

Ethical Issues in Newborn Sequencing Research: The Case Study of BabySeq

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The BabySeq Project is a study funded by the National Institutes of Health and aimed at exploring the medical, behavioral, and economic impacts of integrating genomic sequencing into the care of both healthy newborns and newborns who are sick. Infants were randomly assigned to receive standard of care or standard of care plus sequencing. The protocol and consent specified that only childhood-onset conditions would be returned. When 1 child was found to carry a *BRCA2* mutation despite a negative family history, the research team experienced moral distress about nondisclosure and sought institutional review board permission to disclose. The protocol was then modified to require participants to agree to receive results for adult-onset-only conditions as a precondition to study enrollment. The BabySeq team asserted that their new protocol was in the child's best interest because having one's parents alive and well provides both an individual child benefit and a "family benefit." We begin with a short description of BabySeq and the controversy regarding predictive genetic testing of children for adult-onset conditions. We then examine the ethical problems with (1) the revised BabySeq protocol and (2) the concept of family benefit as a justification for the return of adult-onset-only conditions. We reject family benefit as a moral reason to expand genomic sequencing of children beyond conditions that present in childhood. We also argue that researchers should design their pediatric studies to avoid, when possible, identifying adult-onset-only genetic variants and that parents should not be offered the return of this information if discovered unless relevant for the child's current or imminent health.

In 2014, the *Eunice Kennedy Shriver* National Institute of Children Health and Human Development and the National Human Genome Research Institute funded a consortium of 4 grantees to study newborn sequencing in genomic medicine and public health.¹ One of the awarded projects was entitled The BabySeq Project (Genome Sequence-Based Screening for Childhood Risk and Newborn Illness), a collaboration between Brigham and Women's Hospital, Boston Children's Hospital and the Broad Institute at Harvard University, and Baylor College of Medicine. Its aim was "to explore the medical, behavioral, and economic

impacts of integrating genomic sequencing into the care of study families of both healthy and sick newborns"^{2,3} via a randomized clinical trial in which half of participants were randomly assigned to receive standard of care (family history and standard newborn screening) and half were randomly assigned to have standard of care plus genomic sequencing. For those in the sequencing arm, a newborn genomic screening report was generated, "which lists pathogenic or likely pathogenic variants in genes that have been strongly linked to childhood-onset diseases or diseases for which intervention is possible during

abstract



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childhood.”² For newborns with a specific clinical presentation that potentially had a genetic etiology, an indication-based analysis was performed.²

The study researchers sought to enroll 200 newborns and their parents into each cohort (healthy infants and infants admitted to the NICU), but despite 22 months of recruitment and approaching 3860 families, they were only able to recruit 268 infants (6.9%), 45 of 436 (10.3%) from the NICU and 223 of 3424 (6.5%) from the well-baby nursery.³ Overall, 159 infants were sequenced, 127 healthy infants and 32 infants in the NICU.⁴

In January 2019, Holm et al⁵ reported that a male infant enrolled from the cardiac ICU at Boston Children’s Hospital was identified with a *BRCA2* mutation despite a negative family history. The team wanted to return these results despite the facts that (1) the consent form clearly stated that only childhood-onset conditions would be returned,(2) the institutional review board (IRB) had approved the study knowing that only childhood-onset conditions would be returned, and (3) the study had obtained a US Food and Drug Administration nonsignificant risk determination on the basis of the plan to return only the results of conditions that could manifest in childhood.⁵ The team went back to the IRB and obtained permission to recontact the infant’s parents to offer the return of adult-onset-only findings. The parents consented and were told the results. Although either parent could have been the *BRCA2* carrier, when the findings were shared, the mother recalled some distant paternal relatives with breast and/or ovarian cancer, and she was referred to a familial cancer genetic risk clinic. The authors did not detail whether she went to the familial cancer genetic risk clinic or whether she was found to be the carrier, nor

did the authors detail the perceived benefit from the discovery.

