the BCH NICU), we will consult with the clinical provider to determine appropriate follow-up if a parent exceeds any pre-defined cut-off scores for depression or anxiety on their survey.

***Parental Withdrawal from Study Participation***

Parents may request to withdraw from the study at any time by contacting study staff. One of the study genetic counselors will speak with the parent(s) to discuss their reasons for wanting to withdraw. The genetic counselor will complete a Study Withdrawal Form that indicates whether the participant wishes to withdraw only from future surveys or additionally requests that samples and genome data be destroyed, specifying whether the request is for infant samples, parental samples or both.

Once the Study Withdrawal Form has been received, if the parent(s) elects destruction of samples, the lab will be notified to destroy any remaining blood and buccal samples from the infant, as well as saliva and blood samples from the parents. If analysis of sequence data is ongoing, it will be halted and samples destroyed. Variant files and genome reports will be deleted from laboratory and study records.

Once the GNSRs or IBAs have already been placed in the electronic medical record at BCH, BWH or MGH, they will have become part of clinical care, and cannot be deleted or withdrawn, a point that will be stressed during the consenting appointment. In addition, any sequences that have been uploaded to NIH databases cannot be withdrawn, and this too will be stressed during the consenting appointment.

If an infant dies prior to results disclosure, the infant's parents will be contacted and be given the option of receiving study results. If they do wish to learn the results, they may either return for an in-person results disclosure session, or they may choose to have results disclosed to them over the phone. If parents do not wish to learn of study results immediately, they will be given the option of having results disclosed to them at some point in the future. We will not send study surveys to the infant's parents or physicians. If the genetic cause for the neonate's illness was not found as part of this protocol, parents will be offered enrollment in the Gene Discovery Core of The Manton Center for Orphan Disease Research ("Manton" for short). Manton is a research study through BCH that offers a genomic sequencing test for sick or deceased children to look for the cause of their health problems. As part of the Manton study, if the genomic sequencing test finds genetic variants that might explain the child's health issues, parents receive those results. Parents do not receive other types of genetic results on their child and they do not complete surveys. Parents' participation in Manton will be completely optional.

***Aim 4: The research team will administer surveys to neonatal physicians and community physicians regardless of whether or not they are caring for infants whose families have***

***enrolled in this study. In addition, physicians who receive genomic reports through the study will be surveyed about their understanding and utilization of the genomic reports.***

The availability of non-study physicians who care for infants born at BWH and/or infants admitted to BCH/the BWH or MGH NICU provides an additional opportunity to evaluate the impact of genomic sequencing in a newborn setting; specifically, how such information is perceived, understood and utilized by the babies' pediatricians and other physicians. Non-study physicians will not be required to participate in surveys, but the study team will administer online surveys to those non-study physicians who are willing to participate, in the domains indicated and at the times specified in Table 1. Each survey will be preceded by online text that briefly outlines the purpose of the research study, key investigators, funding source, inclusion criteria, study procedures and duration, remuneration, voluntary nature of participation, confidentiality protections, and study genetic counselors' contact information. Clicking past this page and completing the survey will serve as the physician's consent for each of the surveys. Non-study physicians who do not complete the surveys but who are taking care of infants enrolled in the study will still be free to contact the study physicians and genetic counselors with questions or feedback, just as they would with any clinical consultants. Each non-study physician will be asked to complete the baseline survey once, the end of study survey once, and the post-disclosure survey each time they receive a GNSR/IBA on one of their patients.

Non-study physicians will receive $50 for each survey completed in the form of a gift card.

If a physician no longer wishes to participate in the study surveys, he or she can choose not to complete future surveys. Physicians caring for the infants in this study will continue to receive the clinical reports generated or collected by the study, as well as consultation letters from the study physician and genetic counselor.

**DATA ACCESS AND STORAGE**

An important aspect of this study is the placement of the GNSR and IBA in the medical record for care providers to have access to the medical information on the report. The implications of placing the reports in the medical record are as follows:

- All sample procurement, sample handling, and analysis will be performed in a CLIA-compliant manner and confirmed with established methods such as Sanger sequencing. Samples and results will therefore be conducted as part of the clinical practice of medicine.
- Reports for each participant will be placed in the electronic medical record system for the institution through which they were enrolled (BCH, BWH, or MGH).
- If the medical record of a study participant is transferred to another institution as requested by the family in accordance to the institutions' medical record release policies, the reports generated by the study (family history, clinical consultation note(s) and GNSR/IBA) would also be transferred. A study physician or genetic counselor will be available to discuss the reports with other physicians if requested.
- When infants from BCH/the BWH or MGH NICU are discharged to other hospitals or released home under the care of a local pediatrician, the same results will be transferred as part of the medical records, and the study staff will be available to answer questions from the new health care provider. Many of these families will also return to BCH for specialist care, so their follow-up can be monitored through reviewing medical records in the BCH system.
- Full sequence results, or "raw data" resulting from sequencing will not be placed in the medical records. Only the GNSRs and IBAs will be placed in the medical record.

