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PERSPECTIVE

The BabySeq Project: A clinical trial of genome sequencing in a diverse cohort of infants

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Summary

Efforts to implement and evaluate genome sequencing (GS) as a screening tool for newborns and infants are expanding worldwide. The first iteration of the BabySeq Project (2015–2019), a randomized controlled trial of newborn sequencing, produced novel evidence on medical, behavioral, and economic outcomes. The second iteration of BabySeq, which began participant recruitment in January 2023, examines GS outcomes in a larger, more diverse cohort of more than 500 infants up to one year of age recruited from pediatric clinics at several sites across the United States. The trial aims for families who self-identify as Black/African American or Hispanic/Latino to make up more than 50% of final enrollment, and key aspects of the trial design were co-developed with a community advisory board. All enrolled families receive genetic counseling and a family history report. Half of enrolled infants are randomized to receive GS with comprehensive interpretation of pathogenic and likely pathogenic variants in more than 4,300 genes associated with childhood-onset and actionable adult-onset conditions, as well as larger-scale chromosomal copy number variants classified as pathogenic or likely pathogenic. GS result reports include variants associated with disease (Mendelian disease risks) and carrier status of autosomal-recessive and X-linked disorders. Investigators evaluate the utility and impacts of implementing a GS screening program in a diverse cohort of infants using medical record review and longitudinal parent surveys. In this perspective, we describe the rationale for the second iteration of the BabySeq Project, the outcomes being assessed, and the key decisions collaboratively made by the study team and community advisory board.

Background

The use of genome sequencing (GS) as a screening tool to identify genetic disease risks early in life has drawn increasing attention worldwide.[1–6] However, prior to implementing population-based GS screening programs for newborns and infants, additional evidence is needed regarding the acceptability of GS to families and health care professionals (HCPs), as well as on the clinical utility, psychosocial impacts, and cost consequences. The BabySeq Project was a novel randomized controlled trial (RCT) conducted from 2015 to 2019 that assessed the impact of newborn exome sequencing on medical, psychosocial, and economic outcomes.[2,7–28] While the first iteration of BabySeq made important advances in demonstrating the feasibility of newborn sequencing, its findings had limited generalizability as the families who enrolled were predominantly White, of high socioeconomic status, and highly educated, and because enrollment was limited to a single geographic region of the United States.[13]

To strengthen the evidence base for decision making regarding implementation of screening programs that apply GS early in life, our study team is conducting a second iteration of BabySeq. The RCT expands upon our

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previous approach and aims to enroll a diverse cohort of families from population groups that are underrepresented in genomics research. In this perspective, we describe the rationale for, and the design of, the second iteration of BabySeq.

Study overview and organizational structure

Study overview

The second iteration of BabySeq is a multi-site RCT (Clinicaltrials.gov identifier NCT05161169) of GS as a screening tool for infants enrolled from ethnically diverse communities (Figure 1). The trial is funded by the National Center for Advancing Translational Sciences (NCATS) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and includes three core clinical sites: Boston Children's Hospital (BCH) in Boston, MA; the Icahn School of Medicine at Mount Sinai (ISMMS) in New York City; and the University of Alabama at Birmingham (UAB) in Birmingham, AL. To facilitate enrollment of a larger, more diverse population, additional sites joined the study using other funding mechanisms, including Corewell Health East (formerly Beaumont) in Michigan and Children's Hospital of Philadelphia (CHOP) in Philadelphia, PA. Additional extension sites may join in the future. The study is covered by a central institutional review board (IRB) at BCH, and there is one protocol and study database managed by the coordinating center at Brigham and Women's Hospital (BWH). Participant recruitment began in January 2023.

Trained clinical research coordinators (CRCs) invite parents (defined to include legal guardians) of infants under one year of age seen for well-baby care at participating clinics to enroll in the study. All parent-participants meet with a genetic counselor (GC) and receive a family history report with interpretation and any clinical recommendations based on the parent-reported family history. Infants randomized to the GS arm also receive a GS report of pathogenic or likely pathogenic (P/LP) variants associated with a Mendelian disease risk (MDR), including childhood-onset or childhood-actionable (i.e., conditions for which management may begin in childhood) conditions, and risks for a limited number of highly actionable adult-onset conditions. Carrier status for autosomal-recessive and X-linked genetic conditions are also included in the report. All reports are returned to the parent and the infant's HCP and placed in the infant's electronic medical record (EMR). We chose to use GS rather than exome sequencing for the second iteration of the trial because we wanted to expand our ability to call additional variant types that are important in newborn and infant screening. Specifically, GS affords better sensitivity than exome sequencing for detecting mitochondrial variants, *SMN1* calls, and copy number variants.

Medical and economic outcomes are assessed through review of EMR and administrative data and summarized in descriptive and exploratory analyses. Psychosocial outcomes are assessed through longitudinal parent surveys to test the following three-part hypothesis: parents of infants who receive GS will report (1) no greater disruption to parent-child relationships, (2) no greater disruption to the parents' partner relationship, and (3) no greater personal distress than parents of infants who do not receive GS. Planned statistical analyses are described in the supplemental material.

Study team and organizational structure

BabySeq is an interdisciplinary effort that involves collaboration among several enrollment sites with catchment areas that include racially, ethnically, and socioeconomically diverse populations. Investigators have varied and complementary expertise related to genomic medicine implementation with training in clinical medicine, molecular genetics, genetic counseling, social science, bioethics, public health, health economics and outcomes research, health equity, and community-based research. HudsonAlpha Institute for Biotechnology (Huntsville, AL) developed the HCP educational materials. GS is conducted at the Broad Institute of MIT and Harvard (Cambridge, MA), and DNA extraction and GS interpretation is conducted at the Mass General Brigham Laboratory for Molecular Medicine (Cambridge, MA). Surveys to assess parental outcomes were developed at Baylor College of Medicine (Houston, TX), and the economic analysis will be carried out at the Harvard Pilgrim Health Care Institute (Boston, MA). The study team holds regular virtual meetings, and smaller working groups meet more frequently to discuss specific aspects of the trial.

Community advisory board

To make key decisions and enhance recruitment and participant experiences, we developed a community advisory board (CAB) to solicit input from individuals in the communities where we are enrolling participants. Robust engagement with patients, parents, and advocates as research partners, particularly individuals belonging to groups underrepresented in genomics research, can improve research quality, inform research strategies and analytic plans, enhance recruitment and retention, and ameliorate fear of harm and earned skepticism of research.[29–32] The 10-member CAB includes parents of young children, community leaders, local advocates, and clinicians who predominantly self-identify as Black/African American or Hispanic/Latino from the three core enrollment cities (Boston, New York, and Birmingham). The CAB was instrumental in informing decisions about parent interviews, consent documents, recruitment, enrollment, sample collection, and result reporting. Their feedback helps ensure that the study design and outcomes assessment strategies incorporate the perspectives of underrepresented groups and their HCPs. The CAB continues

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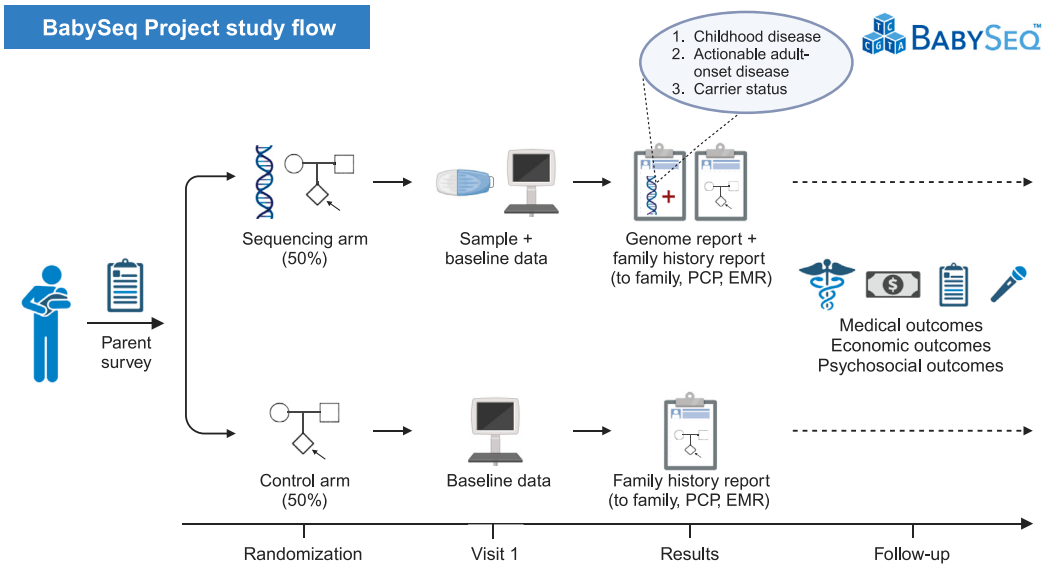

Figure 1. Study flow of the second iteration of the BabySeq Project
PCP, primary care provider; EMR, electronic medical record.

to meet quarterly with study team partners via video conference and provide written input as needed between meetings. They review and suggest edits to study materials; discuss recruitment, retention, and implementation challenges; inform analytic plans and dissemination of findings; and advise on issues as they arise. CAB members are part of the research team and co-author manuscripts and co-present findings based on their availability and interest, and they receive an annual stipend for their time.

Parent interviews

The trial design incorporated formative research, including interviews of local parents to explore concerns toward GS research and how best to address those concerns as we developed our protocol, recruitment strategies, materials, and disclosure methods. The CAB provided valuable insight into which issues should be explored in parent interviews and helped design the interview guide. Interviews were conducted in English and in Spanish at the three core enrollment sites with parents from diverse backgrounds. Qualitative findings were used to revise study materials and develop strategies to approach parents for recruitment.

Health care professionals: Partnership and education

Genomics education program for health care professionals

HCPs in recruitment clinics were invited to participate in BabySeq before infant recruitment began, as we aimed to develop partnerships with trusted local pediatricians. Initially, we invited HCPs working in participating clinics to access an optional brief genomics education curriculum and complete surveys for professional credit. They were informed about the study through presentations at faculty meetings and one-on-one discussions with team members. Clinic champion HCPs at each site who completed the genomics education program helped to launch local recruitment.

The genomics curriculum was developed by collaborators at the HudsonAlpha Institute for Biotechnology and built upon a similar curriculum used to train neonatology HCPs in the SouthSeq project, a Clinical Sequencing Evidence-Generating Research (CSER) Consortium project exploring GS use in the neonatal intensive care unit.[4,33] The education program took about 2 h and included didactic videos as well as a live training session that included facilitated small group discussion about a series of sample reports. Program content focused on GS screening capabilities, BabySeq report structure, how to interpret results and direct follow-up clinical care, how to discuss results with caregivers, and where to find additional resources. HCPs also completed pre- and post-training online surveys to assess their current genetics practices, attitudes about genomics (Genomic Orientation Scale[34]), genetics knowledge (GKnowM knowledge scale[35]), and perceived confidence reading and using GS results.[33] HCPs who elected to participate in the training and surveys earned American Board of Pediatrics Maintenance of Certification Part IV[36] credit for their participation. In years 2–4, feedback will be collected from HCPs through additional surveys or semi-structured interviews with a member of the HudsonAlpha education team.

After clinic champions were trained and initial participants were enrolled, recruitment was expanded so that all HCPs in each clinic can refer patients or allow CRCs to directly approach families. The clinic champion HCPs

who completed the full training are available as a local consultation resource for their colleagues throughout the study. Resources and educational materials including videos, fact sheets, and decision trees developed by HudsonAlpha are available on-demand for all HCPs at each recruitment clinic.

For all enrolled infants, the HCP receives a written family history report. For infants randomized to the GS arm, a study GC discloses GS results to the parent, and the HCP receives the written GS report and disclosure letter within the EMR. The established HCPs manage the ongoing medical care for infant participants, which may include placing referrals or ordering follow-up clinical tests after receipt of a positive GS screening result. The study team is available for questions about follow-up management recommendations as needed.

Infants and parents: Study procedures, recruitment, and randomization

Development of study procedures and materials

Study procedures and materials were shaped by our experience with the first iteration of BabySeq, feedback from the CAB, parent interviews, literature review, and experience in genomics research with diverse populations. Materials including recruitment aids, informed consent forms, and results disclosure templates were carefully reviewed for readability (under 8th grade reading level) and cultural sensitivity. All study materials for families are available in English and Spanish.

Recruitment

Most participants are initially approached by a CRC at a well-child visit with their HCP, although there are also options for remote recruitment. For a parent who expresses interest in participating, we schedule an enrollment session during which a CRC provides additional detail about the study, answers questions, verifies interest, and initiates the informed consent process. Infants are eligible to participate if they (1) are under one year of age; (2) receive well-child pediatric care at an enrollment site; and (3) have one parent (or legal guardian) able to participate in the study. Infants who have already received diagnostic exome or genome sequencing are not eligible. We also do not enroll any infant in which clinical considerations preclude sample collection or whose parent does not consent to the GS report being included in the EMR or sent to the HCP. For infants of a multiple gestation, parents are offered the option to enroll one infant to ensure that survey responses represent their experience for one infant and one randomization arm. We also explain to these parents that if an MDR is identified in one multiple, cascade testing will be available for the other multiple(s) at no charge through the study.

Parents are eligible to participate if they are (1) the biological parent or legal guardian of the infant enrolling, (2) able to make clinical medical decisions, (3) fluent in English or Spanish, (4) available to participate in pre-test genetic counseling and informed consent at the time of recruitment, (5) willing to be available to complete three surveys over 9–12 months, and (6) age 18 years or older. The decision to require consent of only one parent was based in part on feedback from the CAB and from study team experience in the first iteration of BabySeq, in which we required enrollment of two parents. Requiring both parents to consent may be a barrier to enrollment and limit the representativeness of participants.

Enrollment rates, decliner rates and reasons for declining, and participants' demographic information are tracked weekly to assess progress toward the goal of enrolling 500 infants, over 50% of whom are parent-identified as Black/African American or Hispanic/Latino. These data are shared with the CAB for feedback and adjustment of recruitment strategies, resources, and/or study procedures as needed.