Because of their moral distress, the researchers proposed to modify their protocol to offer the optional return of adult-onset-only genetic variants if both parents agreed. In response to the IRB’s concern that some parents might still not receive results under the revised protocol, the researchers modified the amendment to require participants to receive results for adult-onset-only conditions as a precondition to participate in the study.⁵ They explained that this “avoids the ethical dilemma of laboratory personnel knowing something that is widely considered to be actionable but cannot be returned.”⁵ They asserted that their new protocol was in the child’s best interest because “the best interest of the child includes not only the child’s future autonomy to make a decision about what the child wants to know about him- or herself, but also having his or her parents alive and well,”⁵ which they describe as “family benefit.” After a brief description of the debate regarding predictive genetic testing of children for adult-onset-only conditions in the clinical and research settings, we examine (1) the ethical challenges raised by the revised BabySeq protocol and (2) the ethical problems with the concept of family benefit.

BACKGROUND: PREDICTIVE GENETIC TESTING OF CHILDREN FOR ADULT-ONSET-ONLY CONDITIONS

There is a consensus within the pediatric, genetics, and ethics communities, in the United States and globally, that children should not be tested for adult-onset-only conditions.⁶⁻¹⁴ The arguments to support this position are as follows: (1) the information is not clinically relevant to the child, and so testing is “not medically indicated” and could create anxiety without any potential for intervention; and (2) it preserves

the child’s autonomy to decide as an adult whether to undergo testing.

Sequencing raises the possibility of discovering genetic information unrelated to the clinical question, known as “incidental” or “secondary” findings. Although the American College of Medical Genetics and Genomics (ACMG) issued a statement in 2012 that “patients should be given the option of not receiving certain or secondary findings,”¹⁵ new recommendations in 2013 mandated that “laboratories performing clinical sequencing seek and report mutations...in all subjects, irrespective of age...,”¹⁶ a form of opportunistic screening, despite acknowledging that there are “insufficient data on penetrance and clinical utility to fully support these recommendations.”¹⁷ The original list included 57 genes, which was quickly revised to 56 genes, and has now been increased to 59 genes (ACMG 59).¹⁷

Many ACMG members objected to these recommendations.¹⁸⁻²³ In response to the criticism that the new recommendations contradicted earlier policies about predictive genetic testing of children, the ACMG responded that the earlier policies were focused on children with “a known family history of risk, with the expectation that the child will be offered testing at an age when he or she can make an informed decision about testing,”²⁴ whereas opportunistic screening applied to unsuspecting families for whom the information may benefit the child and parents. However, in April 2014, in response to additional stakeholder feedback,²⁵ the ACMG modified its clinical recommendation to allow patients (and parents) to opt out of opportunistic screening and the return of the ACMG 59 results.²⁶

The ACMG guidelines were focused on the clinical setting, whereas BabySeq is a research protocol. Traditionally, research results were

not returned to participants. In 2002, several researchers began to argue for informing clinical trial participants about aggregate results,^{27,28} but many institutions had no policies on when, how, or what results should be returned.²⁹ The arguments in favor of returning results were both ethical (promoting trust and respecting participants as partners in research) and pragmatic (returning results could increase enrollment).

Within the decade, spurred on by public interest, the focus turned to returning individual participants' research results.^{30,31} A large body of scholarship addresses the return of these research results.^{32,33} The National Heart, Lung, and Blood Institute published 2 conference reports focused on reporting genetic results in research studies in which they concluded that participants should not be forced to receive results.^{34,35} Other reports were focused on the return of pediatric results.³⁶⁻³⁹ Members of the Return of Results committees of the Clinical Sequencing Exploratory Research Consortium and the Electronic Medical Records Network Consent, Education, Regulation, and Consultation Working Group, 2 national multicenter projects actively engaged in returning research results, specifically argued that parents should have a right to refuse secondary results in research involving children "unless the return of results is of high health significance to the minor in childhood."⁴⁰

ETHICAL CHALLENGES RAISED BY THE REVISED PROTOCOL

The original BabySeq protocol was focused on the return of childhood-onset conditions, but the research sequencing methods identified a *BRCA2* mutation, 1 of 3 genes classified as adult-onset-only in the ACMG 59 list.

What options did the team have to avoid this discovery? The BabySeq team could have devised an analytic pipeline to deliver only the information intended for the project, or it could have elected to sequence the whole genome or exome but not to interrogate the adult-onset-only regions unless there was substantial reason to suspect that they were pertinent to the child's immediate clinical care rather than to other research goals. International guidelines support a more targeted approach, limiting search to genes relevant to the primary indication when possible.^{41,42} Their failure to employ a more targeted approach created a situation that could have been avoided.

