Challenging the Current Recommendations for Carrier Testing in Children

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abstract

The authors of current professional guidelines generally do not support the return of information about genetic carrier status for infants and children because of a perceived lack of immediate benefit and an abundance of caution regarding potential harm and desire to protect the children's future autonomy. The advent of genomic sequencing, used either as a diagnostic or a screening tool, and the increasing use of this technology in childhood creates the potential for the identification of carrier status in the pediatric period. As part of the BabySeq Project, researchers are exploring the implications of genomic sequencing in both newborns who are healthy and newborns who are sick and developing policies and procedures for the return of carrier status information to the parents and physicians of newborns. In this commentary, we review the history of carrier testing in children and explore the potential benefits, risks, and challenges of returning such results both for the children, their parents, and potential future siblings.

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Over the years, the authors of professional guidelines have generally not supported performing carrier testing in children. In statements, the American Academy of Pediatrics (AAP), the American College of Medical Genetics and Genomics (ACMG),[1] and the American Society of Human Genetics (ASHG)[2] all assert that carrier testing should be not be conducted in children. Exceptions are limited to when carrier status is medically relevant during childhood or when a minor is pregnant or considering reproduction. Outside of these scenarios, the ACMG, AAP, and ASHG emphasize protecting children's future autonomy to decide on carrier testing once they reach the age of majority because there are believed to be no health benefits to justify testing for carrier status in childhood. In their recommendations, the AAP, ACMG, and ASHG specifically address the scenario in which targeted carrier testing is performed and is not used to address the potential for carrier status information to be identified through broader testing, such as genomic sequencing (GS). However, in its "Points to Consider" statement, the ASHG acknowledges that there may be benefits of disclosing carrier-status testing results from newborn screening (NBS), and the authors recommend "additional research to assess the utility of disclosing carrier results generated from NBS for reproductive decision-making and cascade testing."[2] Given that there are those who envision newborn genomic sequencing (nGS) becoming a common medical scenario in the future, even potentially as a component of NBS, research in which the return of carrier status in nGS is explored is particularly timely.[3–5]

Researchers in the BabySeq Project address this ASHG recommendation directly by providing research insights into the potential utility and challenges of returning carrier results identified through nGS. The BabySeq Project is 1 of 4 Newborn Sequencing in Genomic Medicine and Public Health consortium projects funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the National Human Genome Research Institute at the National Institutes of Health to explore "opportunities to use genomic information for broadening our understanding of diseases identified in the newborn period."[6] The BabySeq Project is a randomized trial aimed at assessing the medical, behavioral, and economic impacts of nGS. Half of the enrolled infants are randomly assigned to undergo nGS. Potentially returnable results from nGS are evaluated by the study team according to a specific framework.[7] Genes and variants are assessed on the basis of 3 criteria: (1) the association of the gene with a disease, (2) the pathogenicity of the variant, and (3) the age-related penetrance of the condition. When a variant occurs in a gene with a strong disease-risk association, is likely pathogenic or pathogenic, and is highly penetrant, it is reportable. The disease risks being returned are limited to childhood-onset disorders and highly actionable adult-onset conditions in accordance with the ACMG criteria for the return of secondary findings.[8,9] The same criteria are used to assess all variants regardless of the inheritance pattern of the associated disease. Thus, we return results that reveal a risk for dominant and recessive conditions as well as carrier status for recessive conditions. Once the results are finalized, the family takes part in a results disclosure session with a genetic counselor and study physician to review the identified disease risk and recessive carrier status. To date, we have enrolled >300 newborns and their families in the BabySeq Project and have returned carrier-status variants to >100 families who were randomly assigned to receive nGS.

Although carrier status is detected through a relatively new technology (GS) in the BabySeq Project, the identification of carrier status in newborns is not novel; it has occurred in the context of standard NBS for decades, since the introduction of screening for hemoglobinopathies in the late 1960s and cystic fibrosis in the early 1980s.[10,11] The ACMG and AAP acknowledge the generally accepted consensus that if carrier status information identified via NBS is returned, it should be returned to parents because they are deemed the best surrogates to receive their children's genetic information. Similar to NBS, participants undergoing nGS in the BabySeq Project are infants; hence, the results are returned to the parents and pediatricians as the best available proxies for the infants. Therefore, the provision of carrier information to families in the BabySeq Project is similar to standard NBS in that the identification of carrier status is a secondary result of searching for primary disease risk.

Clearly, the potential for detecting carrier status is much greater with nGS than with traditional NBS. Although most conditions on state NBS panels are inherited in an autosomal recessive manner, only a few of the screening assays are able to detect carrier status. In nGS, on the other hand, there are hundreds to thousands of genes associated with recessive conditions being analyzed, all of which confer carrier status in the heterozygous state. Given that, on average, an individual carries 2 recessive variants,[12] we expected that most infants undergoing nGS as part of the BabySeq Project would have at least 1 carrier-status variant, and in fact, we have identified an average of 2 carrier-status variants (range 0–7) among the infants whose results have been returned to date, with >90% of infants having at least 1 carrier-status variant. Hence, the identification of carrier status is extremely common to the point that

it should be anticipated in anyone undergoing nGS.

