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ARTICLE

Family genetic risk communication and reverse cascade testing in the BabySeq project

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ABSTRACT

Purpose: Genomic sequencing of newborns can initiate disease surveillance and therapy for children and may identify at-risk relatives through reverse cascade testing. We explored genetic risk communication and reverse cascade testing among families of newborns who underwent exome sequencing and were identified as having a risk for an autosomal dominant disease.

Methods: We conducted semistructured interviews with parents of newborns enrolled in the BabySeq Project who had a pathogenic or likely pathogenic variant associated with an autosomal dominant childhood- and/or adult-onset disease returned. We used directed content analysis to derive themes.

Results: From 11 families, all first-degree relatives ($n = 32$, 100%), 29 second-degree relatives (76%), and 26 third-degree relatives (43%) were informed of their risk. All parents ($n = 22$, 69% of first-degree relatives), 4 (11%) second-degree relatives, and 1 (2%) third-degree relatives underwent cascade testing. Most parents preferred to handle risk communication themselves. Parents with positive cascade testing but no associated symptoms were less inclined to share findings with relatives but highly motivated to share results if the variant's associated disease severity was high, as perceived with adult-onset conditions. One new subtheme, family member traits, was identified and defined as a relative's propensity to anxiety/concern after risk communications but did not diminish risk communication.

Conclusion: Findings can inform more effective notification and testing practices for families of newborns at risk for hereditary genetic conditions.

Introduction

Population-based newborn genomic sequencing (NBSeq) is a promising approach to supplement biochemical newborn screening,[1] given its utility in predicting disease.[2,3] NBSeq can evaluate the risk for thousands of genetic disorders simultaneously, allowing for more accurate screening and targeted prevention/treatment of diseases.[4] NBSeq is increasingly feasible and acceptable to parents.[5-7] In addition to benefitting the newborn, NBSeq provides an

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The names of the BabySeq Project Team will appear at the end of the article.

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opportunity to improve family health through cascade testing, or the identification and testing of relatives for hereditary conditions detected in the infant (ie, proband).[8]

Cascade testing is valuable for relatives who are unaware of their genetic risk and would otherwise remain undiagnosed. Cascade testing that begins with a child proband is sometimes called reverse cascade testing.[9] Cascade testing is an application of precision medicine that allows for surveillance, treatment,[10] and/or informed reproductive planning.[11] Thus, cascade testing can improve health and quality of life for relatives[12] and may save lives. However, the reported uptake of reverse cascade testing ranges from 37% to 90%.[12] This variability is associated with multiple barriers,[10] including suboptimal communication with relatives about their potential risk.[10]

Family genetic risk communication may be mediated by the proband/family (termed proband/family-initiated or indirect contact) or health care providers (termed direct contact), depending on a jurisdiction's practice standards as dictated by legal and ethical norms.[13] Data from the United Kingdom and The Netherlands suggest that direct contact may be the most effective method of notifying families of risk and maximizing cascade testing.[14,15] However, provider communication with relatives without consent from the proband raises ethical and legal concerns related to infringement on patient/relative autonomy and breach of patient confidentiality.[14,15] Direct contact after obtaining proband consent is permissible in the United States under The Health Insurance Portability and Accountability Act and state confidentiality laws.[13] However, US providers do not have a legal duty to directly warn relatives of potential risk.[13] Currently in the US, primary responsibility for family risk notification resides with the proband/family,[13] which promotes family autonomy and privacy. Yet, some probands feel ill-equipped to convey risk information or may not understand which relatives are at risk.[10]

To date, most cascade communication studies have involved relatives of adult probands, and as a recent review highlights,[12] a small number of studies explore reverse cascade testing. A few reverse cascade testing studies explore testing in families of infants,[9,16-18] but none explore testing after the receipt of results that indicate risk for adult-onset disorders. Historically, asymptomatic children have not been tested for adult-onset genetic conditions because of concerns about adverse psychological impacts after the return of results and prioritization of the child's best interests and future autonomy.[19,20] However, recent policy statements acknowledge the potential benefit to families from testing children for adult-onset conditions,[19,21] indicating a need for further study.

The BabySeq Project provides a unique opportunity to address this knowledge gap.[22,23] The BabySeq Project began as one of 4 projects in the Newborn Sequencing in Genomic Medicine and Public Health consortium[24] to explore how genomic sequencing in newborns could facilitate understanding of resulting medical, behavioral, and economic outcomes.[23,24] The first phase of the BabySeq Project was a first-of-its-kind randomized controlled trial of exome sequencing in infants with return of results for monogenic disease risk (MDR) for a childhood- and/or adult-onset disorder. For this study, we followed up with parents of BabySeq infants whose exome sequencing results revealed a variant associated with an autosomal dominant (AD) disease. Our aim was to describe the genetic risk communication of these parents with potentially at-risk relatives and subsequent cascade testing among relatives. Because BabySeq included results indicating the risk of adult-onset disease, our study provides a unique opportunity to explore the experience of parents sharing these highly clinically actionable findings.

