

Disclosure of Incidental Findings From Next-Generation Sequencing in Pediatric Genomic Research

abstract



Next-generation sequencing technologies will likely be used with increasing frequency in pediatric research. One consequence will be the increased identification of individual genomic research findings that are incidental to the aims of the research. Although researchers and ethicists have raised theoretical concerns about incidental findings in the context of genetic research, next-generation sequencing will make this once largely hypothetical concern an increasing reality. Most commentators have begun to accept the notion that there is some duty to disclose individual genetic research results to research subjects; however, the scope of that duty remains unclear. These issues are especially complicated in the pediatric setting, where subjects cannot currently but typically will eventually be able to make their own medical decisions at the age of adulthood. This article discusses the management of incidental findings in the context of pediatric genomic research. We provide an overview of the current literature and propose a framework to manage incidental findings in this unique context, based on what we believe is a limited responsibility to disclose. We hope this will be a useful source of guidance for investigators, institutional review boards, and bioethicists that anticipates the complicated ethical issues raised by advances in genomic technology. *Pediatrics* 2013;131:564–571

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ABBREVIATIONS

IRB—institutional review board
NGS—next-generation sequencing

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Next-generation sequencing (NGS) technologies are being used with increasing frequency in pediatric research.¹ Compared with traditional “targeted” genetic analyses that focus on a limited portion of the human genome, NGS produces significantly larger quantities of data, increasing the potential for wide-ranging and clinically meaningful applications. The ability to generate whole exome and whole genome sequences gives investigators a powerful set of tools to pinpoint the location of both previously identified and novel disease-associated genetic variants.^{2,3} The use of samples and data from pediatric subjects has particular value for researchers who wish to address understudied issues in this population, which is especially important for the study of diseases that manifest only in childhood, as in the case of rare pediatric cancers.⁴

With the widespread adoption of these new tools comes an increased likelihood of encountering genetic information that is incidental (or secondary) to the specific aims of a given research protocol.⁵ This is not a new problem; researchers conducting imaging studies (eg, MRI and positron emission tomography scans^{6–8}) have struggled with this issue for some time. Although investigators and ethicists have raised theoretical concerns about incidental findings in the context of targeted genetic research, the adoption of NGS makes this once largely hypothetical issue a foreseeable and more common reality.^{9,10} When researchers sequence an individual’s exome or genome, it is not a question of whether they will generate clinically significant findings unrelated to the research aims, but how many. At present, there is no consensus on how to approach the management of incidental findings in genomic research; institutional review boards (IRBs) lack experience with this issue and vary widely on the extent to which

they believe that researchers should disclose results to subjects.^{11,12}

This problem is particularly complicated with pediatric research participants because their status as minors requires a parent or legal guardian to be the primary decision maker. As these subjects grow older, however, they develop a more sophisticated understanding of their health and begin to form relevant values and preferences,¹³ and it becomes increasingly important to take these preferences into consideration as children reach adulthood; however, it is unclear how to respect these preferences in the context of incidental genomic research findings. Disclosing sensitive genetic information to children before adulthood has the potential to violate their future interests in controlling what information they want to learn about their health, precluding them from declining such testing in the future once they understand the implications of the information. This is especially important in cases in which there is no clinically relevant reason to test for adult-onset diseases while the subject is still a child. At the same time, a strict nondisclosure policy in pediatric research could deprive subjects (or their parents) of important health information that may be relevant to children before they reach adulthood.

Given the lack of consensus surrounding the management of incidental pediatric genomic research findings, our goal in this article was to present a defensible approach to grappling with this problem. Much existing guidance on incidental findings did not anticipate the advent of NGS and the ways in which it differs from targeted genetic studies,¹⁴ particularly in the pediatric context.¹⁵ We propose a set of guidelines on how to manage the disclosure of such findings in pediatric genomic research based on what we view as a limited responsibility to disclose

such findings, grounded in the principles of beneficence and a duty to warn. As pediatric research cohorts increase in number and size, the need for a widely applicable set of guidelines will increase. The framework described in this article applies primarily to researchers who are responsible for the collection of samples and data from participants, and who maintain ongoing links to (and sometimes ongoing relationships with) enrolled participants. Our aim is to help inform the practices of investigators, IRBs, and research institutions as they begin to encounter pediatric incidental findings in the course of genomic research, and to construct a framework for addressing future cases that are likely to arise.