Although the parents in BabySeq were re-consented about whether to receive adult-only-onset information, the revised protocol going forward requires disclosure of all ACMG 59 results to all who undergo sequencing, even if the only person sequenced is a newborn and the results are adult-onset-only conditions. There is no opt-out policy, making the return of results in BabySeq more demanding than the ACMG recommendations, which were designed for the clinical setting, where providers have more stringent obligations to patients than researchers have to participants.^{26,43}

To be clear, participation in BabySeq is voluntary, and most parents (>90%) refuse. Given that sequencing is not standard of care, even for infants in the NICU, the 45 sets of parents who enrolled their NICU infants may have perceived the research protocol as a unique opportunity to learn about their child's condition and to obtain information that could help providers best treat their child. Under the revised protocol, parents may elect to enroll their ill children, although it may mean getting unwanted information that is not relevant to their child's current health status.

That is, the mandatory return of results in BabySeq restricts parental freedom to choose what research results they want to know because it requires the reporting of ACMG 59 results as a precondition of participation even though the mandatory return of genetic research results is not consistent with many of the sequencing guidelines and consensus statements in the United States and globally.³⁸⁻⁴²

In this case, however, a cancer risk variant was identified, and even if it were avoidable, the team was left in the position to decide what to do with the information. A major driver for the mandatory return of results by BabySeq was the moral distress of providers and laboratorians, a not-uncommon emotion when providers and families disagree about what is in a patient's best interest or when patients refuse life-saving interventions.⁴⁴ In the clinical genetics context, providers may experience moral distress when patients refuse actionable genetic testing, fail to obtain appropriate surveillance, or refuse to share actionable genetic information with family. In contrast, in the research setting, providers are often more limited as to what they can offer, do, and say, given protocol restrictions. The providers' distress does not (or at least should not) trump the participants' interests or preferences, particularly if agreed to beforehand in the consent process.

In the case of children, providers and researchers do not get to impose on families their view of what is best. Clinicians could conceivably seek a court order to override parental refusals to obtain genetic testing of children for adult-onset-only disorders, asserting that the parents' actions constituted medical neglect, but they would almost surely fail. Although providers may argue that a particular genetic test is in a child's best interest, the courts will intervene only if the parents' acts are abusive or

neglectful.^{45,46} Courts would not require clinical genetic testing of a young child for a condition that presents in adulthood when no intervention or surveillance is needed in childhood, even in a high-risk family, because the variant does not pose an imminent threat to the child.

The argument that there is an obligation to identify and then report genes associated with adult-onset-only conditions is even more misguided in families of children who are critically ill. In these cases, sequencing is performed in an effort to improve the particular infant's care. Notably, other investigators who have explored the role of sequencing in these infants have specifically chosen not to look for secondary findings.^{47,48} Saunders et al⁴⁷ published a methodology for rapid whole-genome sequencing in the NICU that masked many potential findings for expediency because the aim was to provide information that could inform emergent decision-making. Similarly, in 2016, Smith et al⁴⁸ stated that:

*Only confirmed causative sequence changes that explain the observed phenotype are communicated to the parents by the treating physician and/or a certified genetic counselor. Because the primary analysis is directed toward the neonate with specific clinical findings, we do not evaluate for or report any of the 56 genes identified by the American College of Medical Genetics as reportable incidental findings, unless directly related to the underlying clinical presentation.*⁴⁸

In the case that triggered the protocol change in BabySeq, the child died without leaving the hospital. Knowledge about late-onset conditions were a moot point for the child. If we want to know about parents' risks, we should test them.

One objection to masking is that some genes have >1 function and excluding those associated with adult-onset-only conditions could hide the cause of the child's health problems. Consider, for example, the

case of an infant who carries 2 pathogenic variants of *BRCA2*. *BRCA* causes adult-onset-only breast cancer in the heterozygous state but can cause Fanconi anemia in the homozygous state.^{49,50} Masking the *BRCA* gene could lead to a failure to identify this health risk in a child. However, Alter et al⁵¹ note the following:

*The small group of patients with biallelic mutations in BRCA2 is distinctive in the severity of the phenotype, and early onset and high rates of leukemia and specific solid tumors, and may comprise an extreme variant of Fanconi anemia. Several of the alleles were not associated with cancer in presumed carriers, and thus counseling presents more uncertainties than usual.*⁵¹

That is, children with this form of Fanconi anemia will present with phenotypic findings that would justify *BRCA* genetic testing for diagnostic purposes. Even those who value the identification of both parents as *BRCA* carriers must pause, however, given that several of the variants were not associated with increased cancer risks and reporting back the results might lead to unnecessary screening and interventions. Harms from masking are rare and are outweighed by the benefits of focusing resources on the child's immediate needs.