Informed consent

Informed consent includes a brief description of traditional newborn screening and the opportunity to screen for additional conditions using GS. Specific examples of possible results are shared, including learning about risk for conditions with or without specific treatment, those that may begin in infancy or later in life, and conditions with higher or lower genetic penetrance. Potential risks discussed include uncertainty and anxiety about results, impact on other family members, and the possibility of future genetic discrimination (e.g., potential impact on life insurance) as well as current legal protections. Possible benefits discussed include the chance for both the infant and their family members to learn about treatable health risks that may not otherwise be identified. We inform all potential participants that any follow-up medical costs after a positive result are not covered by the research study but would instead be facilitated through the infant's pediatrician and billed the same way as other clinical services. There is a discussion of privacy, confidentiality, and data sharing, including the requirement to submit de-identified genetic data to dbGAP or another appropriate database. Reanalysis of genetic data is not discussed as this is not planned under the current protocol. The importance of the role of the control group is emphasized, and we explain that the family history report and genetic counseling session could benefit some families even if the infant does not receive GS. The CAB edited the informed consent document to enhance its accessibility to a broad range of potential participants. The informed consent discussion lasts approximately 20 min, and families are given the opportunity to enroll up until their child's first birthday. If the parent chooses to participate, a trained CRC obtains written informed consent using either a paper consent form or electronic consent (REDCap[37] eConsent, accessible by smartphone). There is no formal test of understanding included in the consent process. However,

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CRCs ask questions and use their professional judgment to confirm understanding and the appropriateness of consent. To promote retention, we pair CRCs with families to coordinate participation throughout the study, including meeting parents in-clinic whenever needed. We offer multiple methods of communication including text messaging. We send yearly e-cards on each infant's birthday and maintain a participant-facing website that is regularly updated with information, news, and study results.

Randomization

After the parent provides written informed consent and completes the baseline survey, infants are randomized 1:1 to receive a family history report only (control arm) or family history report plus GS (GS arm). We randomly assign infants equally within strata, in blocks of four. Randomization strata include enrollment site and parent-reported race and ethnicity of the infant. Randomization is completed within REDCap. Parents are notified which group their infant was assigned to and whether a sample needs to be collected (GS arm only; see DNA sample collection and sequencing).

Data collection

Family history information

At enrollment, potential participants' demographic information and other study intake data are collected in a secure REDCap database.[37] A CRC obtains a three-generation family history using a standardized template with scripted questions, or participants can complete an online questionnaire. The scope of the family history is similar to that of a clinical prenatal or pediatric genetic counseling session. The family history is used later to facilitate interpretation and contextualization of the GS report, as well as to create a family history report. If the family history suggests that a more targeted form of genetic testing should be pursued (e.g., there is potential for Lynch syndrome in a parent), the family receives additional genetic counseling through the study and may be referred for a clinical genetics evaluation. If the family history suggests a potential increased risk for common diseases such as coronary artery disease, information on multifactorial familial risk is provided in addition to potential recommendations for primary care follow-up. Additionally, if the family has concerns about a condition that is less likely to have a genetic basis, the GC reviews the lack of known genetic contributions to disease and likely general population risk for the infant. The family history information is self-reported and typically cannot be confirmed by medical records, so this limitation is discussed with parents as appropriate.

DNA sample collection and sequencing

The CAB recommended using minimally invasive methods to collect DNA samples from infants. Prior to beginning recruitment for the second iteration of BabySeq, we conducted a pilot project to explore parental acceptability and DNA yield of less invasive sampling methods than venipuncture. One method, called volumetric absorptive microsampling of capillary blood, uses a standard heel stick along with a novel sample collection kit developed by Neoteryx. The microsampling kit is preferable to standard newborn screening blood spot filter paper to promote sufficient volume and maximal DNA extraction. We collected microsamples from infants under 8 months old and performed laboratory validation to confirm that DNA quantity and quality were adequate for GS. We also confirmed parent acceptability of this sample type through post-sampling surveys.

Using this validated microsampling method, clinical staff collect a heel stick blood sample from infants randomized to the GS arm for DNA extraction. If the infant sample does not yield sufficient DNA for sequencing, a second sample collection is offered. Alternate sample types can also be used as appropriate (e.g., if the infant is having a clinical blood draw, an additional tube may be collected for research; saliva samples may be offered in the future). Samples are shipped to the Mass General Brigham Laboratory for Molecular Medicine or another CLIA-certified lab, where DNA is extracted. The Broad Institute or another CLIA-certified laboratory then performs whole-genome sequencing on the sample using 150-bp paired end Illumina sequencing at an average coverage of $\geq$30× and $\geq$90% completion at 20×. Coverage closer to 40× is typical, and there is consensus among clinical laboratories that 30×–40× is appropriate for most variant types for clinical purposes.[38] Alignment and variant calls are performed using DRAGEN v.3.10.4. The Laboratory for Molecular Medicine performs annotation, filtration, classification, and interpretation of results and generates a GS report. Briefly, variants are filtered to a set of 4,314 genes with some level of published evidence for a gene-disease association and are subsequently filtered to identify (1) variants classified as disease-causing mutations in public databases that have a minor allele frequency <5.0% in the Genome Aggregation Database (gnomAD, http://gnomad.broadinstitute.org/) and (2) nonsense, frameshift, and $\pm$1,2 splice-site variants in disease-associated genes with a minor allele frequency $\leq$0.1% in gnomAD. The evidence for phenotype causality is then evaluated for each variant identified from the filtering strategies listed above and variants are classified based on ACMG/AMP criteria with ClinGen rule specifications.[39] Only those variants with evidence for causing or contributing to disease are reported. All disease-associated variants are confirmed via Sanger sequencing or another orthogonal technology, such as digital droplet PCR.

Samples are not collected from infants randomized to the control arm, a decision based on insight from the CAB. Their guidance was that obtaining a blood sample from an infant who may not undergo GS could cause unnecessary pain and exacerbate mistrust regarding how

the sample was being used or destroyed. Therefore, we adjusted the masking strategy of the study. Parents and study team members are notified after randomization whether the infant is in the GS arm or the control arm and thus whether a sample is needed. Baseline survey responses are collected prior to randomization so that our study outcomes are not compromised.

Related to the decision to require only one parent to enroll alongside their infant, we also decided not to collect parental DNA samples at baseline. This contrasts with our approach in the first iteration of BabySeq, in which we collected samples from both biological parents at baseline and automatically tested parents for carrier status and MDRs identified in the infant. We made this decision based on points raised by the CAB and study team members, including the recognition that biological parents may not be available for testing, that parents may not wish to have testing for themselves, and that storing unused samples may exacerbate mistrust. In addition, focusing testing on the infant best mirrors current newborn screening as well as other screening practices.

The CAB was also instrumental in helping define our approach to cascade testing if an MDR is identified in the infant. Given our desire to reduce financial burden for families who may not be able to access testing outside of the study, we offer the option for cascade testing through the study at no cost for up to two first- or second-degree relatives per family. The decision regarding which family members to test is made in consultation with the family, taking genetic relatedness, family structure, and parent preferences under consideration. Given the high prior probability of a positive result, a GC obtains informed consent for cascade testing. If a relative consents, a saliva collection kit is provided to collect a sample for targeted testing of only the variant associated with the MDR identified in the infant. Of note, we do not offer cascade testing for adult-onset conditions to minor siblings of the proband, since the purpose of this screening is to alert families of an actionable risk about which they may not otherwise know. Once an MDR has been identified in a family, there is limited benefit for another child in the family to have testing for a known adult-onset condition.

Surveys

We administer surveys to parents at baseline, immediately after disclosure of the family history report or family history report plus GS result report, and six months post-disclosure to assess parent-reported outcomes. Completion of the baseline survey is required for enrollment. Parents can choose whether to take surveys in English or Spanish. Surveys may be completed in person, over the phone, or online in REDCap (accessible by smartphone). Multiple reminders to complete each survey are communicated via email, text message, and phone call, and a CRC may also meet the parent in clinic to facilitate survey completion at a convenient time. Parents are offered the option to have a study team member read the survey questions and respond verbally. To maximize the survey data available for analysis, we do not require that parents complete the immediate post-disclosure survey prior to completing the 6-month post-disclosure survey, and we do not require responses to any individual survey questions. Parents are provided with a gift card incentive of $50 for completing each survey ($150 total).

Generating and reporting GS results

We generally follow the same dynamic gene selection process and reporting strategy as was used in the first iteration of BabySeq. Our comprehensive screening and reporting approach is suited to a rapidly changing knowledge environment, and there is no pre-specified list of genes for which results are definitively returned. Rather, we use gene-level criteria and variant-level criteria to determine which results are reported in the GS report.[11] This approach resulted in the curation of 954 genes in the first iteration of BabySeq.[11]

Participant genomes are comprehensively analyzed for potentially pathogenic and likely pathogenic variants across a set of more than 4,300 genes with evidence of having at least some level of published evidence of association to disease.[24] Genes with identified variants meet criteria for inclusion based on (1) the validity of gene-disease association,[40] (2) presumed penetrance, and (3) average age of onset of the disease or clinical actionability in childhood. The GS report includes MDR or carrier status information for genes with a definitive or strong level of evidence based upon established guidelines,[40] high or moderate penetrance, and age of condition onset or actionability before 18 years old. Additional consideration is given to MDR findings associated with low penetrance after consultation with experts across the study team. Gene-level criteria are evaluated using online resources including Medline Plus (formerly Genetics Home Reference), Orphanet, GenCC, ClinVar, HGMD, gnomAD, Online Mendelian Inheritance in Man, and GeneReviews. Only pathogenic or likely pathogenic variants are returned,[39,41,42] consistent with genomic screening modalities.[39,42–44] Variants of uncertain significance (VUSs) that have strong data associated with pathogenicity (VUS-favor pathogenic) will be evaluated for inclusion on a case-by-case basis. Depending upon disease mode of inheritance and variant zygosity, variants are listed under either the MDR, Carrier Status, or Low-Penetrance section of the report. Carrier status for adult-onset disorders is not reported. MDRs for genes on the ACMG secondary findings list v.3.1[45] are reported, including the following adult-onset genes: *BRCA1, BRCA2, PALB2, MLH1, MSH2, MSH6, PMS2, TTR,* and *HFE,* which may be expanded if professional recommendations are updated. All reported variants are confirmed by orthogonal technology. Although preliminary results show similar rates of findings between ancestries, we counsel participants around the limitations of our approach, including the potential for fewer reportable variants in individuals with non-European genetic ancestry

that could be due to ascertainment biases of pathogenic variants in databases.[46]

Reanalysis is not planned. However, as variants are reclassified by the laboratory that affect the interpretation on the report, an amended report will be released to the pediatrician. Further, if the infant develops a phenotype during the course of the study, an indication-based analysis can be ordered by the pediatrician with costs covered by the study.

The Laboratory for Molecular Medicine developed a report template that incorporated the unique reporting requirements of this study. Drafts of the report were reviewed by the study team, and feedback led to changes in content, wording, and layout to make it more accessible to non-genetics HCPs. The GS report categorizes variants in four different sections: (1) MDR for childhood-onset conditions, (2) MDR for a subset of adult-onset conditions deemed highly actionable, (3) carrier status for childhood-onset conditions, and (4) MDR for childhood-onset conditions with low penetrance. Penetrance estimates are gathered from primary literature, and conditions with suspected low penetrance are discussed with the full team to determine final placement on the report. An overall result summary appears at the top of the report to alert the HCP to any important findings on the report. Detailed information about the variant, gene, and associated disease is included after the brief summary section.

Return of results

The turnaround time for GS results is approximately 12 weeks. Results return for the control group follows this same timeline for comparison. All families have a disclosure session with a study GC. The family history report is reviewed, as well as the BabySeq GS report for infants in the GS arm. Parents receive a copy of each report and a more accessible results letter summarizing the findings and the disclosure conversation. The GC then places the reports and results letter in the infant's EMR for access by their HCP and other clinicians. The location of the reports within the EMR is determined by local site preference.

For infants in the GS arm, positive sequencing results are reviewed with the study team as needed prior to disclosure to families. The infant's HCP is directly alerted when a positive result is identified, and the study team is available for guidance on follow-up management if requested. The disclosure conversation takes place in person or virtually, depending on the family's preference. Topics for discussion include estimated penetrance, diagnostic laboratory and imaging tests, potential symptoms of an associated condition, recommended surveillance or treatment protocols, recommendations for cascade screening, and psychosocial support as needed. All follow-up medical care is managed clinically outside of the research study and is billed to insurance or another payer similar to other clinical services. We expect to return MDR findings to approximately 10% of infants, adult-only MDR findings to approximately 1%–2%, and carrier findings to approximately 90%.

Database

A REDCap[37] database has been developed to manage the clinical trial workflow, administer parent and HCP surveys, and collect harmonized outcomes data. This secure, HIPAA-compliant database is hosted inside the coordinating institution firewall. The data collection forms were built based on the first iteration of BabySeq, and the database structure was designed with input from study team members familiar with multi-site clinical trials. Study team members at each site have been assigned to data access groups to view records and identifiable data for participants at only their site. Multilingual capabilities have been implemented to facilitate the administration of parent surveys in Spanish and English. Visual dashboards of aggregate, real-time recruitment and enrollment data have been created and are accessible to study team members on-demand throughout the project.

Data storage and protection

Clinical data collected as part of this research study are entered into the REDCap database.[37] Each recruitment site enters identifiable data about participants that cannot be viewed by other recruitment sites. Any identifiable data exports from REDCap are stored in password-protected computer files stored securely on institutional HIPAA-compliant platforms. Identifiable data are kept to the minimum necessary and only included if required for specific analyses. All reports placed in the EMR of participating infants are subject to all privacy protections afforded clinical information. De-identified clinical data may be shared with other researchers in a secure and standardized manner. Once the study is finalized, clinical data will be stored on secure servers for at least 7 years according to institutional policies.

The study laboratory stores genomic data according to secure HIPAA-compliant procedures and follows all standard practices for clinical genomic data. De-identified genomic data will be uploaded to dbGaP and/or other databases for sharing with qualified research investigators. No protected health information will be uploaded that could lead to the identification of these research participants. Once the study is finalized, genomic data will be stored by the laboratory for at least two years according to national clinical laboratory regulations.