POTENTIAL BENEFITS OF RETURNING CARRIER STATUS IN NEWBORNS

Although in current statements, professional societies recommend against the return of carrier results in children, they also cite the potential benefits of returning such results in childhood.[1,2] On the basis of our experiences in the BabySeq Project, we suggest that these benefits are enhanced when carrier status is returned to the parents of newborns. These parents are typically still in their reproductive years, providing potential benefit to 2 generations. Returning their newborns' carrier status allows parents time to process and understand the information in the context of their families and family planning. Parents can learn more about the condition their children are carriers for and, perhaps for the first time in their lives, carefully consider whether they feel that the risk of having future children who are affected with that condition is significant enough to seek further screening to clarify their reproductive risk. Given that nGS is used to identify carrier status for many more recessive conditions than even the most expanded carrier screening panels offered by prenatal providers, this time to learn more about lesser-known conditions is crucial. Previous studies have revealed that carriers who have children who are affected experience more guilt and self-blame than carriers who do not have children who are affected.[13] Thus, the identification of carrier status in infants who are unaffected, and subsequent cascade parental testing, could reduce psychosocial harm for families in which both parents are in fact carriers for the same condition.

Although it is too early at this time to comment on the direct benefits to the infants in the BabySeq Project, it is not hard to imagine the potential benefits that may come from carrier status being identified early in their lives. Because their parents and pediatricians will both know which conditions the children are carriers for, these children can learn about their carrier status at developmentally appropriate times and may accept and integrate this information into their lives over time. Given the fact that for some conditions, carriers may manifest mild features,[14–16] knowing the children's carrier status may also provide direct clinical benefits to the children. Furthermore, understanding this information before they enter their own reproductive years allows for premeditation of reproductive risk, which is a significant benefit for which prenatal carrier screening (which is most often initiated during a pregnancy) can fall short. Preconception screening options are becoming increasingly available to address this concern, but benefits of this testing will be limited to the fraction of couples who plan a pregnancy in advance, and access may be further restricted depending on insurance companies' coverage of testing.

One finding of the BabySeq Project is that parents identified learning carrier-status results as a benefit of their infants undergoing nGS. On the baseline survey completed before random assignment, parents frequently reported family planning as a perceived benefit of receiving nGS for their infants. Preliminary results from the 10-month postdisclosure surveys revealed that 11% of families had already pursued follow-up visits or testing on the basis of the information they received. In 1 case, parents who pursued cascade testing discovered that they are both carriers for the same severe recessive condition, and they are now undergoing a preimplantation genetic diagnosis for their next pregnancy. Although these outcomes are early and limited, they reveal that there is a subset of families acting on these results in the context of their family planning.

POTENTIAL HARMS OF RETURNING CARRIER STATUS IN NEWBORNS

Historically, there has been substantial concern about returning carrier status because of the potential for misunderstanding genetic information. When sickle cell disease (SCD) screening laws were implemented in the 1970s, at the same time that hemoglobinopathies were being added to some state NBS panels, a lack of public and medical education led to carrier status being equated with disease risk. This misunderstanding led to discrimination of SCD carriers by employers and insurance companies.[17] However, changes in the nearly 5 decades since SCD was added to NBS include significant advancements in public knowledge of genetics and the implementation of legal protections against such discrimination. The Genetic Information Nondiscrimination Act of 2008 was targeted specifically at protecting people with genetic risk, who were identified from genetic testing or family history, from discrimination by health insurers and employers. Although the Genetic Information Nondiscrimination Act does not include protections for all types of insurance, this advancement in legal protections was crucial for broadening the acceptance of genetic testing and screening.

Although the possibility of misconstruing genetic information will always exist, members of the BabySeq Project have endeavored to create a model for appropriate education when returning results. The initial education on carrier status for the parents begins during the consent session, when a genetic counselor explains

autosomal recessive inheritance at an education-appropriate level and discusses the high likelihood of receiving carrier status results if their infants receive nGS. Subsequent education is provided by a genetic counselor and physician during the results disclosure session, which is focused specifically on the carrier-status variants found in the infants. An in-depth explanation of autosomal recessive inheritance, carrier frequency, and residual reproductive risk is provided for each carrier-status variant. Additionally, when no carrier-status results are identified in an infant, carrier risk for parents is still discussed because the sequencing was only done for the child. We also educate the infant's providers through a summary note that accompanies the nGS report sent to the provider. The combination of legal protections and thorough education, coupled with increasing uptake of genetic testing, will hopefully minimize any potential feelings of stigma associated with carrying a recessive condition.