PROBLEMS WITH THE CONCEPT OF FAMILY BENEFIT

In its original recommendation to provide opportunistic screening, the ACMG stated that "after sequencing a child for a primary indication, it becomes relatively easy for a laboratory to report a limited number of variants for conditions that could be medically important to that child's future or to the rest of the family."¹⁶ The ACMG argued that the risks to the child "were outweighed by the potential benefits to the future health of the child and the child's parents of discovering an incidental finding for which intervention might be possible."¹⁶ The real focus was to provide risk information to the

parents who might not otherwise be aware of their own risks, which could lead to preventive or therapeutic interventions that indirectly benefit the child. That is, opportunistic screening offers family benefit.

The ACMG has been arguing for the concept of family benefit at least since coauthoring, with the Health Resources and Services Administration, *Newborn Screening: Toward a Uniform Screening Panel and System* in 2006:

*Historically, screening has focused on conditions for which the improvement in outcome for the infant has been substantial. However...the nature of genetic disease is such that knowledge of its presence can be of value to other family members. Previously, this factor has not been considered by newborn screening programs.*⁵²

Natowicz⁵³ criticized the task force for including "a calculation of the benefits to the family and to society of early intervention—not just the benefit for the baby" because "it shifts the emphasis of newborn screening away from the medical interest of the child alone." Others objected to the fact that family benefit was rated to be as important as clinical treatability when deciding what conditions to include in a uniform screening panel.⁵⁴

Wilfond et al⁵⁵ offered 2 arguments in support of family benefit. One benefit is derivative: by identifying an actionable adult-onset risk, the child benefits because prevention and treatment can promote the parent's health, which enables the parent to care for the child. The other benefit is independent of a direct benefit to the child. It supports respecting the authority of parents to balance the competing interests of family members without state intervention unless their decision falls below a threshold that constitutes abuse and/or neglect.

Wilfond et al⁵⁵ examined the primary objections to testing children for adult-onset-only conditions: (1) the

potential to cause adverse psychological impact and (2) depriving the child of a right to an open future. They argued that these objections failed because (1) the data fail to reveal evidence of significant harm⁵⁶ and (2) respect for parental authority to raise their children according to their own values means respecting parental decisions that foreclose options for their children and shape the direction of their children's lives.⁵⁵

The arguments by Wilfond et al⁵⁵ are flawed, in part, because they are focused on the wrong people. Although families may consider the interests of other family members in their decision-making for a child,^{57,58} the primary focus of health care providers must be the child's well-being.⁵⁹⁻⁶¹ To focus otherwise is to treat the children as means for the ends of others (their parents).⁶² If we want to reduce morbidity and mortality of adults, we can test adults. Interrogation of the areas of the genome that identify adult-onset-only conditions takes additional work and resources by the laboratorians and additional work on the clinicians and researchers in counseling families and providing follow-up evaluation and care. These results are not as easy to interpret and return as they are often made out to be, and they take large amounts of resources that may detract from the research aims. The parents in BabySeq were not demanding these results and had consented to participate without expecting to receive adult-onset-only results. Given the low participation rate in BabySeq, it will be important to see whether the policy change will decrease enrollment.

Second, even if the secondary findings are valid, parental benefits are not ensured unless participants understand their need for follow-up and can afford the necessary testing and treatments. BabySeq is not designed to support the mother beyond making a referral, which she

would attend, presumably, at her own expense. Even if the mother were found to be a carrier, how much more of a risk she actually faces compared with other women who are premenopausal is unknown given that the high pathogenicity of the mutations in the ACMG 59 is based on studies in which high-risk families were enrolled. The meaning of these variants in a woman with a less compelling family history has not been adequately studied. Claims of high risk may be premature or even wrong,^{57,58,63-65} particularly for minorities who are usually underrepresented in genetics research.⁶⁶⁻⁶⁹ In any event, even if she is at high risk, she could not be required to pursue follow-up because it has been decades since the law has required women to undergo even life-saving medical treatment so that they can care for their children.⁷⁰

Third, both the ACMG and Wilfond et al⁵⁵ acknowledge that data about short- and long-term risks and harms (as well as benefits) of returning genetic information about adult-onset-only conditions are scant. They assume that identifying variants alone is a positive outcome before data are obtained on the psychological and health outcomes, and they ignore the risks, which include unnecessary testing due to false-positives or incomplete penetrance, as well as stigma, discrimination, and anxiety. At minimum, the returning of research results that have no immediate clinical indications for the child should be voluntary and not mandatory.