Outcomes assessment

We assess outcomes in three domains: medical, psychosocial, and economic (Table 1). Data on these outcomes are collected by reviewing laboratory results, medical records, and administrative records. We also collect participant-reported outcomes by surveying parents and HCPs and by interviewing HCPs. Surveys are provided in the supplemental material.

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Table 1. Primary and secondary outcomes and measures in the second iteration of the BabySeq Project

Primary outcome(s)	Primary outcome measure	Secondary outcome(s)	Secondary outcome measure
Medical			
identification of Mendelian disease risks (MDRs)	pathogenic and likely pathogenic variants identified	MDR-associated family history	signs or symptoms of MDR present in infant's biological family
carrier status variants	pathogenic and likely pathogenic variants identified as recessive carrier status in infant	intervention prompted by genetic or family history report	healthcare intervention prompted by MDR or recessive carrier variant
MDR-associated phenotype	signs or symptoms of MDR identified by genome sequencing	suspected genetic condition	any phenotype that develops in an infant or a family history suspected to have a genetic cause
Psychosocial			
parenting stress, relationship dysfunction	Parenting Stress Index, 4th Edition Short Form[47]	child vulnerability	Vulnerable Baby Scale[48]
		feelings about genomic testing	Feelings About Genomic Testing Results (FACToR) Questionnaire[49]
relationship satisfaction	Kansas Marital Satisfaction Scale[50]	partner blame	novel item[26]
general anxiety	General Anxiety Disorder-7[51]	general depression	Patient Health Questionnaire (PHQ)-8[52]
		self blame	novel item[26]
Economic (exploratory aim)			
cost of attributable services	cost of health care services associated with surveillance and diagnosis of GS and family history risks	N/A	N/A
cost of genomic services	cost of genetic services infants and parents received after study disclosure session	N/A	N/A
all healthcare costs	all health sector costs observed in medical records and survey questions regarding family out-of-pocket expenses	N/A	N/A

N/A, not applicable.

Medical outcomes

In the medical domain, primary outcomes are identification of MDRs and carrier status variants. For infants with an MDR result, we determine whether the MDR explains existing clinical features, reveals an unsuspected phenotype in the infant or at-risk family member, or explains a family history of a condition. Follow-up medical care and health outcomes are tracked through EMR reviews. We also use EMR reviews to assess any genetic conditions identified through routine clinical care. To evaluate the medical impact of GS on infants and their families, parent surveys include questions to assess any follow-up medical care or services for the infant and other relatives after disclosure of family history report and/or GS findings. Medical outcomes will be summarized descriptively.

Psychosocial outcomes: Parent surveys

Parent surveys (supplemental material) are used to evaluate the effect of GS on psychosocial outcomes by comparing responses on survey instruments between study arms over time. Survey working group members discussed and decided upon which instruments to include based on the following considerations: (1) validation for use in families with demographic characteristics matching enrollment criteria for parents and infants, (2) prior use in the first iteration of BabySeq; (3) participant burden; (4) relevance to the genomics field; and (5) relevance to policy decision making regarding newborn and infant GS screening programs. Novel items were added as needed to assess outcomes that do not have validated instruments. Survey content was refined based on feedback from the larger study team and the CAB. After development of a draft survey, cognitive interviews were conducted with members of the CAB to gather feedback regarding clarity, time to complete, and appropriateness of questions. Once the survey content was finalized, we translated the survey into Spanish, using existing validated Spanish-language versions of instruments where available and having any other instruments professionally translated and reviewed by team members who are fluent in Spanish. Instruments were programmed in REDCap for administration. Hypotheses related to psychosocial outcomes will be tested using longitudinal analyses of scores on instruments that assess parenting stress and relationship dysfunction, relationship satisfaction, and general anxiety (supplemental material – Statistical Analysis Plan).

Economic outcomes

Economic outcomes are assessed as an exploratory aim to quantify the impact of GS on health care utilization and

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associated costs. Our analytic approach is informed by prior trial-based analyses of genetic screening in healthy populations.[53,54] We examine health care utilization and costs in three categories (Table 1): (1) attributable services, defined as health care utilization and costs specifically linked to family history report and/or GS findings, (2) genomic services, to estimate the effect of GS on evaluations for potential genetic conditions and how often it motivates additional genetic testing to clarify findings with ambiguous implications for infants and family members, and (3) all observed health care utilization for the enrolled infant. Applying methods that were previously summarized in the first iteration of BabySeq for attributable services,[21] we will develop lists of services for each infant identified with an MDR or high-risk family history that include specialist encounters, tests, procedures, and devices that may be ordered to diagnose or screen for the associated conditions. We will then review EMRs of the infants to quantify how often, if at all, these services occurred. Lists will be developed with expert input based on condition summaries in GeneReviews,[55] Online Mendelian Inheritance in Man,[56] the National Comprehensive Cancer Network, and UpToDate. Analyses of genomic services and all healthcare costs will be conducted by obtaining all encounter, procedural, and laboratory data from patients' medical records and applying cost weights from standardized reimbursement schedules (e.g., Centers for Medicare and Medicaid Services) or institutional cost data, as available.[54] Although these analyses are likely to be underpowered to detect real differences between randomization arms in health care utilization and total costs, these exploratory analyses will provide critical data regarding the effect of GS on downstream health care spending. These data will be useful for informing policy and program design, as well as future follow-up trials to assess outcomes over a longer time horizon.

Data for economic analyses are sourced from the EMR, institutional data warehouses, the Pediatric Health Information System,[57] and parent surveys. Parent surveys assess health care utilization occurring outside the health system from which the infant was enrolled, and informal health care sector costs (e.g., caregiver time costs, transportation costs) and non-health care expenditures (e.g., time off from work for medical appointments, social services). Parent surveys will also include measures of health-related quality of life that may be used to calculate health state utilities for incorporation into economic evaluations in the future. Given the limited follow-up time for participants, only analyses of short-term health care utilization and costs will be conducted.

Discussion

The second iteration of BabySeq is an RCT of GS as a screening tool in a diverse cohort of at least 500 infants. It builds upon the first iteration of BabySeq by using GS instead of exome sequencing, with study design modifications to encourage participation of families who are underrepresented in genomics research through community engagement. The goal is to generate evidence on the impact of implementing a GS screening program for infants and evaluate the effects of returning a broad range of GS results.

There are several studies around the world that are currently in design or recruitment phases that will assess the use of genomic sequencing as an adjunct test to standard newborn screening, many of which will include larger numbers of participants.[6,58–60] BabySeq is unique in that it uses an RCT framework and examines a wide breadth of GS results, including some actionable adult-onset conditions and some pediatric conditions that currently lack targeted treatments. The majority of parents who completed surveys in the first iteration of the trial were somewhat or very interested in receiving information about actionable conditions that may develop in both childhood (96%) and in adulthood (96%), as well as risk information for childhood-onset (78%) and adult-onset (74%) conditions that do not currently have a prevention, treatment, or cure available.[27] Ensuring equitable access to gene therapies and other high-cost therapeutics as they become available will be critical to realizing the potential of early disease identification.

Through creation of a CAB with diverse parents, caregivers, pediatricians, and advocates, we helped to establish important relationships between members of various underrepresented communities and the study team. We incorporated CAB feedback in multiple aspects of the study. Major changes include deciding not to collect a sample from infants randomized to the control arm, using minimally invasive sample collection methods, not collecting samples from parents at baseline, requiring enrollment of only one parent, and ensuring that the informed consent document and survey instruments are accessible and appropriate. Our team is hopeful that these protocol adjustments, along with continued input from the CAB, will promote enrollment of families more representative of the US population.

By increasing the number of diverse infants who will undergo GS in the second iteration of BabySeq, we hope to begin to develop a better understanding of the prevalence and medical outcomes associated with MDRs. An unexpectedly high proportion of the infants who underwent GS in the first iteration of BabySeq (18/159, 11.3%) were found to have an MDR associated with childhood or adult-onset Mendelian disease.[15] In a more racially and ethnically diverse cohort, we may expect to identify more infants with variants of uncertain significance[61,62] and fewer infants with pathogenic or likely pathogenic variants,[46] as has been previously found in studies of adults at risk for hereditary cancer syndromes. These differences in variant interpretation could lead to lower negative predictive value of GS in diverse newborns. Functional analysis of these variants, as well as analyses of

reportable variant frequencies and participants' medical outcomes, will be essential to understanding other screening characteristics of GS in infants of non-European ancestry, such as positive predictive value of MDRs. In time, GS of thousands of infants will need to be completed to establish better estimates of Mendelian disease penetrance and the positive predictive value of pathogenic and likely pathogenic variants associated with a range of Mendelian disorders.

Results of analyses of psychosocial outcomes in the first iteration of BabySeq showed no evidence of psychosocial harm to parents sustained over the study period.[26] We have chosen to assess psychosocial outcomes again in the second iteration of BabySeq, not because we believe there are additional or greater harms to be found, but rather because we believe that it is important to have data on these outcomes from a more diverse cohort to inform policy and implementation decisions. Improving the generalizability of findings is crucial to ensure that the benefits of such research are equally distributed among members of the population, assuage concerns that persist within the scientific community about potential harms, and support widespread adoption of newborn and infant GS.

Through the BabySeq Project, we aim to assess the clinical utility, psychosocial impacts, and economic value of GS in a racially, ethnically, and socioeconomically diverse cohort of unselected infants. Findings from this project will be useful to inform the design of public health programs that are sustainable and acceptable to families, and that maximize benefits to patients while reducing risk of harm.

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Declaration of interests

H.S.S. has received consulting income from Illumina unrelated to this work. N.D.S. is a member of the Scientific Advisory Board for Neuberg Center for Genomic Medicine. A.L.M. is a paid advisor for Nurture Genomics. B.R.K. is a member of medical advisory boards for Alexion, SpringWorks, Healx, Infixion, and Recursion and has stock options in GenomeMedical. R.C.G. has received compensation for advising Allelica, Atria, Fabric, Genome Web, and Genomic Life and is a cofounder of Genome Medical and Nurture Genomics.

Supplemental information

Supplemental information can be found online at https://doi.org/10.1016/j.ajhg.2024.08.011.

Web resources

International Consortium on Newborn Sequencing, https://www.iconseq.org

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Supplemental information

The BabySeq Project: A clinical trial of genome sequencing in a diverse cohort of infants

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Contents

Statistical Analysis Plan

Aim 1: Develop a recruitment and retention strategy to enroll apparently healthy, ethnically and racially diverse infants into an RCT of GS.

There are no statistical analyses associated with Aim 1

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 from varying ethnic and racial backgrounds, we will conduct longitudinal surveys and compare validated scales between arms of the RCT.

Hypothesis 2a.1: Parents of infants in the FH+GS arm will report no greater disruption to parent-child relationship than those in the FH arm.

Hypothesis 2b.1: Parents of infants in the FH+GS arm will report no greater disruption to the parents' partner relationship than those in the FH arm.

Hypothesis 2c.1: Parents of infants in the FH+GS arm will report no greater personal distress than those in the FH arm.

Data analysis for Aim 2a:

Statistical analyses for Aim 2 will be conducted on survey measures administered at enrollment, immediately after results disclosure sessions, and six months after disclosure sessions. The primary measure for assessing the parent-child relationship is the Parenting Stress Index Short Form (PSI-4).[1] The primary measure for assessing parents' partner relationship is marital satisfaction, as assessed with the Kansas Marital Satisfaction scale.[2] The primary measure for assessing personal distress is the 7-item General Anxiety Index (GAD-7).[3]

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. 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 for exploratory analyses 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 exploratory analysis.

Aim 2b: To assess the medical impact of GS on infants and their families, we will review laboratory results and medical records and survey parents to track symptoms and identify new diagnoses and medical actions attributed to the GS findings. Among infants with a Mendelian disease risk (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 analysis for Aim 2b:
The analysis of these data will largely be descriptive, due in part to the nature of the data with heterogeneous diagnoses, but with the increased sample size in this iteration, there will be a larger set of MDRs to explore.

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

Data analysis for Aim 2c:
Given protocol changes to allow enrollment of infants whose HCPs are not enrolled participants, analyses of Aim 2c will be descriptive.

Exploratory Aim 3: To evaluate healthcare utilization and associated costs of GS.

Aim 3 analyses will be exploratory, given the limited sample size of the study and rarity of Mendelian disease risks. Three types of analyses will be conducted.

- *Attributable services*. Primary analyses of healthcare utilization and costs will expand an "attributable services" approach implemented in related work we have conducted.[4] We will use the notes from disclosure sessions to identify Mendelian disease risks and concerning family histories of disease for infants, and then verify whether the services occurred.
- *Genomic services*. 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 received after disclosure sessions.
- *All costs*. Finally, we will conduct "all costs" analyses where we summarize all health sector costs for services 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.

For analyses of attributable services, we will develop lists of services for each infant identified with an MDR or high-risk family history that include specialist encounters, tests, procedures, and devices that may be ordered to diagnose or screen for the associated conditions. We then review medical records of the newborns to quantify how often, if at all, these services occurred. Lists will be developed with expert input based on condition summaries in GeneReviews,[5] Online Mendelian Inheritance in Man,[6] the National Comprehensive Cancer Network,[7] and UpToDate.[8] Analyses of genomic services and all healthcare costs received will be conducted by obtaining all encounter, procedural, and laboratory data from patients' medical records and applying cost weights from standardized reimbursement schedules (e.g., CMS rates) or institutional cost data, as available.
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.[9] Costs will be assigned to other

downstream healthcare services by multiplying utilization by cost weights derived from the Centers for Medicare and Medicaid Services fee schedules.[10] To facilitate analyses from the societal perspective, we will collect data about family out-of-pocket expenses using survey items.[10] 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. Cost analyses will be exploratory, but we anticipate that we will have 93% power at α=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. 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.

Statistical Analysis Plan References

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Baseline Survey

Thank you for taking part in the BabySeq Project. This survey should take about 20 minutes to complete. Your answers will be saved if you would like to finish the survey later.

We ask that you fill out the entire survey. But, if you don't want to answer any questions or they make you uncomfortable, you are welcome to skip them. Please continue through the survey even if you skip some questions.

We want to learn if genetic testing for babies is helpful to families. Your answers will help us compare genetic testing to regular well-baby care. We also want to know if genetic testing causes any stress to families or helps with medical care in any way.