Materials and Methods

Study design and participants

A qualitative descriptive design[25] was used to collect semistructured telephone interview data. Eligible participants were parents who had, with their infant, been enrolled in the first phase of the BabySeq Project. Eligible parents had an infant whose exome sequencing results revealed a variant associated with an AD disease. Parents were excluded if their infant's variant was not inherited (ie, de novo) or was characterized by autosomal recessive inheritance. The first phase of BabySeq enrolled parents and their newborns from the well-baby nursery at Brigham and Women's Hospital and parents and their newborns from the neonatal and other intensive care units at Brigham and Women's Hospital, Boston Children's Hospital, and Massachusetts General Hospital. The trial design is described elsewhere.[22,23] Briefly, newborns were randomized to either a modified standard of care—family history and standard newborn screening (the control arm)—or to the modified standard of care plus exome sequencing (ES) (the ES arm). Positive results included an MDR for a childhood-onset disorder (about 1000 disorders)[26] and/or highly clinically actionable (ie, availability of screening and targeted disease prevention/treatment) adult-onset-only diseases, meeting criteria used to generate the 2013 American College of Medical Genetics and Genomics list of incidental findings to be reported when identified based on exome or genome sequencing. Adult-onset conditions included hereditary breast and ovarian cancer, Lynch syndrome, and MYH-associated polyposis and related syndromes).[22,23,27] As reported elsewhere, all but 1 of the remaining genes on the 2013 American College of Medical Genetics and Genomics list were already being returned on the basis of the curated list of ~1000 childhood-onset and childhood-actionable conditions, as defined by the interdisciplinary BabySeq research team.[26,28] MDR included heterozygosity for pathogenic or likely pathogenic (P/LP) variants in genes associated with AD diseases, compound heterozygosity for P/LP variants in genes associated with autosomal recessive diseases, or hemizygosity for P/LP variants in genes associated with X-linked

recessive diseases. For parents of newborns with an MDR finding, Sanger sequencing of the indicated gene (identified through the infant's ES results) using parental DNA from a saliva sample (ie, reverse cascade testing) was performed to determine if the newborn's variant finding was de novo or inherited and to identify the inheritance pattern. Of 18 infants (10%) with an MDR, 14 had an inherited variant. Eleven infants had a variant associated with a childhood-onset disease, and 3 infants had a variant associated with an adult-onset disease.[28,29] The BabySeq study team identified all variants associated with an MDR as clinically actionable, based on the availability of screening and targeted disease prevention/treatment.[28,29]

All parents of infants who enrolled in BabySeq met with both a genetic counselor and study physician for a results disclosure session. During this session, parents received detailed information about the family history report based on the pedigree obtained at enrollment, the standard newborn screening report, and if in the sequencing arm, the infant's genomic sequencing results. Genomic sequencing results included gene variant(s) and associated disease risk(s), inheritance information based on parents' cascade testing results returned during the results disclosure session, and implications for the child and family members. At-risk second-degree relatives (SDRs) and third-degree relatives (TDRs) were identified for parents based on the incorporation of parental cascade testing results, in addition to the pedigree. Results disclosure session information was recorded in a detailed note/letter. This letter was uploaded into the infant's medical record and sent home to the parents, to the infant's pediatrician, and to any providers requested by the family, along with the family history report, newborn screening report, and, when relevant, newborn genomic sequencing report, which included P/LP variants and the associated disease risk, home to the parents, to the infant's pediatrician, and to any providers requested by the family.[23] Subsequently, the study genetic counselor served as the primary contact for communication with any additional physicians (particularly physicians caring for adult at-risk family members, when consent was given) to assist in providing information on relevant referrals and documentation for cascade testing, as needed. Formally, this was called the study's Genomic Resource Center. Genomic Resource Center contact information was provided directly to the family, as well as placed in disclosure materials.

Recruitment

The written consent of parents to participate in the first phase of the BabySeq Project allowed us to recontact them for this study. We invited parents of all 14 infants whose ES results revealed an inherited variant associated with an AD childhood- and/or adult-onset disease (ie, hereditary cardiac condition, vascular condition, renal condition, sensory condition, and cancer/condition that may lead to cancer) to participate. Study staff sent an email requesting parent participation in a qualitative interview, which included the study purpose and study team contact information. Up to 2 emails and 3 phone calls were made to parents who did not initially respond. Once a parent agreed to participate, an interview time was scheduled based on parent availability. The average time between the disclosure of ES results for the infant and the interview with the parent was 33.4 months.

Data collection

Parent interviews were conducted in English between March and June of 2020 by the first author (M.K.U.), a PhD-prepared nurse and NICU clinician, who had no prior relationship with participants. A semistructured interview guide, informed by a review of the cascade testing literature, was developed by the study team to include open-ended questions/prompts focusing on parents' dissemination of their child's genetic results to relatives. Questions/prompts explored whether at-risk relatives had been informed about their disease risk, had undergone cascade testing, and the results of testing (see Supplemental Methods). As mentioned, at-risk relatives were identified based on the incorporation of parental cascade testing results and a 3-generation pedigree obtained at BabySeq enrollment and updated during the interview. We considered all SDRs and TDRs of the proband in the lineage of the parent with positive cascade testing results (ie, the parent carrying the same P/LP variant as the infant) to be at-risk, given that it was unclear before parent interviews whether cascade testing when it occurred, had occurred sequentially (ie, proceeded from first-degree relatives [FDRs] to SDR to TDRs). Parents' self-reported demographics collected at BabySeq enrollment were also used for this study. All interviews were audio recorded, after obtaining consent, and lasted 30 to 60 minutes. Participants were compensated $50 (electronic gift card). Study procedures were approved by the Mass General Brigham (2014P001906), Boston Children's Hospital (P00011237), and Baylor College of Medicine Institutional Review Boards (H-35837).