Data generated from the sequencing will be transferred securely and stored securely behind

a firewall. Recruitment information, collected medical and family history and randomization status will be kept in a password-protected database. Any research files will be kept in a locked filing cabinet.

***Sharing Samples and Data for All Subjects***

- Parents' responses on study surveys may be shared with other researchers within and outside BWH, MGH and BCH. These responses will be de-identified unless parents have consented to sharing their identifiable information.
- Phenotype information about the infants in this study will be shared in de-identified form with federal databases such as dbGaP and may be shared with other databases so that they can be made available to qualified researchers outside of BWH, MGH and BCH. Consent language will explicitly point this out to participant families.

***Data Storage and Sharing for Newborns in the Sequenced Group***

- All genetic data from infants will be stored at the LMM for at least two years after the end of the study. Variant files of genomic sequencing data and genomic reports will be stored at the LMM indefinitely.
- Sequence and/or variant file data, along with phenotype data and data extracted from the medical record, will be shared in de-identified form with NIH databases such as dbGaP and may be shared with other databases so that they can be made available to qualified researchers outside of BWH, MGH and BCH, in accordance to the NIH's Genomic Data Sharing policies. Consent language will explicitly point this out to participant families.
- Should a family member request their entire genome or "raw" genomic data, we will first request that they speak with the genetic counselor or study physician to discuss the reasons for their request, and remind them that the protocol does not permit this sharing during the course of the study. However, we will provide the contact information of the sequencing lab and the date of study conclusion upon which they may contact the laboratory to request their data according to the lab's standard clinical practice.

**BIOSTATISTICAL ANALYSIS**

This project, while large and complex, is nevertheless a pilot project designed to explore a large number of areas, generating empirical data that will inform future large-scale trials and future decision-making around the use of sequencing in newborns. The sample size is justified in terms of several key comparisons and hypotheses (see below), but much of the value of the project as a whole will come from descriptive and exploratory analyses that emerge from the many interests and questions raised by the investigators in genomic sequencing, sequence interpretation, clinical genetics, ethics and policy that are part of this multi-disciplinary team.

Descriptive statistics will be used to characterize parents in terms of demographic variables, personal and family history, perceptions of genetic concepts, health care utilization/ cost-effectiveness and dispositions. Descriptive statistics will also be used to characterize the medical impact, psychological impact and personal utility of genomic sequencing of newborns. For measures where we have both baseline and follow-up survey data we will use standard pre-post analyses (e.g., paired t-tests, repeated measures analyses) to assess whether significant changes occurred in these domains following receipt of test results. An initial step in our quantitative data analytic plan will be to determine potential differences between the two groups of respondents, healthy infants and sick infants. Given that healthy infants do not have any particular underlying condition for which a genetic test may be ordered (unlike the sick patients), it will be important to determine the appropriateness of pooling parents of patients from these two groups across analyses, or whether they should be analyzed separately. We will therefore examine whether

respondents from the two groups differ at baseline on key demographic characteristics as well as on our main outcomes of interest. Additionally, we will be analyzing the impact on medical care for participants admitted to BCH/the BWH or MGH NICU and post-discharge care for both well and sick infants. We anticipate conducting analyses related to duration of stay, number of tests ordered, administrative/ visit fees, and costs of diagnostic work-ups. For qualitative analyses, a qualitative investigator will lead analysis of raw data interviews. Interviews will be transcribed verbatim and stripped of identifying information before analysis. Analysis will focus on themes related to parents' motivations for requesting and expectations of their child's raw genomic information.

A number of hypotheses have been identified as particularly salient to the goals of the project.