When the questions ask about "your child", they mean your baby who is part of the BabySeq Project. Please answer the questions thinking about this baby (even if you have other children).

If you are taking the survey on your phone, we suggest turning the phone length-wise so it is easier to see. Please don't use your browser's "back" button during the survey.

Once you finish the survey, a study team member will review your answers. We may contact you if we have any questions or need more information. Then, we will send you a gift card for $50.

If you have questions about the BabySeq Project, you can contact your local site here: [site contact information]

Would you like to start the survey now?

- o Yes
- o No

Genomic Orientation Scale

Horrow C, Pacyna JE, Lee MK, Sharp RR. Measuring attitudes about genomic medicine: Validation of the genomic orientation scale (GO Scale). *Value in Health*. 2021;24(7):1030-1037. doi:10.1016/j.jval.2021.02.001

First, we will ask how you feel about genomic medicine. Genomic medicine means using our genes (DNA) as part of healthcare. It can be used for both babies and for adults.

Within the next 5 years, how likely or unlikely is it that genomic medicine will...

Very unlikely	Unlikely	Neither likely nor unlikely	Likely	Very likely

1. help doctors choose the best drugs for patients
2. increase the number of unnecessary tests
3. help prevent common diseases
4. detract from disease prevention efforts we know work well
5. help doctors diagnose rare diseases earlier
6. distract doctors from looking for non-genetic causes of disease
7. help people live longer
8. divert healthcare resources that could be better used for other purposes
9. give patients more control over their health
10. create a burden of worry where there wasn't one before
11. be difficult for many patients to understand
12. help doctors focus on the unique needs and goals of each patient
13. make it harder for doctors to engage each patient as a person
14. increase the cost of healthcare
15. increase the cost of prescription drugs
16. increase inequality in healthcare
17. create new forms of discrimination
18. be too expensive for most people
19. make it more difficult for patients to receive medical care they need
20. be a standard part of general medical checkups

21. not be available in most hospitals and clinics
22. benefit nearly all aspects of medicine
23. be beneficial to you
24. cause you harm
25. do a lot of good
26. create many problems

Vulnerable Baby Scale

Kerruish NJ, Settle K, Campbell-Stokes P, Taylor BJ. Vulnerable Baby Scale: Development and piloting of a questionnaire to measure maternal perceptions of their baby's vulnerability. *J Paediatr Child Health*. 2005;41(8):419-423. doi:10.1111/j.1440-1754.2005.00658.x

The next group of questions ask about your experience being a parent. There are no right or wrong answers.

These questions will help us study relationships between parents and children. We want to learn whether genetic testing might affect these relationships.

27. How often do you generally check on your baby while they are asleep at night?
    1) Not at all
    2)
    3) 1-2 times each night
    4)
    5) Frequently (at least every 30 minutes)

28. If your baby was awake and playing, for how long would you leave them unattended?
    1) Not at all
    2)
    3) About 15 minutes
    4)
    5) More than an hour

29. If a friend came to visit and they had a cold, would you:
    1) Not allow them in the house
    2)
    3) Allow them in but not let them hold the baby
    4)
    5) Allow them in and not restrict contact

30. How often does your baby seem to get stomach aches or other pains?
    1) All the time
    2)
    3)
    4)
    5) Not at all

31. How concerned are you that your baby is not as healthy as they should be?
    1) Very concerned
    2)
    3)
    4)
    5) Not at all concerned

32. In general, when you compare your baby's health to that of other children the same age, do you think your baby is:
    1) Less healthy
    2)
    3)

4)
5) More healthy

33. How worried are you that your baby may become seriously ill?
1) Very worried
2)
3)
4)
5) Not at all worried

34. How worried are you about Sudden Infant Death Syndrome (SIDS)?
1) Very worried
2)
3)
4)
5) Not at all worried

35. If you left your baby with someone else, would you make contact with them while you were away?
1) Yes, always
2)
3) Sometimes
4)
5) No, never

36. In the last 2 weeks, how often have you contacted a health professional (e.g. general practitioner, after hours emergency doctor, nurse, etc.) about your baby?
1) Not at all
2)
3) Once a week
4)
5) Daily or more

Relationship Status

Next, we'll ask some questions about your partner and relationship (if applicable).

These questions will help us learn about relationships between partners. We want to learn whether study information might affect these relationships.

37. Which of these best describes you?
    - o Single (never married)
    - o Married or living with a partner
    - o Widowed
    - o Divorced
    - o Separated

38. Is your partner the biological parent of your baby?
    - o Yes
    - o No
    - o Prefer not to answer

Kansas Marital Satisfaction Scale

Schumm WR, Paff-Bergen LA, Hatch RC, et al. Concurrent and discriminant validity of the Kansas Marital Satisfaction Scale. *J Marriage Fam*. 1986;48(2):381. doi:10.2307/352405

39. How satisfied are you with your marriage or partnership?
    - o Extremely dissatisfied
    - o Very dissatisfied
    - o Somewhat dissatisfied
    - o Mixed
    - o Somewhat satisfied
    - o Very satisfied
    - o Extremely satisfied

40. How satisfied are you with your partner as a spouse or potential spouse?
    - o Extremely dissatisfied
    - o Very dissatisfied
    - o Somewhat dissatisfied
    - o Mixed
    - o Somewhat satisfied
    - o Very satisfied
    - o Extremely satisfied

41. How satisfied are you with your relationship with your spouse or significant other?
    - o Extremely dissatisfied
    - o Very dissatisfied
    - o Somewhat dissatisfied
    - o Mixed
    - o Somewhat satisfied
    - o Very satisfied
    - o Extremely satisfied

Blame

Pereira S, Smith HS, Frankel LA, et al. Psychosocial Effect of Newborn Genomic Sequencing on Families in the BabySeq Project: A Randomized Clinical Trial. *JAMA Pediatr*. 2021;175(11):1132. doi:10.1001/jamapediatrics.2021.2829

42. Do you think you passed potentially harmful genes on to your baby?
    - Definitely
    - Probably
    - Unsure
    - Probably not
    - Definitely not

43. How much do you blame yourself for passing potentially harmful genes on to your baby?
    - Not at all
    - A little
    - Somewhat
    - A lot

44. Do you think your baby's other biological parent passed potentially harmful genes on to your baby?
    - Definitely
    - Probably
    - Unsure
    - Probably not
    - Definitely not

45. How much do you blame your baby's other biological parent for passing potentially harmful genes on to your baby?
    - Not at all
    - A little
    - Somewhat
    - A lot

Parenting Stress Index

Abidin, R.R. (2012). Parenting Stress Index, Fourth Edition (PSI-4). Lutz, FL: Psychological Assessment Resources.

[licensed scale]

Adult Health-Related Quality of Life – EQ-5D

Rabin, R., & de Charro, F. (2001). EQ-5D: a measure of health status from the EuroQol Group. *Annals of Medicine*, 33(5), 337–343. https://doi.org/10.3109/07853890109002087

[licensed scale]

GAD-7

Spitzer RL, Kroenke K, Williams JBW, Löwe B. A Brief Measure for Assessing Generalized Anxiety Disorder: The GAD-7. *Arch Intern Med*. 2006;166(10):1092. doi:10.1001/archinte.166.10.1092

The next group of questions ask about how you have been feeling mentally. We want to learn whether study information might affect parents' well-being.

Over the last 2 weeks, how often have you been bothered by any of the following problems?

Not at all	Several days	More than half the days	Nearly every day

46. Feeling nervous, anxious or on edge
47. Not being able to stop or control worrying
48. Worrying too much about different things
49. Trouble relaxing
50. Being so restless that it is hard to sit still
51. Becoming easily annoyed or irritable
52. Feeling afraid, as if something awful is about to happen

53. If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?
    - Not difficult at all
    - Somewhat difficult
    - Very difficult
    - Extremely difficult

PHQ-8

Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: Validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606-613. doi:10.1046/j.1525-1497.2001.016009606.x

Over the last 2 weeks, how often have you been bothered by any of the following problems?

Not at all	Several days	More than half the days	Nearly every day

54. Little interest or pleasure in doing things

55. Feeling down, depressed, or hopeless

56. Trouble falling or staying asleep, or sleeping too much

57. Feeling tired or having little energy

58. Poor appetite or overeating

59. Feeling bad about yourself—or that you are a failure or have let yourself or your family down

60. Trouble concentrating on things, such as reading the newspaper or watching television

61. Moving or speaking so slowly that other people could have noticed? Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual

62. If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?
    - Not difficult at all
    - Somewhat difficult
    - Very difficult
    - Extremely difficult

Infant Health-Related Quality of Life – EQ-TIPS

[formerly known as TANDI]

Verstraete, J., Ramma, L., & Jelsma, J. (2020). Validity and reliability testing of the Toddler and Infant (TANDI) Health Related Quality of Life instrument for very young children. *Journal of patient-reported outcomes*, 4(1), 94. https://doi.org/10.1186/s41687-020-00251-4

[licensed scale]

Medical and Economic

63. Please select any health problems your child has experienced related to:
    - No medical problems
    - Eyes or vision (examples: problems seeing, something different about their eyes)
    - Ears, nose, or throat (examples: hearing loss, trouble swallowing)
    - Teeth or gums (examples: tooth decay, too many or too few teeth)
    - Lungs or breathing (examples: asthma)
    - Heart or blood vessels (examples: heart murmur)
    - Digestion or stomach (examples: reflux, constipation)
    - Kidneys or bladder (examples: trouble urinating)
    - Bones (examples: scoliosis or curved spine, chest bone that curves in or out, broken bones)
    - Muscles (examples: torticollis / neck weakness, trouble moving certain body parts)
    - Skin (examples: unusual skin color, lumps or bumps)
    - Brain or nervous system (examples: developmental delays)
    - Behavior or mental issues (examples: significant problems with sleep, crying, or feeding)
    - Blood or bleeding (examples: easy bleeding or bruising)
    - Growth (examples: slow growth or failure to thrive)
    - Cancer
    - Allergies
    - Immune system (examples: frequent infections)

64. Please tell us more about these health problems: [free text]

65. Does your baby have a diagnosis for these health problems?
    - Yes
    - No
    - Not sure

65a. Please describe: [free text]

66. Has your child seen a doctor for these health problems?
    - Yes
    - No
    - Not sure

66a. Please describe: [free text]

67. Has your child seen a genetics doctor outside of the BabySeq Project?
    - Yes
    - No
    - Not sure

67a. Please describe: [free text]

68. Has your child had any other genetic testing outside of the BabySeq Project?
- Yes
- No
- Not sure

69. Please describe: [free text]

70. Has your baby been admitted to the hospital since they were born?
- Yes
- No

71. How many times has your baby been admitted to the hospital since they were born?
- 1
- 2
- 3 or more

72. Location of hospitalization 1: [free text]

73. Reason for hospitalization 1: [free text]

74. Number of days in hospital: [free text]

75. Was there an out-of-pocket cost (co-pay) for hospitalization 1?
- Yes
- No
- Not sure

76. What was the out-of-pocket cost (co-pay)? [free text] (U.S. dollars)

77. Did you or your spouse/partner take any time off from work to care for your baby during hospitalization 1?
- Yes
- No

78. Number of days you took off from work: [free text]

79. Number of days your spouse/partner took off from work: [free text]

80. Location of hospitalization 2: [free text]

81. Reason for hospitalization 2: [free text]

83. Number of days in hospital: [free text]

84. Was there an out-of-pocket cost (co-pay) for hospitalization 2?
- Yes
- No
- Not sure

85. What was the out-of-pocket cost (co-pay)? [free text] (U.S. dollars)
86. Did you or your spouse/partner take any time off from work to care for your baby during hospitalization 2?

- Yes
- No

87. Number of days you took off from work: [free text]

88. Number of days your spouse/partner took off from work: [free text]

89. Location of hospitalization 3: [free text]

90. Reason for hospitalization 3: [free text]

91. Number of days in hospital: [free text]

92. Was there an out-of-pocket cost (co-pay) for hospitalization 3?

- Yes
- No

93. What was the out-of-pocket cost (co-pay)? [free text] (U.S. dollars)

94. Did you or your spouse/partner take any time off from work to care for your baby during hospitalization 3?

- Yes
- No

95. Number of days you took off from work: [free text]

96. Number of days your spouse/partner took off from work: [free text]

97. Please describe any other hospitalizations: [free text]

98. Has your baby taken any medications since they were born?

- Yes
- No

99. Please describe: [free text]

100. Was there an out-of-pocket cost (co-pay) for these medications?

- Yes
- No
- Not sure

101. What was the out-of-pocket cost (co-pay)? [free text] (U.S. dollars)

Next, we will ask about health insurance, and any problems getting medical care.
We want to learn what resources might help more children get healthcare.

102. Is your child covered by health insurance or some other kind of health care plan?

(Include health insurance obtained through employment or purchased directly, as well as government programs like Medicare and Medicaid that provide medical care or help pay medical bills.)

- Yes
- No
- Not sure
- Prefer not to answer

103. What kind or kinds of health insurance or health care coverage do they have? (Check all that apply)

- Private health insurance, employment based
- Private health insurance, directly purchased
- Government plan like Medicaid or Children's Health Insurance Program (MassHealth, Child Health Plus, ALLKids)
- Government plan, Military health care
- International
- Other type of insurance
- I don't know
- Prefer not to answer

104. Other type of insurance (Please Describe): [free text]

105. Are you yourself covered by health insurance or some other kind of health care plan?
(Include health insurance obtained through employment or purchased directly, as well as government programs like Medicare and Medicaid that provide medical care or help pay medical bills.)

- Yes
- No
- Not sure
- Prefer not to answer

106. What kind or kinds of health insurance or health care coverage do you have? (Check all that apply)

- Private health insurance, employment based
- Private health insurance, directly purchased
- Government plan like Medicaid (including MassHealth, New York Medicaid, Alabama Medicaid)
- Government plan, Military health care
- International
- Other type of insurance
- I don't know
- Prefer not to answer

107. Other type of insurance (Please Describe): [free text]

108. There are many reasons why you might not take your child to a doctor. We would like to know if any of these situations have applied to you in the last 6 months.