Data analysis

Deidentified audio files were professionally transcribed and reviewed for accuracy. Dedoose, a web-based platform for analyzing qualitative data, was used to facilitate data management, coding, and analysis. Data were analyzed using directed content analysis, an approach whereby previous research/theory is used to focus the analysis and validate or extend existing knowledge.[30] The Family Communication of Genetic Risk (FCGR) conceptual framework[31] was used to identify initial themes and subthemes because its description of family communication around genetic risk and testing behaviors of at-risk relatives aligns with this study's focus. We deductively coded data to the 4 main themes and 22 subthemes identified in the FCGR

framework. We concurrently applied inductive coding to identify additional themes/subthemes when themes from the FCGR framework did not conceptually match our data. We captured communication occurrence and initial outcomes of communication by applying frequency analysis to interview data describing the extent of risk communication across families and reverse cascade testing uptake. We then coded the remaining interview data to the themes/subthemes identified by the FCGR framework, adding additional inductive codes as indicated.

To establish the coding framework and facilitate robust qualitative coding,[32] 2 coders (M.K.U. and H.S.S.) independently coded 3 interview transcripts (~20%), which were selected to represent a range of findings related to AD disease risk, providing a diverse sample of the data for initial coding. Codes from the FCGR framework and inductive codes were used, as indicated.[30] Coders then independently coded the remaining 10 interviews, meeting biweekly to refine the codebook and resolve coding differences using consensus. Coders ensured rigor by maintaining an audit trail of analytic processes and decisions and through peer debriefing.[32]

Table 1 Demographic characteristics of parents interviewed ($N = 13$) from 11 families

Parent Characteristic	*n*
Mean age, y (SD)	40.23 (2.83)
Range	37-46
Sex, *n* (%)	
Male	6 (46.2)
Female	7 (53.8)
Race, *n* (%)	
Non-Hispanic White	9 (69.2)
Other	2 (15.4)
Did not report	2 (15.4)
Education, *n* (%)	
Bachelor's degree	5 (38.5)
Master's degree or higher	7 (53.8)
Did not report	1 (7.7)
Household income, *n* (%)	
$100-$199K	5 (38.5)
>$200K	6 (46.1)
Did not report	2 (15.4)
Married or partnered, *n* (%)	13 (100.0)
First child	2 (15.4)

K, thousand.

Results

We contacted 14 eligible families, 11 of whom responded (13 parents) and completed interviews (79% family response rate). In 8 families, we interviewed the parents with positive cascade testing results. We interviewed both parents in 2 families. In 1 family, the interviews were conducted separately, whereas in the other, the parents requested to be interviewed together. Parent characteristics are presented in Table 1. Parents were primarily female ($n = 7$, 53.8%), non-Hispanic White ($n = 9$, 69.2%), had completed graduate school ($n = 7$, 53.8%), had a household income $\geq$ $100K ($n = 11$, 84.6%), had other children ($n = 11$, 84.6%), and all were partnered ($n = 13$, 100%). The average time between the disclosure of ES results for the infant and the interview with the parent was 33.4 months. Figure 1 shows BabySeq infants who had an MDR result and variants for infants of families who participated in interviews. Nine infants had a variant associated with a childhood-onset disease, whereas 2 infants had a variant associated with an adult-onset disease. As previously reported, variant findings for infants in 2 families interviewed prompted the discovery of a previously unrecognized subclinical phenotype in the infant (Figure 1).[29]

Table 2 describes risk communication occurrence and cascade testing outcomes for at-risk relatives. A total of 131 at-risk relatives ($n = 32$ FDRs [parents and siblings], $n = 38$ SDRs [aunts, uncles, and grandparents], and $n = 61$ TDRs [first cousins, half aunts, half uncles, great aunts, great uncles, and great grandparents]) were identified across families interviewed. All FDRs ($n = 32$, 100%) were informed of their risk by the BabySeq study team; parents were given information about the risk for the probands' sibling(s). Parents of infants informed at-risk SDRs ($n = 29$, 76%) and TDRs ($n = 26$, 43%). In only 1 family interviewed, the parent did not communicate her infant's results to SDRs or TDRs. As noted under study methods, all parents received cascade testing as part of the research protocol. Only 4 at-risk (11%) SDRs and 1 (2%) TDRs were informed of their risk and initiated cascade testing; however, none were relatives of infants with a clinical phenotype (Figure 1). Although 2 SDRs and 1 TDR had positive cascade testing results, the parents interviewed did not have information on whether these relatives had an observable clinical phenotype. The majority of probands' siblings and SDRs/TDRs had not sought cascade testing at the time of the interview ($n = 81$, 74%). Parents were unsure of whether cascade testing was sought for one-fifth ($n = 23$, 23%) of SDRs/TDRs.