Fourth, although Wilfond et al⁵⁵ believe that the data are sufficiently equivocal that pediatricians should be neutral in counseling parents about requesting secondary findings, we argue that pediatricians should take a directive stance in opposition. A neutral position suggests not only that there is equipoise about the benefits and risks but also that the

offer is morally neutral, which it is not. All pediatric professional statements argue against predictive genetic testing of children for adult-onset conditions to respect the child's interests to decide for or against testing as an adult.⁶⁻¹⁴ As such, the provider should counsel against such testing, even if the provider may accede to the parental demands.

Rather than requiring testing and reporting results of adult-onset genetic disorders in children on the basis of benefit to others in the family, providers and researchers should oppose testing and reporting of results even if parents can insist on getting them. Pediatric providers are moral agents and should counsel directly against predictive testing and reporting of results for adult-onset-only conditions in children in both the clinical and research settings, as Carl Elliott explains:

Finally, it is important to realize that the doctor is not a mere instrument of the patient's wishes...[but] is also a moral agent who should be held accountable for his actions. If a patient undergoes a harmful procedure, the moral responsibility for that action does not belong to the patient alone; it is shared by the doctor who performs it. Thus a doctor is in the position of deciding not simply whether a subject's choice is reasonable or morally justifiable, but whether he is morally justified in helping the subject accomplish it.⁷¹

THE CONTROVERSY SURROUNDING THE DISCLOSURE OF SECONDARY FINDINGS

Requiring that all parents who authorize sequencing of their child be informed about adult-onset-only conditions included in the ACMG 59 assumes that the benefits of opportunistic screening outweigh the risks and harms, which has not been proven.^{72,73} In fact, those sections of the genome associated with adult-onset-only conditions should not be analyzed at all unless pertinent to that child's immediate medical care. Although we believe that there is much to be learned from BabySeq and the other newborn sequencing in

genomic medicine and public health projects, the researchers should not intentionally search for adult-onset-only conditions.

Even if secondary findings are not intentionally sought, cases may occur in which known variants for later-onset conditions are identified: expect the unexpected.⁷⁴ We believe that studies should be designed to minimize the risk of identifying genes associated with adult-onset-only conditions. We believe that a policy of nondisclosure of adult-onset-only conditions is ideal, even when such genes are identified incidentally. This needs to be explained in the consent process so that parents do not expect otherwise. We support this position out of respect for the child's future autonomy as an adult to decide what genetic information he or she wants and with whom he or she wants to share it.

We realize that there are those who disagree (who support disclosure of all ACMG high-risk alleles and other actionable secondary findings^{55,75,76}). At minimum, all participants and their surrogates should have the right to refuse learning about all research findings, even if researchers will feel distressed about knowing information that they believe is useful and actionable. The strongest case for mandatory disclosure is when researchers identify childhood-onset conditions for which early treatment would have health benefits for the child. If such information will be disclosed regardless of parental preferences, parents must understand this before consenting to sequencing so that they can make an informed decision about whether to enroll their child.

Parents may assert an interest in "knowing everything" and may experience significant distress and anger that some of their child's results, particularly in the context of research, are withheld from them.^{28,30} Clearly, researchers need to educate

parents that everything is not and cannot be returned and that research teams do not interrogate or disclose every variant of unknown significance because of time, cost, and the sheer size of the genome (6 billion bp). Nor are researchers under any obligation to interrogate the genome fully, but, again, this must be made clear in the consent process. However, participants may be able to request and obtain their raw data under the Health Information Portability and Accountability Act to seek additional analyses not provided by the researchers.^{32,77}

How secondary research findings will be handled needs to be addressed upfront through a robust and transparent consent process. Additional psychosocial and clinical data about the benefits and harms that accrue from the return of results should be collected to inform future policy discussions.

ABBREVIATIONS

ACMG: American College of Medical Genetics and Genomics
IRB: institutional review board

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