- I could not afford it.
- It was too difficult to get there.
- I do not like doctors and avoid going.
- I did not want to get bad news.
- I did not have time.
- I decided to take care of it on my own.
- I decided to wait and see if the problem would go away on its own.
- The doctor was not available to see my child.

- Other
- Not applicable
- Prefer not to answer

109. Please describe other reason: [free text]

The next questions ask about your work, and any help you might have needed since your baby was born.

We want to study if study information affects whether parents can work, and what they have to pay for.

110. Are you working now?
- Yes
- No

111. Since your baby was born until today, did you pay for household help (housekeeping, cleaning, etc.)?
- Yes
- No

112. For how many weeks? [free text]

113. On average, what was the cost per week? [free text] (U.S. dollars)

114. Since your baby was born until today, have you hired caretakers or babysitters for your other children in order to attend healthcare related appointments or hospitalizations for your baby?
- Yes
- No
- I do not have any other children

115. For how many weeks? [free text]

116. On average, what was the cost per week? [free text] (U.S. dollars)

The next questions ask about healthcare you might have needed since your baby was born.

We want to learn if study information changes how much parents have to pay for healthcare.

Since your baby was born until today, have you used any of the following services?

117. Telephone conversation with a medical professional (e.g. nurse, nurse practitioner, doctor)
- Yes
- No

118. How many conversations? [free text]

119. Telehealth appointment with a medical professional (e.g. nurse, nurse practitioner, doctor)
- Yes
- No

120. How many telehealth appointments? [free text]

121. Was there an out-of-pocket cost (co-pay) for telehealth appointments?
- Yes
- No
- Not sure

122. What was the total out-of-pocket cost (co-pay)? [free text] (U.S. dollars)

123. Visit to your baby's primary care doctor (pediatrician, family practitioner)
- Yes
- No

124. How many visits to your baby's primary care doctor? [free text]

125. Was there an out-of-pocket cost (co-pay) for visits to your baby's primary care doctor?
- Yes
- No
- Not sure

126. What was the total out-of-pocket cost (co-pay)? [free text] (U.S. dollars)

127. Visit with a geneticist and/or genetic counselor outside of this project for you:
- Yes
- No

128. How many visits with a geneticist and/or genetic counselor for you? [free text]

129. Location: [free text]

130. Was there an out-of-pocket cost (co-pay) for your visits with a geneticist and/or genetic counselor?
- Yes
- No
- Not sure

131. What was the total out-of-pocket cost (co-pay)? [free text] (U.S. dollars)

132. Visit with a geneticist and/or genetic counselor outside of this project for your spouse or partner:
- Yes
- No

133. How many visits with a geneticist and/or genetic counselor for your spouse/partner? [free text]

134. Location: [free text]

135. Was there an out-of-pocket cost (co-pay) for your partner's visits with a geneticist and/or genetic counselor?
- Yes
- No
- Not sure

136. What was the total out-of-pocket cost (co-pay)? (U.S. dollars)

137. Visit with a geneticist and/or genetic counselor outside of this project for your baby:
- Yes
- No

138. How many visits with a geneticist and/or genetic counselor for your baby? [free text]

139. Location: [free text]

140. Was there an out-of-pocket cost (co-pay) for your baby's visits with a geneticist and/or genetic counselor?
- Yes
- No
- Not sure

141. What was the total out-of-pocket cost (co-pay)? [free text] (U.S. dollars)

142. Since your baby was born until today, have you used any of the following services? Please select all that apply.
- Early Intervention Visits for your baby
- Physical therapy or occupational therapy for your baby
- Speech therapy for your baby
- Applied behavior analysis (ABA) for your baby
- Any other therapies for your baby
- None of the above

143. What other type(s) of therapy? Please specify. [free text]

144. How many Early Intervention visits? [free text]

145. How many physical therapy or occupational therapy visits? [free text]

146. How many speech therapy visits? [free text]

147. How many applied behavior analysis (ABA) visits? [free text]

Demographics

Finally, we will ask some demographic questions about you and your baby. We want to learn how study information affects people from different backgrounds (cultures, languages, and ethnic origins)

We hope that this information can help genetic testing be more fair in the future.

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

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

150. What language do you prefer to speak with your child's doctors?
- English
- Spanish
- Another language
- Prefer not to answer

151. Which other language? [free text]

Administered in both English and Spanish surveys
152. How well do you speak English?
- Native English-speaker
- Very well
- Well
- Not well
- Prefer not to answer

Administered in Spanish survey only
153. How well do you speak Spanish?
- Native Spanish-speaker
- Very well
- Well
- Not well

- Prefer not to answer

154. What is the highest grade or level of school you completed or the highest degree you received? Please check one.

- Less than high school
- Some high school
- High school graduate
- Some post-high school training
- Associate (2-year) college degree or certificate
- Bachelor's degree
- Graduate or professional degree
- Prefer not to answer

155. What was your household's total family income (before taxes) from all sources in the last year? Please check one.

- Less than $20,000
- $20,000 to $39,999
- $40,000 to $59,999
- $60,000 to $79,999
- $80,000 to $99,999
- $100,000 to $139,999
- $140,000 or more
- Prefer not to answer

156. How many people (children and adults) lived in your household over the past year? [free text]

157. Does anyone in your household receive benefits from the Supplemental Nutrition Assistance Program (SNAP) or Special Supplemental Nutrition Program for Women, Infants, and Children (WIC)?

- Yes
- No
- I don't know
- Prefer not to answer

158. Is there anything else you would like to tell us about yourself or your feelings about the BabySeq Project? [free text]

Post-Disclosure Survey

Thank you for taking part in the BabySeq Project. This survey should take about 20 minutes to complete. Your answers will be saved if you would like to finish the survey later.

We ask that you fill out the entire survey. But, if you don't want to answer any questions or they make you uncomfortable, you are welcome to skip them. Please continue through the survey even if you skip some questions.

We want to learn if genetic testing for babies is helpful to families. Even if you were in the group that did not get genetic testing, your thoughts are important to us. Your answers will help us compare genetic testing to regular well-baby care. We also want to know if genetic testing causes any stress to families or helps with medical care in any way.

When the questions ask about "your child", they mean your baby who is part of the BabySeq Project. Please answer the questions thinking about this baby (even if you have other children).

If you are taking the survey on your phone, we suggest turning the phone length-wise so it is easier to see. Please don't use your browser's "back" button during the survey.

Once you finish the survey, a study team member will review your answers. We may contact you if we have any questions or need more information. Then, we will send you a gift card for $50.

If you have questions about the BabySeq Project, you can contact your local site here: [site contact information]

Would you like to start the survey now?

- o Yes
- o No

Disclosure

These questions ask about the information you learned from the BabySeq Project. This will help us study if projects like BabySeq are helpful to families.

1. Did your understanding of your family's health risks change as a result of taking part in the BabySeq Project?
    - Yes
    - No

    Please describe: [free text]

2. Did you learn about any recommended changes to your baby's medical care as a result of taking part in the BabySeq Project?
    - Yes
    - No

    Please describe: [free text]

3. Did you learn about any recommended changes to your family's medical care as a result of taking part in the BabySeq Project?
    - Yes
    - No

    Please describe: [free text]

FACToR

Li M, Bennette CS, Amendola LM, et al. The Feelings About genomiC Testing Results (FACToR) Questionnaire: Development and preliminary validation. *J Genet Couns*. 2019;28(2):477-490. doi:10.1007/s10897-018-0286-9

The next questions ask about how you felt after receiving information from the study staff as a part of the BabySeq Project.

This information could include your family history report and/or your child's genetic test results.

Language is modified from original scale to be applicable to both randomization arms

Please indicate how much you had each specific feeling in the past week by selecting one answer for each question: not at all, a little, somewhat, a good deal, or a great deal.

Not at all	A little	Somewhat	A good deal	A great deal

4. How upset did you feel about the information you received as a part of the BabySeq Project?
5. How happy did you feel about the information you received as a part of the BabySeq Project?
6. How anxious or nervous did you feel about the information you received as a part of the BabySeq Project?
7. How relieved did you feel about the information you received as a part of the BabySeq Project?
8. How sad did you feel about the information you received as a part of the BabySeq Project?
9. How frustrated did you feel about recommendations for your child's care based on the information you received as a part of the BabySeq Project?
10. How uncertain did you feel about what the information you received as a part of the BabySeq Project means for your child?
11. How uncertain did you feel about what the information you received as a part of the BabySeq Project means for your risk of disease?
12. How uncertain did you feel about what the information you received as a part of the BabySeq Project means for other family members' risk of disease?
13. How much did you feel that you understood clearly your child's choices for care based on the information you received as a part of the BabySeq Project?
14. How concerned did you feel that the information you received as a part of the BabySeq Project would affect your child's ability to get or keep health insurance?
15. How helpful was the information you received as a part of the BabySeq Project in planning for your child's future?

16. How concerned did you feel that the information you received as a part of the BabySeq Project might make it hard for your child to get or keep a job?

17. How guilty did you feel about the information you received as a part of the BabySeq Project?

18. How much loss of control over your child's life did you feel because of the information you received as a part of the BabySeq Project?

Genomic Orientation Scale

Horrow C, Pacyna JE, Lee MK, Sharp RR. Measuring attitudes about genomic medicine: Validation of the Genomic Orientation Scale (GO Scale). *Value in Health*. 2021;24(7):1030-1037. doi:10.1016/j.jval.2021.02.001

The next group of questions ask how you feel about genomic medicine. Genomic medicine means using our genes (DNA) as part of healthcare. It can be used for both babies and for adults.

Within the next 5 years, how likely or unlikely is it that genomic medicine will...

Very unlikely	Unlikely	Neither likely nor unlikely	Likely	Very likely

19. help doctors choose the best drugs for patients
20. increase the number of unnecessary tests
21. help prevent common diseases
22. detract from disease prevention efforts we know work well
23. help doctors diagnose rare diseases earlier
24. distract doctors from looking for non-genetic causes of disease
25. help people live longer
26. divert healthcare resources that could be better used for other purposes
27. give patients more control over their health
28. create a burden of worry where there wasn't one before
29. be difficult for many patients to understand
30. help doctors focus on the unique needs and goals of each patient
31. make it harder for doctors to engage each patient as a person
32. increase the cost of healthcare
33. increase the cost of prescription drugs
34. increase inequality in healthcare
35. create new forms of discrimination
36. be too expensive for most people
37. make it more difficult for patients to receive medical care they need

38. be a standard part of general medical checkups

39. not be available in most hospitals and clinics

40. benefit nearly all aspects of medicine

41. be beneficial to you

42. cause you harm

43. do a lot of good

44. create many problems

GENEtic Utility (GENE-U)

Only administered to those in the sequencing arm

Smith HS, Morain SR, Robinson JO, et al. Perceived Utility of Genomic Sequencing: Qualitative Analysis and Synthesis of a Conceptual Model to Inform Patient-Centered Instrument Development. *Patient*. 2022;15:317-328. doi:10.1007/s40271-021-00558-4

Think about the experience of genetic testing for your child. Based on that experience with genetic testing and the results that your child received, select the answer choice that best describes your agreement with each statement from strongly disagree to strongly agree.

- **Select the option "strongly disagree" if the test results did not affect you or your decisions.**
- **Select the option "neither agree nor disagree" if you do not have an opinion or feel that the statement does not apply.**
- **If your child is no longer living, we understand that it may be difficult to answer questions that ask about your child. You can select "neither agree nor disagree" if you feel that the statement does not apply. Please answer to the best of your ability. You may also skip any question.**

Strongly Disagree	Disagree	Neither Agree Nor Disagree	Agree	Strongly Agree

This test gave me:

45. Answers about my child's health.

46. Information that helped healthcare providers give my child the best care.

47. Information that will be useful for other family members when they consider having children.

Because my child had this test:

48. My child avoided additional clinical tests.

49. Doctors know to look for certain changes in my child's body.

50. My child's genetic information will help other people in the future.

51. My child's diet is now healthier.

52. I can make better decisions about my child's health insurance coverage.

Because of the test results:

53. I can be a better parent to my child.

54. I have made changes that had a positive impact on me and my family (e.g., quit job, changed job, went back to school, moved).

55. I have gained support from families who are living with similar experiences.

56. My child has gained access to accommodations such as specialized schooling plans.

After having this test, I feel:

57. Down or depressed.

58. Guilty that my child inherited my genes.

59. Worried more often.

60. Relief that I know information about my child's health risks.

61. I blame myself for any health issues my child might have.

62. More peace of mind.

Because of testing:

63. I feel more prepared to decide whether to have more children.

64. I am concerned about the privacy of my child's genetic information.

65. After having this test, I feel that I have lost some of the joy of being a new parent.

Vulnerable Baby Scale

Kerruish NJ, Settle K, Campbell-Stokes P, Taylor BJ. Vulnerable Baby Scale: Development and piloting of a questionnaire to measure maternal perceptions of their baby's vulnerability. *J Paediatr Child Health*. 2005;41(8):419-423. doi:10.1111/j.1440-1754.2005.00658.x

The next group of questions ask about your experience being a parent. There are no right or wrong answers.

These questions will help us study relationships between parents and children. We want to learn whether genetic testing might affect these relationships.

66. How often do you generally check on your baby while they are asleep at night?
    1) Not at all
    2)
    3) 1-2 times each night
    4)
    5) Frequently (at least every 30 minutes)

67. If your baby was awake and playing, for how long would you leave them unattended?
    1) Not at all
    2)
    3) About 15 minutes
    4)
    5) More than an hour

68. If a friend came to visit and they had a cold, would you:
    1) Not allow them in the house
    2)
    3) Allow them in but not let them hold the baby
    4)
    5) Allow them in and not restrict contact

69. How often does your baby seem to get stomach aches or other pains?
    1) All the time
    2)
    3)
    4)
    5) Not at all

70. How concerned are you that your baby is not as healthy as they should be?
    1) Very concerned
    2)
    3)
    4)
    5) Not at all concerned

71. In general, when you compare your baby's health to that of other children the same age, do you think your baby is:
    1) Less healthy
    2)
    3)

4)
5) More healthy

72. How worried are you that your baby may become seriously ill?
1) Very worried
2)
3)
4)
5) Not at all worried

73. How worried are you about Sudden Infant Death Syndrome (SIDS)?
[1 to 5 scale, from “Very worried” to “Not at all worried”]
1) Very worried
2)
3)
4)
5) Not at all worried

74. If you left your baby with someone else, would you make contact with them while you were away?
1) Yes, always
2)
3) Sometimes
4)
5) No, never

75. In the last 2 weeks, how often have you contacted a health professional (e.g. general practitioner, after hours emergency doctor, nurse, etc.) about your baby?
1) Not at all
2)
3) Once a week
4)
5) Daily or more

Relationship Status

Next, we'll ask some questions about your partner and relationship (if applicable).