Qualitative themes and subthemes describing family genetic risk communication are described below. Data from interviews were mapped to all 4 themes and 14 of the 22 subthemes of the FCGR framework, and 1 new subtheme, not defined by the FCGR framework, was identified. Exemplar quotes for themes and subthemes are described in Table 3.

Influential factors in communication

Influential factors describe factors that motivate parent genetic risk communication decisions.[31] The FCGR framework defines four types of influential factors: (1) family, (2) disease, (3) individual, and (4) sociocultural.

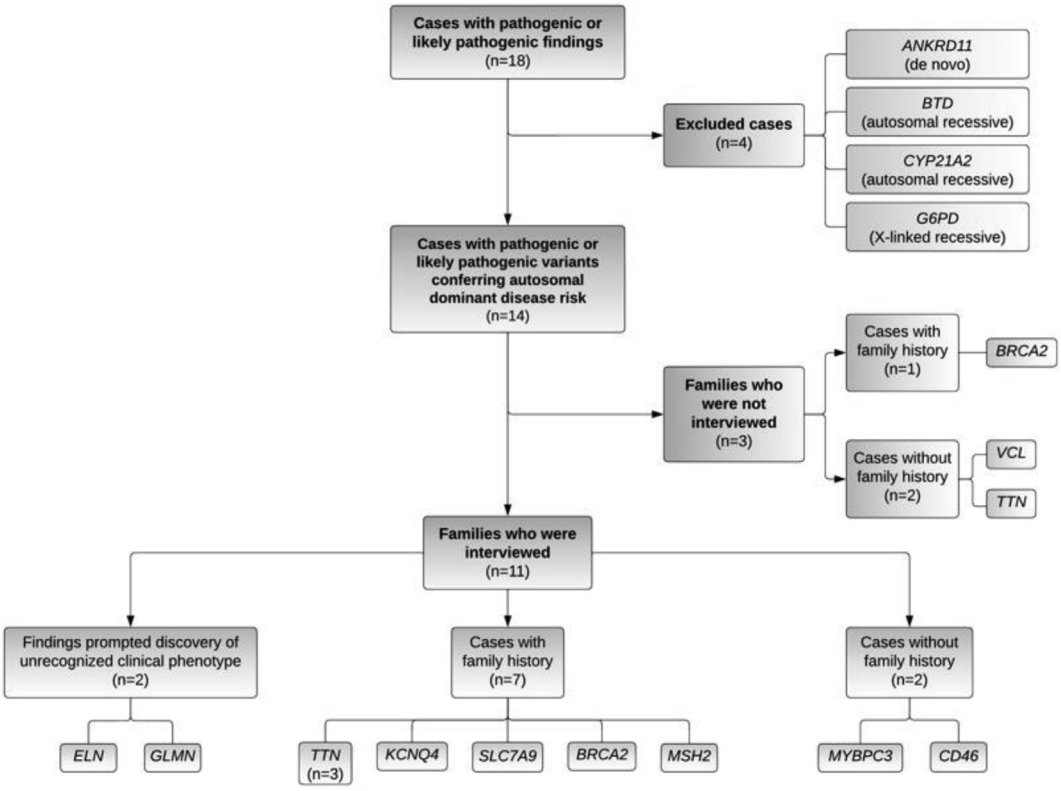

Figure 1 **Flowchart of BabySeq infants with monogenic disease risk and parents participating in qualitative interviews.**

Influential factors: Family

Family factors describe characteristics of the family that affect communication about genetic risk.[31] This theme included 4 subthemes. Family contact and closeness were a motivating factor for sharing genetic risk information, which allowed for monitoring of physical symptoms of genetic disease in at-risk relatives. Parents in 2 families viewed their close relationship with relatives as a private, intimate setting for sharing genetic risk information and did not want others to join what they felt was a delicate conversation. Some

Table 2 Communication occurrence and reverse cascade testing of at-risk living relatives across 11 families interviewed

	Communication of Risk *n* (% of Row)			Testing and Diagnosis *n* (% of Row) [Conditional % of Row][a]			
Type of Relative	Not Informed (*n* = 31)	Unknown if Informed (*n* = 13)	Informed (*n* = 87)	Tested and Results Known (*n* = 25)	Tested and Unknown Results (*n* = 2)	Uncertain if Tested (*n* = 23)	Not Tested (*n* = 81)
FDR (*n* = 32)	0	0	32 (100)	22 (69) [69]	0	0	10 (43)
Sibling (*n* = 10)	0	0	10 (100)	0	0	0	10 (100)
Parent (*n* = 13)	0	0	22 (100)	22 (100) [100]	0	0	0
SDR (*n* = 38)	7 (19)	2 (5)	29 (76)	2 (5) [7]	2 (5) [7]	9 (24)	25 (66)
Maternal aunt/uncle (*n* = 14)	3 (21)	0	11 (79)	1 (7) [9]	1 (7) [9]	4 (29)	8
Paternal aunt/uncle (*n* = 2)	0	0	2 (100)	0	0	1 (50)	1 (50)
Maternal grandparent (*n* = 14)	2 (14)	2 (14)	10 (72)	1 (7) [10]	1 (7) [10]	2 (14)	10 (71)
Paternal grandparent (*n* = 8)	2 (25)	0	6 (75)	0	0	2 (25)	6 (75)
TDR (*n* = 61)	24 (39)	11 (18)	26 (43)	1 (2) [4]	0	14 (23)	46 (75)
Cousin (*n* = 18)	8 (44)	2 (12)	8 (44)	0	0	4 (22)	14 (78)
Half-aunt/uncle (*n* = 2)	0	0	2 (100)	0	0	1 (50)	1 (50)[b]
Great-uncle/aunt (*n* = 37)	15 (41)	6 (16)	16 (43)	1[c] (3) [6]	0	6 (16)	30 (81)
Great-grandparent (*n* = 4)	1 (25)	3 (75)	0	0	0	3 (75)	1 (25)