***Hypothesis 1: Parents of newborns randomized to genomic sequencing will report no greater distress or disruptions to parent-child relationships than parents of newborns randomized to standard newborn screening***

We hypothesize that scores of anxiety, depression, and distress among parents of newborns receiving genomic sequencing in addition to standard newborn screening will be no greater than scores among parents of newborns who receive standard newborn screening only. We will conduct a repeated measures analysis of variance to compare the trends on each measure over time in the genomic sequencing and standard newborn screening groups. The regression models for these analyses will consider the Edinburgh Postnatal Depression Scale anxiety and depression scores, separately, in addition to Parental Stress Scores, IES scores, as the dependent variables with randomization arm, cohort (healthy and sick newborns), time, and the interaction between time and randomization arm as the primary independent variables. These analytical procedures permit a choice of correlation structures (e.g., exchangeable or autoregressive) or the use of the robust empirical covariance structure computed by the "sandwich" estimator (generalized estimating equations) to account for the association among repeated observations within the same individual over time.[247] In addition, these procedures use all available observations for analyses and do not exclude those participants who may have a missing observation at one or two time points. A significant interaction effect in these models suggests that the two groups have different trends (change scores) over time. Finally, we will adjust for covariates such as age, gender, race, and education in the regression models to evaluate potential differences in trends between the randomization arms, while accounting for potential differences in these covariates. Following guidelines from the CONSORT Statement[248] we will define non-inferiority as evident if 95% confidence intervals for mean differences between protocols is entirely less than a pre-specified margin of 5 points after adjusting for other factors. Given the sample size proposed, we estimate that we will have at least 90% power for analyses of each outcome examined in Hypothesis 1.

***Hypothesis 2: Parents of sick newborns randomized to genomic sequencing will report greater post-disclosure utility of the genomic sequencing compared to parents of healthy newborns randomized to genomic sequencing.***

We will measure personal utility as a function of (1) satisfied expectations, (2) decisional regret, (3) attitudes toward genomic sequencing and (4) willingness to pay for genomic services. As socioeconomic backgrounds of the BWH, MGH and BCH infants may be different, we may adjust for reported or imputed family income. We will use multiple linear regression on measures of expectations, attitudes and willingness to pay to test whether changes from baseline on each measure is greater among parents with sick newborns are greater than changes from baseline among parents of healthy newborns, after adjusting for covariates such as age, gender, race, and education. Similarly, multiple linear regression will test whether parents of sick newborns have lower decisional regret about pursuing genomic sequencing than parents of healthy newborns, after adjusting for key covariates. Assuming 120 parents in each cohort among those randomized to genomic sequencing arm, and similar variances among outcomes as observed in other studies,[249-

[251] we will have over 99% power to detect differences on each outcome that have been clinically meaningful in other studies (i.e., a difference of 1 on a 7-point scale for expectations,[251] a difference of 16 on a 0-100 scale for decisional regret,[249] and a difference of approximately $150 on a willingness to pay scale)[250] assuming Type I error rates of 5%.

***Hypothesis 3: Parents of newborns randomized to genomic sequencing will request more healthcare services than parents of newborns randomized to standard newborn screening.***

Healthcare service requests will be assessed through a series of yes/no items where parents will report whether or not they sought specific follow-up services for their child, such as referrals to specialists, as well as an adapted subscale of the Billings and Moos Coping Measure.[252] Responses to these items will be analyzed using generalized estimating equations and multiple linear regression to compare randomization arms on summary scores after adjusting for key covariates. Assuming 240 parents in each randomization arm, and assuming that among those in the genomic sequencing arm, similar variances in outcomes are observed as in other studies,[249-251] we will have over 95% power to detect differences on both information seeking[253] and service requests[254] that have been clinically meaningful in other studies (i.e., a difference of 1.0 on a 10-point scale for information seeking, a difference of 0.5 on a 4-point scale for service utilization) assuming Type I error rates of 5%.

## RISKS AND DISCOMFORTS

### *Common Risks to Infants*

Venipuncture carries a risk of minor discomfort and bruising. There can be minor transient oral bleeding at the time of sample collection using a buccal swab.

### *Uncommon Risks to Infants*

There are theoretical risks of disclosing unexpected genetic risk information about an infant. Children who later learn about genetic risk information from their parents may have preferred not to have learned this, and learning it could provoke psychological distress in the child. If parents learn that infants are at increased risk for a particular medical condition, risks to the child include alteration of the parent-child relationship. There is also potential for various forms of discrimination (insurance, employment) as the child ages into adulthood. There are currently no systematic data available substantiating these risks. Additional medical tests that are stimulated by genomic reports in infants may lead to iatrogenic harms that would not have occurred in the absence of genetic information. As with any research study, there is a risk for the loss of privacy or confidentiality.

### *Common Risks to Parents*

Venipuncture (if performed) carries a risk of minor discomfort and bruising. There are no known risks to sample collection using saliva collection.