These questions will help us learn about relationships between partners. We want to learn whether study information might affect these relationships.

76. Which of these best describes you?
    - o Single (never married)
    - o Married or living with a partner
    - o Widowed
    - o Divorced
    - o Separated

77. Is your partner the biological parent of your baby?
    - o Yes
    - o No
    - o Prefer not to answer

Kansas Marital Satisfaction Scale

Schumm WR, Paff-Bergen LA, Hatch RC, et al. Concurrent and Discriminant Validity of the Kansas Marital Satisfaction Scale. *J Marriage Fam*. 1986;48(2):381. doi:10.2307/352405

78. How satisfied are you with your marriage or partnership?
    - o Extremely dissatisfied
    - o Very dissatisfied
    - o Somewhat dissatisfied
    - o Mixed
    - o Somewhat satisfied
    - o Very satisfied
    - o Extremely satisfied

79. How satisfied are you with your partner as a spouse or potential spouse?
    - o Extremely dissatisfied
    - o Very dissatisfied
    - o Somewhat dissatisfied
    - o Mixed
    - o Somewhat satisfied
    - o Very satisfied
    - o Extremely satisfied

80. How satisfied are you with your relationship with your spouse or significant other?
    - o Extremely dissatisfied
    - o Very dissatisfied
    - o Somewhat dissatisfied
    - o Mixed
    - o Somewhat satisfied
    - o Very satisfied
    - o Extremely satisfied

Blame

Pereira S, Smith HS, Frankel LA, et al. Psychosocial Effect of Newborn Genomic Sequencing on Families in the BabySeq Project: A Randomized Clinical Trial. *JAMA Pediatr*. 2021;175(11):1132. doi:10.1001/jamapediatrics.2021.2829

81. Do you think you passed potentially harmful genes on to your baby?
    - Definitely
    - Probably
    - Unsure
    - Probably not
    - Definitely not

82. How much do you blame yourself for passing potentially harmful genes on to your baby?
    - Not at all
    - A little
    - Somewhat
    - A lot

83. Do you think your baby's other biological parent passed potentially harmful genes on to your baby?
    - Definitely
    - Probably
    - Unsure
    - Probably not
    - Definitely not

84. How much do you blame your baby's other biological parent for passing potentially harmful genes on to your baby?
    - Not at all
    - A little
    - Somewhat
    - A lot

Parenting Stress Index

Abidin, R.R. (2012). Parenting Stress Index, Fourth Edition (PSI-4). Lutz, FL: Psychological Assessment Resources.

[licensed scale]

Adult Health-Related Quality of Life – EQ-5D

Rabin, R., & de Charro, F. (2001). EQ-5D: a measure of health status from the EuroQol Group. *Annals of Medicine*, 33(5), 337–343. https://doi.org/10.3109/07853890109002087

[licensed scale]

GAD-7

Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing Generalized Anxiety Disorder: The GAD-7. *Arch Intern Med*. 2006;166(10):1092. doi:10.1001/archinte.166.10.1092

The next group of questions ask about how you have been feeling mentally. We want to learn whether genetic testing might affect parents' well-being.

Over the last 2 weeks, how often have you been bothered by any of the following problems?

Not at all	Several days	More than half the days	Nearly every day

85. Feeling nervous, anxious or on edge

86. Not being able to stop or control worrying

87. Worrying too much about different things

88. Trouble relaxing

89. Being so restless that it is hard to sit still

90. Becoming easily annoyed or irritable

91. Feeling afraid, as if something awful is about to happen

92. If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?
    - Not difficult at all
    - Somewhat difficult
    - Very difficult
    - Extremely difficult

PHQ-8

Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: Validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606-613. doi:10.1046/j.1525-1497.2001.016009606.x

Over the last 2 weeks, how often have you been bothered by any of the following problems?

Not at all	Several days	More than half the days	Nearly every day

93. Little interest or pleasure in doing things

94. Feeling down, depressed, or hopeless

95. Trouble falling or staying asleep, or sleeping too much

96. Feeling tired or having little energy

97. Poor appetite or overeating

98. Feeling bad about yourself—or that you are a failure or have let yourself or your family down

99. Trouble concentrating on things, such as reading the newspaper or watching television

100. Moving or speaking so slowly that other people could have noticed? Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual

101. If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

- Not difficult at all
- Somewhat difficult
- Very difficult
- Extremely difficult

Infant Health-Related Quality of Life – EQ-TIPS

[formerly known as TANDI]

Verstraete, J., Ramma, L., & Jelsma, J. (2020). Validity and reliability testing of the Toddler and Infant (TANDI) Health Related Quality of Life instrument for very young children. *Journal of patient-reported outcomes*, 4(1), 94. https://doi.org/10.1186/s41687-020-00251-4

[licensed scale]

Medical and Economic

102. Please select any health problems your child has experienced related to:
- No medical problems
- Eyes or vision (examples: problems seeing, something different about their eyes)
- Ears, nose, or throat (examples: hearing loss, trouble swallowing)
- Teeth or gums (examples: tooth decay, too many or too few teeth)
- Lungs or breathing (examples: asthma)
- Heart or blood vessels (examples: heart murmur)
- Digestion or stomach (examples: reflux, constipation)
- Kidneys or bladder (examples: trouble urinating)
- Bones (examples: scoliosis or curved spine, chest bone that curves in or out, broken bones)
- Muscles (examples: torticollis / neck weakness, trouble moving certain body parts)
- Skin (examples: unusual skin color, lumps or bumps)
- Brain or nervous system (examples: developmental delays)
- Behavior or mental issues (examples: significant problems with sleep, crying, or feeding)
- Blood or bleeding (examples: easy bleeding or bruising)
- Growth (examples: slow growth or failure to thrive)
- Cancer
- Allergies
- Immune system (examples: frequent infections)

103. Please tell us more about these health problems: [free text]

104. Does your baby have a diagnosis for these health problems?
- Yes
- No
- Not sure

104a. Please describe: [free text]

105. Has your child seen a doctor for these health problems?
- Yes
- No
- Not sure

105a. Please describe: [free text]

106. Has your child seen a genetics doctor outside of the BabySeq Project?
- Yes
- No
- Not sure

106a. Please describe: [free text]

107. Has your child had any other genetic testing outside of the BabySeq Project?
- Yes
- No
- Not sure

108. Please describe: [free text]

109. Has your baby been admitted to the hospital since the last time you took a survey for the BabySeq Project (about 4 months ago)?

- Yes
- No

110. How many times has your baby been admitted to the hospital since the last time you took a survey for the BabySeq Project?

- 1
- 2
- 3 or more

111. Location of hospitalization 1: [free text]

112. Reason for hospitalization 1: [free text]

113. Number of days in hospital: [free text]

114. Was there an out-of-pocket cost (co-pay) for hospitalization 1?

- Yes
- No

115. What was the out-of-pocket cost (co-pay)? [free text] (U.S. dollars)

116. Did you or your spouse/partner take any time off from work to care for your baby during hospitalization 1?

- Yes
- No

117. Number of days you took off from work: [free text]

118. Number of days your spouse/partner took off from work: [free text]

119. Location of hospitalization 2: [free text]

120. Reason for hospitalization 2: [free text]

121. Number of days in hospital: [free text]

122. Was there an out-of-pocket cost (co-pay) for hospitalization 2?

- Yes
- No

123. What was the out-of-pocket cost (co-pay)? [free text] (U.S. dollars)

124. Did you or your spouse/partner take any time off from work to care for your baby during hospitalization 2?

- Yes
- No

125. Number of days you took off from work: [free text]

126. Number of days your spouse/partner took off from work: [free text]

127. Location of hospitalization 3: [free text]

128. Reason for hospitalization 3: [free text]

129. Number of days in hospital: [free text]

130. Was there an out-of-pocket cost (co-pay) for hospitalization 3?
- Yes
- No

131. What was the out-of-pocket cost (co-pay)? [free text] (U.S. dollars)

132. Did you or your spouse/partner take any time off from work to care for your baby during hospitalization 3?
- Yes
- No

133. Number of days you took off from work: [free text]

134. Number of days your spouse/partner took off from work: [free text]

135. Please describe any other hospitalizations: [free text]

136. Has your baby taken any medications since the last time you took a survey for the BabySeq Project (about 4 months ago)?
- Yes
- No

137. Please describe: [free text]

138. Was there an out-of-pocket cost (co-pay) for these medications?
- Yes
- No

139. What was the out-of-pocket cost (co-pay)? [free text] (U.S. dollars)

140. Is your child covered by health insurance or some other kind of health care plan?
(Include health insurance obtained through employment or purchased directly, as well as government programs like Medicare and Medicaid that provide medical care or help pay medical bills.)
- Yes
- No
- Not sure
- Prefer not to answer

141. What kind or kinds of health insurance or health care coverage do they have? (Check all that apply)
- Private health insurance, employment based
- Private health insurance, directly purchased
- Government plan like Medicaid or Children's Health Insurance Program (MassHealth, Child Health Plus, ALLKids)

- Government plan, Military health care
- International
- Other type of insurance
- I don't know
- Prefer not to answer

142. Other type of insurance (Please Describe): [free text]

The next questions ask about your work, and any help you might have needed since the last time you took a survey for BabySeq (about 4 months ago).

We want to study if genetic testing affects whether parents can work, and what they have to pay for.

143. Are you working now?
- Yes
- No

144. Since the last time you took a survey for the BabySeq Project (about 4 months ago) until today, did you pay for household help (housekeeping, cleaning, etc.)?
- Yes
- No

145. For how many weeks? [free text]

146. On average, what was the cost per week? [free text] (U.S. dollars)

147. Since the last time you took a survey for the BabySeq Project until today, have you hired caretakers or babysitters for your other children in order to attend healthcare related appointments or hospitalizations for your baby?
- Yes
- No
- I do not have any other children

148. For how many weeks? [free text]

149. On average, what was the cost per week? [free text] (U.S. dollars)

The next questions ask about healthcare you might have needed since your baby was born.

We want to learn if genetic testing changes how much parents have to pay for healthcare.

Since the last time you took a survey for the BabySeq Project (about 4 months ago) until today, have you used any of the following services?

150 Telephone conversation with a medical professional (e.g. nurse, nurse practitioner, doctor)
- Yes
- No

151. How many conversations? [free text]

152. Telehealth appointment with a medical professional (e.g. nurse, nurse practitioner, doctor)
    - Yes
    - No

153. How many telehealth appointments? [free text]

154. Was there an out-of-pocket cost (co-pay) for telehealth appointments?
    - Yes
    - No
    - Not sure

155. What was the total out-of-pocket cost (co-pay)? [free text] (U.S. dollars)

156. Visit to your baby's primary care doctor (pediatrician, family practitioner)
    - Yes
    - No

157. How many visits to your baby's primary care doctor? [free text]

158. Was there an out-of-pocket cost (co-pay) for visits to your baby's primary care doctor?
    - Yes
    - No
    - Not sure

159. What was the total out-of-pocket cost (co-pay)? [free text] (U.S. dollars)

160. Visit with a geneticist and/or genetic counselor outside of this project for you:
    - Yes
    - No

161. How many visits with a geneticist and/or genetic counselor for you? [free text]

162. Location: [free text]

163. Was there an out-of-pocket cost (co-pay) for your visits with a geneticist and/or genetic counselor?
    - Yes
    - No
    - Not sure

164. What was the total out-of-pocket cost (co-pay)? [free text] (U.S. dollars)

165. Visit with a geneticist and/or genetic counselor outside of this project for your spouse or partner:
    - Yes
    - No

166. How many visits with a geneticist and/or genetic counselor for your spouse/partner? [free text]

167. Location: [free text]

168. Was there an out-of-pocket cost (co-pay) for your partner's visits with a geneticist and/or genetic counselor?

- Yes
- No
- Not sure

169. What was the total out-of-pocket cost (co-pay)? [free text] (U.S. dollars)

170. Visit with a geneticist and/or genetic counselor outside of this project for your baby:
- Yes
- No

171. How many visits with a geneticist and/or genetic counselor for your baby? [free text]

172. Location: [free text]

173. Was there an out-of-pocket cost (co-pay) for your baby's visits with a geneticist and/or genetic counselor?
- Yes
- No
- Not sure

174. What was the total out-of-pocket cost (co-pay)? [free text] (U.S. dollars)

175. Since the last time you took a survey for the BabySeq Project until today, have you used any of the following services? Please select all that apply.
- Early Intervention Visits for your baby
- Physical therapy or occupational therapy for your baby
- Speech therapy for your baby
- Applied behavior analysis (ABA) for your baby
- Any other therapies for your baby
- None of the above

176. What other type(s) of therapy? Please specify. [free text]

177. How many Early Intervention visits? [free text]

178. How many physical therapy or occupational therapy visits? [free text]

179. How many speech therapy visits? [free text]

180. How many applied behavior analysis (ABA) visits? [free text]

181. Is there anything else you would like to tell us about your experiences with the BabySeq Project? [free text]

6-Month Survey

Thank you for taking part in the BabySeq Project. This survey should take about 20 minutes to complete. Your answers will be saved if you would like to finish the survey later.

We ask that you fill out the entire survey. But, if you don't want to answer any questions or they make you uncomfortable, you are welcome to skip them. Please continue through the survey even if you skip some questions.

We want to learn if genetic testing for babies is helpful to families. Even if you were in the group that did not get genetic testing, your thoughts are important to us. Your answers will help us compare genetic testing to regular well-baby care. We also want to know if genetic testing causes any stress to families or helps with medical care in any way.

When the questions ask about "your child", they mean your baby who is part of the BabySeq Project. Please answer the questions thinking about this baby (even if you have other children).

If you are taking the survey on your phone, we suggest turning the phone length-wise so it is easier to see. Please don't use your browser's "back" button during the survey.