FDR, first-degree relative; *SDR*, second-degree relative; *TDR*, third-degree relative.

[a]Conditional % of row for the tested columns is the number tested out of the number informed about their risk.

[b]Relative advised not to test upon follow-up with providers.

[c]Relative tested and received negative results; no variant diagnosed.

Table 3 Exemplar quotes of themes and subthemes influencing parents' genetic risk communication with at-risk relatives

Theme	Subtheme	Example Quote (Study ID)
Influential factors: family	Family contact and closeness	"I talked to my closest sister the most. And just getting the support from her and knowing that she understands what I'm going through… But if you have a difficult family, and everybody is everywhere or a different part of the country and stuff like that, you might want to FaceTime them or having a conversation through, I don't know, a group or something…" (10)
	Established family dynamics	"It all depends on the dynamic in the family. But we've always kind of led our lives as being open books. We've been open to sharing everything going on in our lives, be it [child's] situation …So we're pretty open about everything with our family." (2)
	Milestones/life happenings	"Because of what we were dealing with, with our dad, that was the context that we talked about this information through… So I think it was less hard to talk about with them because of what my dad– we've been dealing with my dad [and his illness] for so long." (5)
	Family member traits[a]	"[I would say be considerate of] your audience, knowing how they will react to certain information, knowing that [some] people are more hypochondriac, much more sensitive about their health or more concerned or kind of will figure out what they want to do with the information." (6)
Influential factors: individual	Moral conviction or altruism	"I thought there was a benefit [in sharing] to understand the genetic history of the family and how it impacts [relatives] and knowing the information will be beneficial as [relatives] get older or have kids." (9)
	Prevent harm/worry	"I did struggle with whether to [convey] it or not [to relatives] because sometimes it's not necessarily information that other people would want, and I'm forcing it upon them." (3)
	Need for support	"My mom, for sure, [I told] just to let her know what's going on, just in case. Because those are the people that, if you get the bad news, you want to be able to talk or cry about it." (11)
Influential factors: disease	Understanding of disease	"I did mention the gene. But it was the ability to do more than the gene, I would say, is kind of what I mean. Because I think saying, you have deficiency of kind of that gene, that doesn't mean much in isolation. But I think being able to talk about the symptoms, what the practical implications of that are were the part that made it easier and more impactful to share." (1)
	Disease experience	"[Child] has some type of genetic mutation; she got it from me. The skeptic in me started to dismiss how much we need to worry about this. I have this [mutation] too and if I've been fine this whole time, then I just feel like [Child's] going to be fine, too. We didn't share it with anyone [i.e., relatives]; we didn't really feel we needed to. I don't think we would worry about it too much until somebody got sick." (4)
Influential factors: socio-cultural	Discrimination concerns	"Would [genetic results] put [relative] in a bad spot for life insurance, being it would be a pre-existing condition?" (2)
	Privacy concerns	"We tried to, while maintaining people's sense of privacy, spread the information as well as we could. My wife's feeling, I know, was that she felt an obligation to share it with her parents and she thought that they should feel an obligation to share it with other relatives. We wanted to say, 'Hey, you have the information. Now go get yourself checked out and we think you should be sharing this because it could help someone.'" (8)
Communication strategies	Content	"[I explained] that when [Child] was born, we had an opportunity to take part in genetic testing. They found a marker on [Child] and me that in all likelihood could affect you guys as well. Here's what they told me and here's what that could mean. But this is information you can share with your doctor– and I said, here's what I'm doing. I'm establishing a relationship so that I can keep an eye on it." (5)
	Delivery	"It was more just like when they talk on a daily basis with each other, like, 'Oh, hey, by the way, we got [Child's] genetic results. Here's what he's positive for. You may just want to keep an eye on that.' And more informal, not like a formal like sit down where we hand them information, here's everything we know type of thing." (7)

(continued)

Table 3 Continued

Theme	Subtheme	Example Quote (Study ID)
Outcomes of communication	Family functioning	"It's the sense, when you share it with someone from whom that genetic trait has been passed, that it's an accusatory conversation. Not that you are treating it that way, but that it's felt to be that way. Or even if it's not accusatory, the fact that there is guilt at having unknowingly passed it on. And I think that's what makes it most uncomfortable. People are generally fairly private about their health and having an open discussion about a negative health data point that doesn't just impact you but impacts everyone on down your family line, that can be an uncomfortable light to shine. Conversations tend to sometimes be anxiety-inducing. And then it goes back to normal. So no lasting impact on the relationship whatsoever. Still a very close and strong relationship." (8)
	Family follow-up	"I did have the challenge of knowing what test needs to be done. It's like who do you contact? You can't call Quest up and be like, 'I'd like to get a gene test.' I think figuring out how others who are not close to you, because my family is out of state, outside of a research center, how they go about requesting testing." (6)
	Responsibility complete	"I kind of feel like my job's done. I told the affected side. It's up to them what they decide to do with it at this point. So I'm just crossing my fingers everybody's safe. I've provided the information and I feel like I could have done nothing and then I'd feel really bad if somebody came down with something. So I feel like I've checked my box in that regard." (3)

FCGR, Family Communication of Genetic Risk; *ID*, identification.