### *Uncommon Risks to Parents*

The risks to the parents of the infants enrolled in this study is that they could learn genetic risk information that makes them anxious, generates discord between parents, impairs bonding with their child, causes them to treat their child as vulnerable, or causes their clinicians to recommend medical testing or procedures that they did not anticipate. We may test the parental DNA to confirm/ determine inheritance of a result found in their child. These results will be reported on the child's GNSR. We will not return parental DNA findings that were not first identified in the child. We will not return information about misattributed paternity or ancestry that could cause emotional distress unless medically necessary for the health of the infant, but the chain of events initiated by genetic follow-up within a family could reveal these issues as it sometimes does in the clinical practice of genetics. There may be medical costs from tests ordered and/or additional office visits as a result

from specific genetic information discovered. Additional medical tests may lead to iatrogenic harms that would not have occurred in the absence of genetic information. As with any research study, there is a risk for the loss of privacy or confidentiality.

***Minimizing Risks to Infants and Parents***

Study physicians and genetic counselors will oversee the interpretation and disclosure of sequencing results consistent with the current practice of medicine. Elements of that care and additional protocol measures taken to mitigate risk to infants and parents will include the following:

- Parents enrolled in this study will undergo a detailed informed consent process, including a Pre-enrollment Genetic Counseling Session, which includes discussion of each of these risks and prepares the parent for the possible results that could be discovered.
- Study staff will oversee collection of family history information to ensure it is as robust as possible in order to assist in interpreting genome results and to allow for risk counseling.
- Disclosure of all results will be led by the study physician and genetic counselor.
- Study personnel will take every precaution to keep subjects' personal identifiers confidential and protect each subject's privacy.
- The study team feels that the benefit of potential early diagnosis and treatment for highly actionable adult onset conditions likely outweighs the risk of disclosing this information, which is consistent with the clinical recommendations of the American College of Medical Genetics and Genomics, which recommends return of these findings in children, regardless of age, as the findings in the child may have important implications for the health of the parent.
- All decisions about medical follow-up will be led by the study physician and genetic counselor and all non-study physicians caring for enrolled infants will be alerted that this specialty team is available for consultation.
- Families will be sent an annual letter reminding them of their participation in the study and providing them with study staff contact information should they have questions or wish to withdraw.
- Interview data will be stored on BCM,BCH, or BWH encrypted and password-protected computers.

***Risks to Non-study Physicians Caring for Enrolled Infants***

Study physicians will be generating clinical consultation notes for all study participants. As in other aspects of the practice of medicine, these specialized consultations may or may not be useful in the care of these patients.

Non-study physicians caring for these infants could be confused by novel information that is outside of their expertise and comfort zone and concerned that they will make inappropriate decisions with regard to the patients that are under their care. Pediatricians may feel uncomfortable with genomic information in the medical record about their patients derived from this study. It is also possible that genetic information may be used inappropriately by non-study physicians, leading to unnecessary diagnostic tests or harm to the infant.

***Minimizing Risks to Non-study Physicians Caring for Enrolled Infants***

A study physician and genetic counselor will be available and on-call at all times through a common study pager, to support families and to support any non-study care providers who have questions or concerns. Risks will further be mitigated by the role of the study physicians in following the study patients over time, and making recommendations based on the genomic reports. Even after the termination of the study, clinical geneticists at BWH and BCH will be available for consultative follow-up to families and non-study physicians.

## POTENTIAL BENEFITS

### *Potential Benefits to Infants and Parents*

There is a possibility that information learned through this study would provide an infant and the infant's parents with more information about genetic disorders/risk in their family. Furthermore, it may be possible to identify a genetic predisposition in an individual before it manifests in symptoms, potentially allowing therapies and treatments to begin earlier. Identifying genetic information may provide personal utility, such as financial planning and family planning.

Sick infants in this study could benefit from a molecular diagnosis discovered through genomic sequencing, or could benefit from receiving drug response variants to help guide treatment decisions.

### *Potential Benefits to Non-study Physicians Caring for Enrolled Infants*

Non-study physicians may benefit from receiving consultations results generated through this study that may give useful information regarding the clinical care of their patients. Non-study physicians may learn more about genetics and genomic sequencing as a result of participating in this study. Non-study physicians may also benefit from a strengthened relationship with the parents who are enrolled in this study.

### *Potential Benefits to Society*

This study aims to identify the potential benefits and pitfalls of adding genomic sequencing to standard NBS in a pilot population of information-seeking families. We believe that the potential advancement of scientific and public health knowledge from this study will allow guidance for future implementation of sequencing as a voluntary addition to standard NBS. Results from this study may provide insights into how genomic information may be incorporated into pediatric medicine and identify areas of further study for subsequent randomized trials to examine the impact of delivering genomic information to physicians and their patients and families.