CHALLENGES IN THE RETURN OF CARRIER STATUS IN NEWBORNS

Although advances in legal protections and our focus on education can help minimize the potential harms of returning carrier status in infancy, challenges remain. A significant issue encountered in the BabySeq Project is how to handle carrier-status variants that also have a dominant adult-onset disease association, such as *BRCA2* or *MUTYH* mutations. In the case of a *BRCA2* mutation, which can impart both carrier status for Fanconi anemia and dominant adult-onset risk of cancers,[18] the complexity is lessened because parents are also consented for the return of risk for highly actionable adult-onset conditions, including pathogenic *BRCA1* and *BRCA2* variants. However, for genes such as *MUTYH*, for which the heterozygous adult-onset disease risk does not meet our penetrance criteria for reporting, only the associated carrier status is being reported. Although this solution was necessitated by our decision and supported by the institutional review board to return only adult-onset conditions that are highly actionable, a partial disclosure of risk is not what most participating families expect from the study and may be perceived as unacceptable.

The methodology of sequencing itself poses challenges in results interpretation by both professionals and parents. Because next-generation sequencing is not adequate for detecting structural variants or trinucleotide repeat expansions, it cannot be used to capture carrier-status variants for all conditions. This necessitates a thorough explanation of residual risk with parents to reduce the chance of negative sequencing being interpreted as a false-negative result for all recessive conditions. The high potential for variants of uncertain significance (VUS) to be identified through sequencing also creates challenges in what to call these variants. Risks in overcalling VUS could lead to parents pursuing in vitro fertilization with a preimplantation genetic diagnosis for a variant that may not actually lead to a disease. However, risks in undercalling VUS could lead to false reassurance and the potential to have an affected child. Although concerns about conveying test limitations and variant interpretation are not unique to considering sequencing in childhood, they warrant careful consideration.

An additional challenge that has arisen is the availability and cost of follow-up testing for parents. Because nGS in the BabySeq Project is performed in the newborn only, parents who wish to further clarify their risk for subsequent pregnancies need to pursue their own testing (so-called cascade testing). Given the expansive number of carrier-status variants that are identifiable on nGS, parents who desire to fully understand their risk of having a child with the recessive diseases that their infant is a carrier for may need to undergo sequencing of a number of genes (as many as 7 in some cases in the BabySeq Project) to determine their risk for future pregnancies. Currently, most commercial carrier testing includes panels of the most common recessive conditions or involves single-gene testing when there is a known recessive condition in the family. The need for multigene sequencing in which conditions that are rare are potentially targeted is not currently met by commercially available tests. This can put a burden on prenatal health care providers, who are trying to coordinate cascade testing, and on parents, who may find that their insurance carriers do not cover such atypical testing. Until the infrastructure for such follow-up exists, the potential benefits for the parents may not be easily accessible. Furthermore, the economics and cost/benefit ratios of such testing are not addressed here but will be major drivers leading to, or preventing, the availability of comprehensive testing in the future.

Ensuring appropriate communication of this information, both between health care professionals and families, presents an additional challenge. As mentioned, we cannot protect against the possibility of carrier status erroneously being copied from an nGS report into a clinician's record as disease risk, but we do focus on the clarity of our reports and accompanying letters to mitigate this risk. A more uncertain and uncontrollable communication question is if, and how, this information will be relayed to the infants when they grow up. It will likely be many years between the disclosure of carrier status from nGS to the time when parents are ready to inform their children. Given the long time frame, even the best intentions to pass the information

along may be lost. The further away parents are from learning the information themselves, the less confident they may be when explaining it to their children. This highlights the necessity of clearly documenting this information in the medical record and the onus we are placing on pediatricians. It also begs the questions of whose responsibility it is to ensure the disclosure of this information and how to ensure it occurs.

CONCLUSIONS

Current recommendations related to carrier testing in childhood will need to be adapted to account for variants detected by using newer testing methodologies. The integration of GS into pediatric care has created the opportunity for far more carrier-status variants to be detected at an earlier age than with targeted technologies aimed at risk assessment in reproductive planning. The use of GS in children and infants may be inevitable; Francis Collins, the former director of the National Human Genome Research Institute, has been quoted as saying, "Whether you like it or not, a complete sequencing of newborns is not far away."[3] In this context, the members of the BabySeq Project are providing an important platform for investigating how parents and providers receive carrier-status results for newborns. Preliminary findings reveal that parents have an interest in receiving this type of information, and some even integrate it into their own family planning. Although barriers remain, including scaling the necessary infrastructure for cascade testing, appropriate education, and integration into a child's life, the testing and counseling needed to support this is developing rapidly. Furthermore, although the risks of returning carrier status in childhood cited by professional organizations are notable, many are historically rooted and mitigated by current legislation and the increasing availability of genetic counseling. Rather than regarding carrier status as a byproduct of sequencing newborns for disease risk, we posit that carrier-status risk for minors who are sequenced should be regarded as a primary finding because of its potential to benefit multiple generations.

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ABBREVIATIONS

AAP: American Academy of Pediatrics
ACMG: American College of Medical Genetics and Genomics
ASHG: American Society of Human Genetics
GS: genomic sequencing
NBS: newborn screening
nGS: newborn genomic sequencing
SCD: sickle cell disease
VUS: variants of uncertain significance

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