[a]Designates an additional subtheme identified through inductive analysis of study data, not represented by the FCGR conceptual framework.

parents shared genetic risk information with close (ie, first-degree) relatives but not more distant relatives, whom they knew less well. Others disclosed first to close relatives, then to distant relatives. In 1 family, after a parent shared genetic risk information with his mother, she assumed the communicator role herself because of her established relationships with relatives and passed the information on to SDRs and TDRs. Parents referenced geographically dispersed families, families who lacked relational closeness, and estranged familial relationships as barriers that either prevented or made risk communication difficult.

Established family dynamics describe communication and/or relational patterns and styles already present within the family that affect risk communication.[31] Parents within families characterized by an open communication style found it easy to communicate genetic risk information and felt confident they would receive support from relatives when doing so. Parents in four families routinely involved their partners in risk communication, which helped cover details they may have forgotten or could not comprehensively explain. Two families reported a closed, or private, communication style. In 1 of these families, parents were open to sharing genetic findings with at-risk relatives, but the proband's maternal grandparents were less open to passing on risk information to other relatives and only did so when urged by the proband's parents. In another family, although the proband's mother had an open communication style, the proband's father felt risk information was more private. Combined with his estranged relationship with some family members, this communication preference led him to not share risk information.

Milestones/life happenings, in the context of our study, primarily described relatives' acute or long-term illnesses as influential in risk communication. A relative's illness, especially if possibly associated with the proband's findings, could create a context for, or trigger, risk communication and relatives' cascade testing. For 1 parent, a relative's early death from cancer motivated cascade testing conversations with the deceased family member's children. In another family, a relative's need for a heart transplant led the family to consider risk communication, but, as noted below, they did not initiate communication out of a desire to prevent worry.

Family member traits were a new subtheme that we identified, not part of the FCGR framework, which describes the importance of knowing your audience. This subtheme involves anticipation of relatives' propensity to anxiety or concern after risk communication and did not prevent parents' sharing of their child's results but prompted greater sensitivity.

Influential factors: Disease

Disease factors describe characteristics of the AD disease associated with the P/LP variant that affect the likelihood of communicating relatives' genetic risk.[31] This theme included 2 subthemes. Understanding of disease describes parents' perceived knowledge of the AD-associated disease and disease risk for others.[31] Parents gained disease understanding from the BabySeq team, health care specialists, online/print literature, or support groups. Parents felt equipped to share their child's genetic information when they knew the genetic variant but more so when they understood variant implications, including inheritance patterns or sex-related risk differences (ie, *BRCA2*), potential disease symptoms, health consequences, and recommended follow-up. Parents' understanding of disease severity also affected their sharing. Receipt of a finding associated with a life-threatening condition prompted parents to share more

readily than for a disease that was not associated with a shortened life expectancy.

Disease experience involves an individual's experience with the disease, including their testing results, symptoms, and disease coping. Parents who had not seen the disease develop in themselves, despite positive reverse cascade testing, or who perceived their child's genetic results as not serious, were less inclined to share findings.

Influential factors: Individual

Individual factors describe characteristics of parents that influence the likelihood of sharing genetic risk information.[31] This theme included three subthemes. Many parents share genetic risk information because of a moral conviction or altruism, or feeling responsibility, obligation, duty, or concern for relatives' health and longevity.[31] Parents who shared for altruistic reasons felt information could be particularly helpful to relatives undergoing reproductive decision making.

A desire to prevent psychological harm or worry was a factor that limited parents' sharing of genetic risk information. Some relatives were already experiencing worry; therefore, parents hesitated to initiate risk communication unless necessary. One parent's father was preparing for a heart transplant and the parent felt that sharing genetic risk information would only add worry about passing on a heritable cardiovascular trait. Other parents did not share genetic risk information for fear that relatives would worry about those in the family whose ES results revealed a variant associated with an AD disease. Still, other parents recognized that sharing genetic risk information with relatives who they perceived as not wanting this information could be harmful.

Two parents shared genetic risk information with relatives out of a need for support. These parents had a need to talk and express emotion (ie, cry) with relatives about the inherited results, as well as seek advice about how to go about sharing results with extended relatives.

Influential factors: Sociocultural

Sociocultural factors describe cultural or societal characteristics that may influence parents' sharing of genetic risk information.[31] This theme included 2 subthemes. Parents described discrimination concerns or fears that positive genetic testing might prevent relatives from obtaining health insurance or increase insurance premiums. Even parents who understood health insurance protections under the Genetic Information Non-discrimination Act, which were routinely explained under the BabySeq protocol, were concerned that future policy changes could eliminate these protections. Other parents were concerned about the ability of relatives with positive genetic testing to obtain life insurance.