### Costs

There is no cost to participate in the study. Families will be informed that while genomic sequencing, interpretation and meetings with study physician and genetic counselor will be covered by the research study, any additional follow-up testing or consultations recommended by study physicians or other physicians involved in the infant's care will not be covered by the research study, and may or may not be covered by their insurance. This is addressed in the consent form and will be discussed during the Pre-enrollment Genetic Counseling and informed consent session.

### Equitable Selection of Subjects

Study participants will include newborns and their parents who are interested in newborn genomic sequencing and who are English speaking. Within this group, every effort will be made to enroll a diversity of ethnicity. We recognize that participants may not be representative of the general population in terms of their attitudes toward and interest in sequencing, health behaviors, or demographics (e.g. socioeconomic status). We will keep these limitations in mind when analyzing and interpreting results.

Given the wide range of potential findings from the study and their implications for the health of the newborn and family, we will exclude those who do not speak English to ensure that participants thoroughly understand the informed consent process, implications of study participation and study results, and content of their consultations with the study genetic counselor and physician.

Individuals with impaired decision-making capacity will be excluded from the study because of the need for parents to thoroughly understand the informed consent process, implications of

study participation and study results, and content of their consultations with the study genetic counselor and physician.

## MONITORING AND QUALITY ASSURANCE

### *Data and Safety Monitoring*

As described above, genomic results will be disclosed in the context of an in-person clinical visit with a genetic counselor/study physician team who will adhere to current clinical standards of medical practice in all regards. To collect research outcomes, we will administer validated scales of emotional impact and family bonding to parents immediately post-disclosure, and at 3 months and 10 months post-disclosure, and if future funding allows, and families agree, we will seek to follow families in both arms on an annual basis until the end of the study or until their child reaches age 18. The study physicians will use their clinical judgment, along with standardized scales administered through the protocol, to identify any families experiencing emotional distress or confusion and will schedule additional clinical follow-up visits and phone calls as needed with these families, and when appropriate discuss survey answers with clinicians already involved with the family (i.e. a social worker or clinical mental health provider). Study physicians and genetic counselors will also be available to the non-study physicians who receive the genomic reports to help ensure that the data from these reports is used in an appropriate way. All families will be asked to return in person to their study site at approximately 10 months post-results disclosure for a consultation with a study physician and genetic counselor, at which time additional referrals (if needed) can be made and management recommendations communicated to the infant's community/primary care physician. If the family is unable to come to an in-person visit, a videoconferencing call will be set up. In the rare cases that both an in-person visit and a video conference is not possible, a phone call check-in may be made as well. We will also be requesting and reviewing the infant's records at this time as well.

Additionally, the members of our external advisory board (EAB) who will also serve as a Data Safety Monitoring Board (DSMB) are:

Bruce R. Korf, MD, PhD (Chair)
Leslie Biesecker, MD
Steve Cederbaum, MD
Alex Kemper, MD, MPH
Jim Lupski, MD, PhD
Sharon Terry, MA

Any serious adverse events (e.g. major psychiatric decline requiring clinical intervention, hospitalization, death that is linked to the disclosure of genomic information) will be reported both to the IRB and the DSMB at the time that the event is identified. For all other metrics, the EAB/DSMB will review data annually. The EAB/DSMB will review recruitment statistics, decline and drop-out rates and reasons, as well as any non-serious adverse events (e.g. changes in anxiety or distress scales that do not rise to the level of serious adverse events). We will ask the committee to review this information and generate a report to be submitted to the IRB during the protocol's continuing review. Any special reports that come from the DSMB in these instances will be submitted to the IRB as soon as they are available.

### *Outcomes Monitoring*

Please refer to sections 3.1 and 3.2 above for a description of the ways in which we will carefully monitor infant and parent outcomes.

***Adverse Event Reporting Guidelines***

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.

**PRIVACY AND CONFIDENTIALITY**

All reports placed in the medical records of participating infants will be subject to all privacy protections afforded clinical information. As such, they will be vulnerable to discovery by insurance companies within the limits of the law and under current protections afforded by the Genetic Insurance Nondiscrimination Act and the Massachusetts Law which extends GINA's protections (175 §120E).

Outcomes data collected as part of this research study will be kept in locked cabinets and on password protected computer files.

When genomic data are uploaded to dbGaP and/or other databases for sharing with qualified research investigators, no 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 unscrupulous individuals to identify research participants through these datasets. This possibility will be discussed in the Pre-enrollment Genetic Counseling Sessions and in the consent process.

We will obtain a Certificate of Confidentiality as another layer of confidentiality protection for participants in this study.

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