Once you finish the survey, a study team member will review your answers. We may contact you if we have any questions or need more information. Then, we will send you a gift card for $50.

If you have questions about the BabySeq Project, you can contact your local site here: [site contact information]

Would you like to start the survey now?

- o Yes
- o No

Results & Follow-up Care

These questions ask about the results you learned from the BabySeq Project. Results include your family history report and/or your child's genetic test report. This will help us study if projects like BabySeq are helpful to families.

1. Do you think that taking part in the BabySeq Project affected your child's medical care?
    - Yes, results made their care better
    - Yes, results made their care worse
    - No, results did not affect their care
    - Not sure

    Please describe: [free text]

2. Did your understanding of your family's health risks change as a result of taking part in the BabySeq Project?
    - Yes
    - No

    Please describe: [free text]

3. Did you learn about any recommended changes to your baby's medical care as a result of taking part in the BabySeq Project?
    - Yes
    - No

    Please describe: [free text]

4. Did you learn about any recommended changes to your family's medical care as a result of taking part in the BabySeq Project?
    - Yes
    - No

    Please describe: [free text]

5. Has the number of biological children you plan to have changed as a result of taking part in the BabySeq Project?
    - Yes
    - No

    Please describe: [free text]

6. Did you talk about your child's study results with your/your child's doctors or health care providers?
    - Yes
    - Not yet but I plan to
    - No and I don't plan to

    Please describe: [free text]

7. Based on your child's study results, has anyone in your family gotten follow up medical care or testing (for example: blood tests, medication, health screenings, special doctor visits, etc.)?
    - Yes
    - No

8. Who from your family got, or plans to get, any follow up medical care or testing? Check all that apply.

- Myself
- My baby's other parent
- My baby who is enrolled in the BabySeq Project
- One or more of my other children, not including my baby who is enrolled in the BabySeq Project

9. Please describe the follow up medical care or testing for yourself. [free text]

10. Has this follow up medical care or testing already been done (for you)?
    - Yes
    - No

11. Was there an out-of-pocket cost (co-pay)?
    - Yes
    - No
    - Not sure

12. What was the out-of-pocket cost (co-pay)? [free text] (US dollars)

13. Please describe the follow up medical care or testing for your baby's other parent. [free text]

14. Has this follow up medical care or testing already been done (for your baby's other parent)?
    - Yes
    - No

15. Was there an out-of-pocket cost (co-pay)?
    - Yes
    - No
    - Not sure

16. What was the out-of-pocket cost (co-pay)? [free text] (US dollars)

17. Please describe the follow up medical care or testing for your baby who is enrolled in the BabySeq Project. [free text]

18. Has this follow up medical care or testing already been done (for your baby)?
    - Yes
    - No

19. Was there an out-of-pocket cost (co-pay)?
    - Yes
    - No
    - Not sure

20. What was the out-of-pocket cost (co-pay)? [free text] (US dollars)

21. Please describe the follow up medical care or testing for one or more of your other children, not including your baby who is enrolled in the BabySeq Project [free text]

22. Has this follow up medical care or testing already been done (for your other children)?
    - Yes

- No

23. Was there an out-of-pocket cost (co-pay)?
    - Yes
    - No
    - Not sure

24. What was the out-of-pocket cost (co-pay)? [free text] (US dollars)

FACToR

Li M, Bennette CS, Amendola LM, et al. The Feelings About genomiC Testing Results (FACToR) Questionnaire: Development and Preliminary Validation. *J Genet Couns*. 2019;28(2):477-490. doi:10.1007/s10897-018-0286-9

The next questions ask about how you felt after receiving information from the study staff as a part of the BabySeq Project.

This information could include your family history report and/or your child's genetic test results.

Language is modified from original scale to be applicable to both randomization arms

Please indicate how much you had each specific feeling in the past week by selecting one answer for each question: not at all, a little, somewhat, a good deal, or a great deal.

Not at all	A little	Somewhat	A good deal	A great deal

25. How upset did you feel about the information you received as a part of the BabySeq Project?
26. How happy did you feel about the information you received as a part of the BabySeq Project?
27. How anxious or nervous did you feel about the information you received as a part of the BabySeq Project?
28. How relieved did you feel about the information you received as a part of the BabySeq Project?
29. How sad did you feel about the information you received as a part of the BabySeq Project?
30. How frustrated did you feel about recommendations for your child's care based on the information you received as a part of the BabySeq Project?
31. How uncertain did you feel about what the information you received as a part of the BabySeq Project means for your child?
32. How uncertain did you feel about what the information you received as a part of the BabySeq Project means for your risk of disease?
33. How uncertain did you feel about what the information you received as a part of the BabySeq Project means for other family members' risk of disease?
34. How much did you feel that you understood clearly your child's choices for care based on the information you received as a part of the BabySeq Project?
35. How concerned did you feel that the information you received as a part of the BabySeq Project would affect your child’s ability to get or keep health insurance?
36. How helpful was the information you received as a part of the BabySeq Project in planning for your child's future?

37. How concerned did you feel that the information you received as a part of the BabySeq Project might make it hard for your child to get or keep a job?

38. How guilty did you feel about the information you received as a part of the BabySeq Project?

39. How much loss of control over your child's life did you feel because of the information you received as a part of the BabySeq Project?

40. Since receiving your/your child's study results, have you shared the information with any biological family members (blood relatives)?
    - Yes
    - I did not share this information with anyone, and I do not plan to
    - I have not shared this information yet, but plan to in the future
    - I don't have blood relatives to share this information with

41. Which of the following relatives have you shared your/your child's study results with? Select all that apply.
    - My child's other biological parent
    - My child(ren)
    - My siblings (brothers or sisters)
    - My parents
    - My other biological family members (blood relatives)
    - My child's other biological parent's family members

42. Which other biological family members (blood relatives)? [free text]

43. Which of your child's other biological parent's family members? [free text]

Genomic Orientation Scale

Horrow C, Pacyna JE, Lee MK, Sharp RR. Measuring attitudes about genomic medicine: Validation of the Genomic Orientation Scale (GO Scale). *Value in Health*. 2021;24(7):1030-1037. doi:10.1016/j.jval.2021.02.001

The next group of questions ask how you feel about genomic medicine. Genomic medicine means using our genes (DNA) as part of healthcare. It can be used for both babies and for adults.

Within the next 5 years, how likely or unlikely is it that genomic medicine will...

Very unlikely	Unlikely	Neither likely nor unlikely	Likely	Very likely

44. help doctors choose the best drugs for patients
45. increase the number of unnecessary tests
46. help prevent common diseases
47. detract from disease prevention efforts we know work well
48. help doctors diagnose rare diseases earlier
49. distract doctors from looking for non-genetic causes of disease
50. help people live longer
51. divert healthcare resources that could be better used for other purposes
52. give patients more control over their health
53. create a burden of worry where there wasn't one before
54. be difficult for many patients to understand
55. help doctors focus on the unique needs and goals of each patient
56. make it harder for doctors to engage each patient as a person
57. increase the cost of healthcare
58. increase the cost of prescription drugs
59. increase inequality in healthcare
60. create new forms of discrimination
61. be too expensive for most people
62. make it more difficult for patients to receive medical care they need
63. be a standard part of general medical checkups

64. not be available in most hospitals and clinics
65. benefit nearly all aspects of medicine
66. be beneficial to you
67. cause you harm
68. do a lot of good
69. create many problems

GENEtic Utility (GENE-U)

Only administered to those in the sequencing arm

Smith HS, Morain SR, Robinson JO, et al. Perceived Utility of Genomic Sequencing: Qualitative Analysis and Synthesis of a Conceptual Model to Inform Patient-Centered Instrument Development. *Patient*. 2022;15:317-328. doi:10.1007/s40271-021-00558-4

Think about the experience of genetic testing for your child. Based on that experience with genetic testing and the results that your child received, select the answer choice that best describes your agreement with each statement from strongly disagree to strongly agree.

- **Select the option "strongly disagree" if the test results did not affect you or your decisions.**
- **Select the option "neither agree nor disagree" if you do not have an opinion or feel that the statement does not apply.**
- **If your child is no longer living, we understand that it may be difficult to answer questions that ask about your child. You can select "neither agree nor disagree" if you feel that the statement does not apply. Please answer to the best of your ability. You may also skip any question.**

Strongly Disagree	Disagree	Neither Agree Nor Disagree	Agree	Strongly Agree

This test gave me:

70. Answers about my child's health.

71. Information that helped healthcare providers give my child the best care.

72. Information that will be useful for other family members when they consider having children.

Because my child had this test:

73. My child avoided additional clinical tests.

74. Doctors know to look for certain changes in my child's body.

75. My child's genetic information will help other people in the future.

76. My child's diet is now healthier.

77. I can make better decisions about my child's health insurance coverage.

Because of the test results:

78. I can be a better parent to my child.

79. I have made changes that had a positive impact on me and my family (e.g., quit job, changed job, went back to school, moved).

80. I have gained support from families who are living with similar experiences.

81. My child has gained access to accommodations such as specialized schooling plans.

After having this test, I feel:

82. Down or depressed.

83. Guilty that my child inherited my genes.

84. Worried more often.

85. Relief that I know information about my child's health risks.

86. I blame myself for any health issues my child might have.

87. More peace of mind.

Because of testing:

88. I feel more prepared to decide whether to have more children.

89. I am concerned about the privacy of my child's genetic information.

90. After having this test, I feel that I have lost some of the joy of being a new parent.

Vulnerable Baby Scale

Kerruish NJ, Settle K, Campbell-Stokes P, Taylor BJ. Vulnerable Baby Scale: Development and piloting of a questionnaire to measure maternal perceptions of their baby's vulnerability. *J Paediatr Child Health*. 2005;41(8):419-423. doi:10.1111/j.1440-1754.2005.00658.x

The next group of questions ask about your experience being a parent. There are no right or wrong answers.

These questions will help us study relationships between parents and children. We want to learn whether genetic testing might affect these relationships.

91. How often do you generally check on your baby while they are asleep at night?
    1) Not at all
    2)
    3) 1-2 times each night
    4)
    5) Frequently (at least every 30 minutes)

92. If your baby was awake and playing, for how long would you leave them unattended?
    1) Not at all
    2)
    3) About 15 minutes
    4)
    5) More than an hour

93. If a friend came to visit and they had a cold, would you:
    1) Not allow them in the house
    2)
    3) Allow them in but not let them hold the baby
    4)
    5) Allow them in and not restrict contact

94. How often does your baby seem to get stomach aches or other pains?
    1) All the time
    2)
    3)
    4)
    5) Not at all

95. How concerned are you that your baby is not as healthy as they should be?
    1) Very concerned
    2)
    3)
    4)
    5) Not at all concerned

96. In general, when you compare your baby's health to that of other children the same age, do you think your baby is:
    1) Less healthy
    2)
    3)

4)
5) More healthy

97. How worried are you that your baby may become seriously ill?
1) Very worried
2)
3)
4)
5) Not at all worried

98. How worried are you about Sudden Infant Death Syndrome (SIDS)?
1) Very worried
2)
3)
4)
5) Not at all worried

99. If you left your baby with someone else, would you make contact with them while you were away?
1) Yes, always
2)
3) Sometimes
4)
5) No, never

100. In the last 2 weeks, how often have you contacted a health professional (e.g. general practitioner, after hours emergency doctor, nurse, etc.) about your baby?
1) Not at all
2)
3) Once a week
4)
5) Daily or more

Relationship Status

Next, we'll ask some questions about your partner and relationship (if applicable).

These questions will help us learn about relationships between partners. We want to learn whether study information might affect these relationships.

101. Which of these best describes you?
- o Single (never married)
- o Married or living with a partner
- o Widowed
- o Divorced
- o Separated

102. Is your partner the biological parent of your baby?
- o Yes
- o No
- o Prefer not to answer

Kansas Marital Satisfaction Scale

Schumm WR, Paff-Bergen LA, Hatch RC, et al. Concurrent and discriminant validity of the Kansas Marital Satisfaction Scale. *J Marriage Fam*. 1986;48(2):381. doi:10.2307/352405

103. How satisfied are you with your marriage or partnership?
- o Extremely dissatisfied
- o Very dissatisfied
- o Somewhat dissatisfied
- o Mixed
- o Somewhat satisfied
- o Very satisfied
- o Extremely satisfied

104. How satisfied are you with your partner as a spouse or potential spouse?
- o Extremely dissatisfied
- o Very dissatisfied
- o Somewhat dissatisfied
- o Mixed
- o Somewhat satisfied
- o Very satisfied
- o Extremely satisfied

105. How satisfied are you with your relationship with your spouse or significant other?
- o Extremely dissatisfied
- o Very dissatisfied
- o Somewhat dissatisfied
- o Mixed
- o Somewhat satisfied
- o Very satisfied
- o Extremely satisfied

Blame

Pereira S, Smith HS, Frankel LA, et al. Psychosocial Effect of Newborn Genomic Sequencing on Families in the BabySeq Project: A Randomized Clinical Trial. *JAMA Pediatr*. 2021;175(11):1132. doi:10.1001/jamapediatrics.2021.2829

106. Do you think you passed potentially harmful genes on to your baby?
    - Definitely
    - Probably
    - Unsure
    - Probably not
    - Definitely not

107. How much do you blame yourself for passing potentially harmful genes on to your baby?
    - Not at all
    - A little
    - Somewhat
    - A lot

108. Do you think your baby's other biological parent passed potentially harmful genes on to your baby?
    - Definitely
    - Probably
    - Unsure
    - Probably not
    - Definitely not

109. How much do you blame your baby's other biological parent for passing potentially harmful genes on to your baby?
    - Not at all
    - A little
    - Somewhat
    - A lot

Parenting Stress Index

Abidin, R.R. (2012). Parenting Stress Index, Fourth Edition (PSI-4). Lutz, FL: Psychological Assessment Resources.

[licensed scale]

Adult Health-Related Quality of Life – EQ-5D

Rabin, R., & de Charro, F. (2001). EQ-5D: a measure of health status from the EuroQol Group. *Annals of medicine*, 33(5), 337–343. https://doi.org/10.3109/07853890109002087

[licensed scale]

GAD-7

Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing Generalized Anxiety Disorder: The GAD-7. *Arch Intern Med*. 2006;166(10):1092. doi:10.1001/archinte.166.10.1092

The next group of questions ask about how you have been feeling mentally. We want to learn whether genetic testing might affect parents' well-being.