Parents also had privacy concerns. Parents sought to reconcile the notion that relatives might want to keep their genetic risk private with the importance of relatives receiving and sharing genetic risk information with other relatives.

Communication strategies

This theme describes methods used by parents to conduct risk communication[31] and includes 2 subthemes. Content describes information used by parents to communicate relatives' genetic risk.[31] Parents offered varying amounts of risk information, some sharing the genetic variant and others discussing the condition associated with the findings and recommended follow-up or next steps (ie, specialist).

Delivery describes the modalities, styles, tones, or approaches used to communicate genetic risk.[31] Parents utilized in-person conversations with nearby relatives but used phone calls and emails with geographically distant relatives. Several parents gave relatives their infant's BabySeq return results report. One parent shared a pamphlet received from a support group, whereas another shared a letter written by a genetic counselor. Most parents took an informal, incremental approach to risk conversations, sharing information with 1 relative at a time as they received it, through everyday conversations, rather than formal gatherings with the entire family. Most parents preferred initiating communication with relatives themselves. Two families involved a provider during risk conversations and another expressed interest in having a provider join, whereas 2 other families would have benefited from stock language to facilitate risk conversations.

Outcomes of communication

This theme describes emotions, behaviors, and actions resulting from families after risk communication[31] and includes 3 subthemes. Family functioning describes the positive and negative changes in family dynamics after risk communication.[31] Some relatives responded positively to risk communication, displaying a sense of relief or reassurance when perceived risk was low. Parents felt that family relationships would not have been negatively influenced had the results involved high risk. Other risk communication conversations, because they affected the entire family, were uncomfortable, stressful, or anxiety producing. Risk conversations could feel accusatory, given the inherited nature of the variant; however, no parents reported a negative impact on familial relationships after risk communication. Some relatives initially felt concerned for the child and parent with positive genetic testing, but risk communication did not affect relatives' treatment of the child/parent long term. In some families, risk communication strengthened relationships because of more frequent conversations.

Family follow-up describes the relatives' behaviors after risk communication. In some cases, risk communication did not result in relatives seeking cascade testing, despite urging. In other cases, relatives sought testing immediately or verbalized intent to seek follow-up. Relatives who verbalized intent to seek future testing were either still talking with providers or had competing life demands, such as

caretaking. Other relatives would consider cascade testing after public health (ie, COVID-19) restrictions are lifted. Still, other relatives died before testing was sought. A barrier to pursuing cascade testing, particularly for relatives living outside of Massachusetts, was knowing how to request cascade testing.

Responsibility complete describes parents' discharge of responsibility to relatives after risk communication.[31] Parents communicated risk to relatives but felt that relatives could act on the information as they saw fit. Parents did not view relatives' uptake of testing as within their purview or control.

Discussion

Maximizing the detection of monogenic conditions is crucial for not only reducing the risk of adverse health outcomes in probands but also relatives.[12] We interviewed parents from 11 families who enrolled in the first phase of the BabySeq Project, whose infant's ES results revealed an inherited P/LP variant associated with an AD childhood- and/or adult-onset disease, to explore parents' sharing of infants' results with SDRs and TDRs and relatives' cascade testing. Using directed content analysis, we found that our data conceptually matched themes from the FCGR framework and identified only 1 new subtheme. Parents identified several family, disease, individual, and sociocultural factors that influence family genetic risk communication. Additionally, parents described their communication strategies when initiating risk communication, which included an informal, incremental sharing approach. Finally, parents reported communication occurrence and outcomes of risk communication, which included over half of SDRs and TDRs ($n = 55$, 55%) being informed of their risk but only 5 (5%) of those seeking cascade testing.

Our findings on cascade communication align with previous studies, which show that communication of genetic risk to more distant relatives occurs less often than to FDRs, although the BabySeq protocol included the return of results and reverse cascade testing for parents. Stoffel et al[33] found that 98% of probands tested for Lynch syndrome disclosed their genetic results to an FDR, whereas only 67% disclosed to SDRs or TDRs. Findings from other studies examining family communication of long QT syndrome and inherited cardiac conditions have shown similar communication patterns.[34,35] We found that the majority of probands' siblings (ie, FDRs) had not yet had cascade testing, although parents were aware of their risk. For some parents, this was due to COVID-19-related disruptions in accessing health care or parental hesitation to expose siblings to health care settings where COVID-19 could be prevalent. Other parents had not yet had the proband's siblings tested but were considering testing in the future. Taken together, these findings demonstrate that reverse cascade testing uptake can be low. Our cascade testing findings align with a recent UK-based study, investigating the uptake of cascade testing after ES for critically ill children, showing that, although the majority of parents ($n = 30/34$, 88%) were provided risk counseling, only 3 (9%) sought cascade testing.[36] However, Cernat et al[12] showed that reverse cascade testing uptake is variable across conditions and is much higher in some studies. Future studies could explore reasons for this variability and interventions effective in maximizing reverse cascade testing.

Our findings related to disease factors influential to risk communication are noteworthy. Parents who had not developed symptoms associated with their positive cascade testing results were less inclined to share findings with relatives. This finding differs from a previous study, which found that individuals without symptoms found it easier to communicate risk to relatives.[37] Parents in our study also reported that disease severity motivated them to share genetic results with relatives, particularly when their infant had a variant associated with an adult-onset disease (*BRCA2* or *MSH2*). Previous quantitative studies have not found disease severity to affect risk communication[38,39]; therefore, further quantitative investigation could clarify whether the identification of a variant associated with an adult-onset disease is a significant factor in risk communication. Individuals with *BRCA1/2* or *MSH2* variants have an elevated risk of developing certain types of cancer[40]; therefore, enhanced screening and early intervention in these families is warranted. Genetic counseling strategies have the potential to increase proband-mediated risk communication in these families.[41] However, additional research is required to identify best practices for enhancing genetic risk disclosure, particularly in families with communication challenges, as well as among younger relatives, male relatives, and relatives in the paternal lineage, all groups that typically have lower rates of genetic testing.[41]

We identified 1 new subtheme under family influential factors—family member traits. This subtheme describes relatives' propensity to anxiety or concern after risk communication. Once a relative's risk is identified, an important factor for engagement in the diagnostic and treatment process is one's adaptive coping.[42] Providers may be especially skilled in supporting relatives' coping and maximizing follow-up engagement.[43] Interestingly, we found that, although 2 families utilized providers during risk conversations, parents in only 1 other family would have welcomed a provider; most families preferred to handle risk communication themselves. This finding aligns with a study exploring risk communication in families of children with familial hypercholesterolemia, in which the majority of parents preferred indirect contact.[44] Although data from non-US countries show that direct contact may be the most effective method of relative notification, our study confirmed what other studies have shown—indirect contact, although perhaps less effective, may be preferred by the proband or family.[14,15] At the same time, our findings highlight what still other studies have shown—that health care professionals may serve as facilitators to the uptake of cascade testing, alongside families, when welcomed.[15] Given the current US regulatory landscape, acceptable

provider-initiated strategies that are proven to promote family risk communication and cascade testing include sharing of information (ie, a family letter),[14,44] assistance in identifying at-risk relatives,[14,44] support in developing a dissemination plan,[44] and provider recommendation or referral to a genetic counselor/genetics clinic.[44]

Study findings should be interpreted within the context of study limitations. Parents self-reported on the receipt of their child's genetic results 2 years prior and relayed family sharing over this time period, which introduced the possibility of recall bias and did not capture relatives' cascade testing beyond this time frame. Also, we relied on parent proxy reports for relatives' follow-up testing behaviors, which may reduce data accuracy. Given that we considered all SDRs and TDRs of the proband in the lineage of the parent with positive cascade testing results to be at risk, the percentage of TDRs informed and tested could be deflated. Parents in our sample had high yearly incomes and education and few were from underrepresented groups, potentially affecting parent willingness to participate in both the first phase of the BabySeq Project and our subsequent interviews and possibly facilitating their comfort with communicating complex genetic information. Finally, parents in our sample expressed a preference to know genetic information, which reflects an openness to genetic information that may not be common in the general population. Future studies that explore perspectives of more diverse parent samples, in terms of demographics and views about genetics, are crucial to developing a more comprehensive view of family communication of genetic risk information and cascade testing in the pediatric setting.

Data Availability

Given the nature of qualitative data, the data are not available for public use. Deidentified, aggregated data are available upon request.

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Author Contributions

Conceptualization: M.K.U., I.A.H.; Data Curation: C.G.; Formal analysis: M.K.U., H.S.S.; Funding Acquisition: M.K.U., A.H.B.; Investigation: M.K.U.; Methodology: M.K.U.; Project Administration: M.K.U., C.G.; Validation: M.K.U., H.S.S.; Writing-original draft: M.K.U.; H.S.S.; Writing-review and editing: S.P., C.G., A.L.M., A.H.B., R.C.G., I.A.H.

Ethical Declaration

Approval to conduct this human subjects research was obtained by the Institutional Review Boards at Partners (now Mass General Brigham), Boston Children's Hospital, and Baylor College of Medicine. Verbal informed consent was obtained from all participants before being included in the study, as required by the Institutional Review Boards. Individual-level data were deidentified.

Conflict of Interest

Alan H. Beggs has received funding from the National Institutes of Health, Muscular Dystrophy Association (USA), Alexion Pharmaceuticals Inc, Audentes Therapeutics Inc, Dynacure SAS, and Pfizer Inc; has consulted and received compensation or honoraria from Audentes Therapeutics, Biogen, F. Hoffman-LaRoche AG, GLG Inc, Guidepoint Global LLC, and Kate Therapeutics Inc; and holds equity in Kinea Bio and Kate Therapeutics Inc. Robert C. Green is an advisor for AIA, SavvySherpa, Verily, and Wamberg Genomic Advisors and cofounder of Genome Medical, Inc. Amy L. McGuire is a consultant for Geisinger Research, the Greenwall Foundation, Morgridge Institute for Research, and Danaher Life Sciences. Hadley Stevens Smith has received consulting income from Illumina, Inc, unrelated to this work. All other authors declare no conflicts of interest.

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Additional Information

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