Over the last 2 weeks, how often have you been bothered by any of the following problems?

Not at all	Several days	More than half the days	Nearly every day

110. Feeling nervous, anxious or on edge

111. Not being able to stop or control worrying

112. Worrying too much about different things

113. Trouble relaxing

114. Being so restless that it is hard to sit still

115. Becoming easily annoyed or irritable

116. Feeling afraid, as if something awful is about to happen

117. If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?
    - o Not difficult at all
    - o Somewhat difficult
    - o Very difficult
    - o Extremely difficult

PHQ-8

Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: Validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606-613. doi:10.1046/j.1525-1497.2001.016009606.x

Over the last 2 weeks, how often have you been bothered by any of the following problems?

Not at all	Several days	More than half the days	Nearly every day

118. Little interest or pleasure in doing things

119. Feeling down, depressed, or hopeless

120. Trouble falling or staying asleep, or sleeping too much

121. Feeling tired or having little energy

122. Poor appetite or overeating

123. Feeling bad about yourself—or that you are a failure or have let yourself or your family down

124. Trouble concentrating on things, such as reading the newspaper or watching television

125. Moving or speaking so slowly that other people could have noticed? Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual

126. If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?
    - Not difficult at all
    - Somewhat difficult
    - Very difficult
    - Extremely difficult

Infant Health-Related Quality of Life – EQ-TIPS

[formerly known as TANDI]

Verstraete, J., Ramma, L., & Jelsma, J. (2020). Validity and reliability testing of the Toddler and Infant (TANDI) Health Related Quality of Life instrument for very young children. *Journal of patient-reported outcomes*, 4(1), 94. https://doi.org/10.1186/s41687-020-00251-4

[licensed scale]

Medical and Economic

127. Please select any health problems your child has experienced related to:
    - o No medical problems
    - o Eyes or vision (examples: problems seeing, something different about their eyes)
    - o Ears, nose, or throat (examples: hearing loss, trouble swallowing)
    - o Teeth or gums (examples: tooth decay, too many or too few teeth)
    - o Lungs or breathing (examples: asthma)
    - o Heart or blood vessels (examples: heart murmur)
    - o Digestion or stomach (examples: reflux, constipation)
    - o Kidneys or bladder (examples: trouble urinating)
    - o Bones (examples: scoliosis or curved spine, chest bone that curves in or out, broken bones)
    - o Muscles (examples: torticollis / neck weakness, trouble moving certain body parts)
    - o Skin (examples: unusual skin color, lumps or bumps)
    - o Brain or nervous system (examples: developmental delays)
    - o Behavior or mental issues (examples: significant problems with sleep, crying, or feeding)
    - o Blood or bleeding (examples: easy bleeding or bruising)
    - o Growth (examples: slow growth or failure to thrive)
    - o Cancer
    - o Allergies
    - o Immune system (examples: frequent infections)

128. Please tell us more about these health problems: [free text]

129. Does your baby have a diagnosis for these health problems?
    - o Yes
    - o No
    - o Not sure

129a. Please describe: [free text]

130. Has your child seen a doctor for these health problems?
    - o Yes
    - o No
    - o Not sure

130a. Please describe: [free text]

131. Has your child seen a genetics doctor outside of the BabySeq Project?
    - o Yes
    - o No
    - o Not sure

131a. Please describe: [free text]

132. Has your child had any other genetic testing outside of the BabySeq Project?
    - o Yes
    - o No
    - o Not sure

133. Please describe: [free text]

134. Has your baby been admitted to the hospital since the last time you took a survey for the BabySeq Project (about 6 months ago)?

- Yes
- No

135. How many times has your baby been admitted to the hospital since the last time you took a survey for the BabySeq Project?

- 1
- 2
- 3 or more

136. Location of hospitalization 1: [free text]

137. Reason for hospitalization 1: [free text]

138. Number of days in hospital: [free text]

139. Was there an out-of-pocket cost (co-pay) for hospitalization 1?

- Yes
- No

140. What was the out-of-pocket cost (co-pay)? [free text] (U.S. dollars)

141. Did you or your spouse/partner take any time off from work to care for your baby during hospitalization 1?

- Yes
- No

142. Number of days you took off from work: [free text]

143. Number of days your spouse/partner took off from work: [free text]

144. Location of hospitalization 2: [free text]

145. Reason for hospitalization 2: [free text]

146. Number of days in hospital: [free text]

147. Was there an out-of-pocket cost (co-pay) for hospitalization 2?

- Yes
- No

148. What was the out-of-pocket cost (co-pay)? [free text] (U.S. dollars)

149. Did you or your spouse/partner take any time off from work to care for your baby during hospitalization 2?

- Yes
- No

150. Number of days you took off from work: [free text]

151. Number of days your spouse/partner took off from work: [free text]

152. Location of hospitalization 3: [free text]

153. Reason for hospitalization 3: [free text]

154. Number of days in hospital: [free text]

155. Was there an out-of-pocket cost (co-pay) for hospitalization 3?
- Yes
- No

156. What was the out-of-pocket cost (co-pay)? [free text] (U.S. dollars)

157. Did you or your spouse/partner take any time off from work to care for your baby during hospitalization 3?
- Yes
- No

158. Number of days you took off from work: [free text]

159. Number of days your spouse/partner took off from work: [free text]

160. Please describe any other hospitalizations: [free text]

161. Has your baby taken any medications since the last time you took a survey for the BabySeq Project (about 6 months ago)?
- Yes
- No

162. Please describe: [free text]

163. Was there an out-of-pocket cost (co-pay) for these medications?
- Yes
- No

164. What was the out-of-pocket cost (co-pay)? [free text] (U.S. dollars)

165. Is your child covered by health insurance or some other kind of health care plan?
(Include health insurance obtained through employment or purchased directly, as well as government programs like Medicare and Medicaid that provide medical care or help pay medical bills.)
- Yes
- No
- Not sure
- Prefer not to answer

166. What kind or kinds of health insurance or health care coverage do they have? (Check all that apply)
- Private health insurance, employment based
- Private health insurance, directly purchased
- Government plan like Medicaid or Children's Health Insurance Program (MassHealth, Child Health Plus, ALLKids)

- Government plan, Military health care
- International
- Other type of insurance
- I don't know
- Prefer not to answer

167. Other type of insurance (Please Describe): [free text]

168. Are you yourself covered by health insurance or some other kind of health care plan? (Include health insurance obtained through employment or purchased directly, as well as government programs like Medicare and Medicaid that provide medical care or help pay medical bills.)

- Yes
- No
- Not sure
- Prefer not to answer

169. What kind or kinds of health insurance or health care coverage do you have? (Check all that apply)

- Private health insurance, employment based
- Private health insurance, directly purchased
- Government plan like Medicaid (including MassHealth, New York Medicaid, Alabama Medicaid)
- Government plan, Military health care
- International
- Other type of insurance
- I don't know
- Prefer not to answer

170. Other type of insurance (Please Describe): [free text]

171. There are many reasons why you might not take your child to a doctor. We would like to know if any of these situations have applied to you in the last 6 months.

- I could not afford it.
- It was too difficult to get there.
- I do not like doctors and avoid going.
- I did not want to get bad news.
- I did not have time.
- I decided to take care of it on my own.
- I decided to wait and see if the problem would go away on its own.
- The doctor was not available to see my child.
- Other
- Not applicable
- Prefer not to answer

172. Please describe other reason: [free text]

The next questions ask about your work, and any help you might have needed since the last time you took a survey for BabySeq (about 6 months ago).

We want to study if genetic testing affects whether parents can work, and what they have to pay for.

173. Are you working now?
- Yes
- No

174. Since the last time you took a survey for the BabySeq Project (about 6 months ago) until today, did you pay for household help (housekeeping, cleaning, etc.)?
- Yes
- No

175. For how many weeks? [free text]

176. On average, what was the cost per week? [free text] (U.S. dollars)

177. Since the last time you took a survey for the BabySeq Project until today, have you hired caretakers or babysitters for your other children in order to attend healthcare related appointments or hospitalizations for your baby?
- Yes
- No
- I do not have any other children

178. For how many weeks? [free text]

179. On average, what was the cost per week? [free text] (U.S. dollars)

Since the last time you took a survey for the BabySeq Project (about 6 months ago) until today, have you used any of the following services?

180. Telephone conversation with a medical professional (e.g. nurse, nurse practitioner, doctor)
- Yes
- No

181. How many conversations? [free text]

182. Telehealth appointment with a medical professional (e.g. nurse, nurse practitioner, doctor)
- Yes
- No

183. How many telehealth appointments? [free text]

184. Was there an out-of-pocket cost (co-pay) for telehealth appointments?
- Yes
- No
- Not sure

185. What was the total out-of-pocket cost (co-pay)? [free text] (U.S. dollars)

186. Visit to your baby's primary care doctor (pediatrician, family practitioner)
- Yes
- No

187. How many visits to your baby's primary care doctor? [free text]

188. Was there an out-of-pocket cost (co-pay) for visits to your baby's primary care doctor?
- Yes
- No
- Not sure

189. What was the total out-of-pocket cost (co-pay)? [free text] (U.S. dollars)

190. Visit with a geneticist and/or genetic counselor outside of this project for you:
- Yes
- No

191. How many visits with a geneticist and/or genetic counselor for you? [free text]

192. Location: [free text]

193. Was there an out-of-pocket cost (co-pay) for your visits with a geneticist and/or genetic counselor?
- Yes
- No
- Not sure

194. What was the total out-of-pocket cost (co-pay)? [free text] (U.S. dollars)

195. Visit with a geneticist and/or genetic counselor outside of this project for your spouse or partner:
- Yes
- No

196. How many visits with a geneticist and/or genetic counselor for your spouse/partner? [free text]

197. Location: [free text]

198. Was there an out-of-pocket cost (co-pay) for your partner's visits with a geneticist and/or genetic counselor?
- Yes
- No
- Not sure

199. What was the total out-of-pocket cost (co-pay)? [free text] (U.S. dollars)

200. Visit with a geneticist and/or genetic counselor outside of this project for your baby:
- Yes
- No

201. How many visits with a geneticist and/or genetic counselor for your baby? [free text]

202. Location: [free text]

203. Was there an out-of-pocket cost (co-pay) for your baby's visits with a geneticist and/or genetic counselor?
- Yes
- No
- Not sure

204. What was the total out-of-pocket cost (co-pay)? [free text] (U.S. dollars)

205. Has your child been referred to Early Intervention (depending on where you live, this might also be referred to as Birth to 3 or Early On)?

- Yes
- No
- I'm not sure

206. Who referred you? [free text]

207. Has your child been evaluated for Early Intervention?

- Yes
- No
- I'm not sure

208. Does your child have an Individualized Family Service Plan (IFSP) or Early Intervention Plan?

- Yes
- No
- I'm not sure

209. Did your child become eligible for Early Intervention because of your BabySeq study results?

- Yes
- No
- I'm not sure

210. Did you experience any delays or challenges in getting your child evaluated or enrolled in Early Intervention?

- Yes
- No
- I'm not sure
- Not applicable

211. Please describe any delays/challenges, or any other thoughts you have about Early Intervention: [free text]

212. Has your child received any therapy services in the last 6 months (ex. physical therapy, speech therapy)?

- Yes
- No
- I'm not sure

213. What type of services did your child receive?

- Physical therapy
- Occupational therapy
- Speech therapy
- Applied behavior analysis (ABA)
- Other

214. What other type(s) of therapy? Please specify. [free text]

215. Did your child become eligible for physical therapy because of your BabySeq study results?

- Yes
- No
- I'm not sure

216. How many of the last 6 months did your child visit physical therapy?
    - 1 month
    - 2 months
    - 3 months
    - 4 months
    - 5 months
    - 6 months

217. How many visits to physical therapy did your child have per month? [free text]

218. Was physical therapy helpful for your child?
    - Yes
    - No
    - I'm not sure

219. Why or why not? [free text]

220. Did your child become eligible for occupational therapy because of your BabySeq study results?
    - Yes
    - No
    - I'm not sure

221. How many of the last 6 months did your child visit occupational therapy?
    - 1 month
    - 2 months
    - 3 months
    - 4 months
    - 5 months
    - 6 months

222. How many visits to occupational therapy did your child have per month? [free text]

223. Was occupational therapy helpful for your child?
    - Yes
    - No
    - I'm not sure

224. Why or why not? [free text]

225. Did your child become eligible for speech therapy because of your BabySeq study results?
    - Yes
    - No
    - I'm not sure

226. How many of the last 6 months did your child visit speech therapy?
    - 1 month
    - 2 months

- 3 months
- 4 months
- 5 months
- 6 months

227. How many visits to speech therapy did your child have per month? [free text]

228. Was speech therapy helpful for your child?
- Yes
- No
- I'm not sure

229. Why or why not? [free text]

230. Did your child become eligible for applied behavior analysis (ABA) because of your BabySeq study results?
- Yes
- No
- I'm not sure

231. How many of the last 6 months did your child visit applied behavior analysis (ABA)?
- 1 month
- 2 months
- 3 months
- 4 months
- 5 months
- 6 months

232. How many visits to applied behavior analysis (ABA) did your child have per month? [free text]

233. Was applied behavior analysis (ABA) helpful for your child?
- Yes
- No
- I'm not sure

234. Why or why not? [free text]

235. Did your child become eligible for [free text response from item 214] because of your BabySeq study results?
- Yes
- No
- I'm not sure

236. How many of the last 6 months did your child visit [free text response from item 214]?
- 1 month
- 2 months
- 3 months
- 4 months
- 5 months
- 6 months

237. How many visits to [free text response from item 214] did your child have per month? [free text]

238. Was [free text response from item 214] helpful for your child?
- Yes
- No
- I'm not sure

239. Why or why not? [free text]

240. Has your child received home nursing care in the last 6 months?
- Yes
- No
- I'm not sure

241. Did your baby become eligible for home nursing care because of your BabySeq study results?
- Yes
- No
- I'm not sure

242. How many home nursing care visits? [free text]

243. Is there anything else you would like to tell us about your experiences with the BabySeq Project? [free text]