AN EMERGING OBLIGATION TO DISCLOSE INCIDENTAL GENETIC RESEARCH FINDINGS

Although there are several ways in which the term “incidental findings” is used, we define it here as information generated as the result of research procedures that is unrelated to the aims of the study.¹⁶ There has been significant debate about investigators’ responsibility to return incidental findings to individual research participants in genomic research, and the existing literature provides conflicting guidance.^{17–20} Although there is no clear consensus on whether an ethical obligation exists, the trend in the literature seems to indicate growing acceptance of the notion that there is at least a limited duty to disclose.

Uncertainty about the principles underlying this obligation, however, is apparent in a range of proposals for managing incidental genetic research findings.^{21–24} For example, although there seem to be areas of consensus among researchers and subjects about the general criteria according to which incidental findings should be returned,

there are a variety of opinions about how to define the threshold for returning incidental findings. One proposal suggests that findings with a strong or possible net benefit should be disclosed,¹⁶ whereas others cite the goals of minimizing risks and maximizing benefits²² or establishing ways to distinguish levels of clinical significance²¹ as starting points for deciding what incidental findings are appropriate to disclose. Beskow and Burke²³ suggest that findings should be disclosed when they indicate the high probability of a serious condition for which effective intervention is readily available, whereas recent guidelines from the National Heart, Lung, and Blood Institute state that genetic research results should be offered to study participants if the finding is actionable with important health implications, the test is analytically valid, and the participant has consented to receive this information.²⁵ Taken together, the literature suggests an emerging consensus on a limited duty to disclose that is grounded in and influenced by a number of factors.

DISCLOSURE IN PEDIATRIC RESEARCH

Issues associated with the disclosure of incidental genetic research findings are further complicated when dealing with pediatric research participants. Although they have limited decisional capacity at the time they are enrolled in a study, their minority status is transient, and they can eventually make informed decisions about their health as they approach the age of majority. Parents have fairly wide discretion in what they tell their children and how they include their children in decisions about that child's health and health care; however, this discretion is not absolute. As children grow older, they develop a greater understanding about their health, and it becomes important

to consider their preferences independent of parental opinion.²⁶

There is no clear guidance about whether or when pediatric incidental genomic research findings should be disclosed to parents and/or to children once they are old enough to be able to make informed choices about whether to receive them themselves. However, clinical practice recommendations for diagnostic and predictive genetic testing in children in the clinical context provide some guidance. For example, joint guidance by the American Society for Human Genetics and the American College of Medical Genetics recommends that only genetic test results with clear and timely direct benefit to that child should be generated and disclosed to parents.²⁷ American Academy of Pediatrics guidelines state that genetic testing for adult-onset conditions should be deferred until adulthood, or at least until an adolescent has sufficient decision-making capabilities; and testing to predict late-onset disorders is "inappropriate when the genetic information has not been shown to reduce morbidity and mortality through interventions initiated in childhood."²⁸ Although questions about the management of incidental findings are not about genetic test results per se, but rather about information that has been generated in the course of genomic research, these clinical practice guidelines are nonetheless consistent with the idea that disclosing incidental findings that do not offer a clear and timely benefit, especially regarding late-onset disorders, is also inappropriate. This is pertinent because disclosure of sensitive research information to children removes the option of declining genetic testing when they reach the age of majority. Some diseases, such as Alzheimer or Huntington, will not typically manifest until well after the age of majority, and disclosure of such information could lead to psychosocial harms that a child would have to cope with for the rest of

his or her life.^{28–31} An individual could reasonably not want to know genetic results in certain circumstances, such as when there is only a slight probability of developing the disease or when there are no known treatments. Research suggests that as few as 15% of individuals with a Huntington disease-affected parent choose to learn their own disease status.³²

Parental and family interests also need to be taken into account in addition to the child's interests. Parents might have an interest in withholding certain kinds of incidental genomic research findings from a child that could have a negative effect on the family as a whole, such as a predisposition to a psychiatric illness.³³ On the other hand, some have argued that disclosure of incidental pediatric genomic research findings could have a positive effect on family relationships and coping; for example, by decreasing parental anxiety and allowing for future planning, even when these results reveal a future risk of illness that is neither immediate nor actionable.³⁴ Moreover, results that do not have immediate significance for a child may be highly relevant to a parent or family member, such as carrier status results that could aid reproductive decision making. Incidental findings that are beneficial for a parent or family member are not necessarily beneficial or even neutral for a child; it is an added challenge to balance the potential benefits to some family members against the possible harms and loss of autonomy for the affected child.

The desirability of receiving genetic information depends on the nature of the information as well as the conditions involved. Empirical data on the preferences of cancer research participants, for example, has shown that both adolescents and their parents are interested in receiving clinically relevant information related to their cancer

that are uncovered in research studies in which they are enrolled. One study demonstrated that both parents and adolescents believe there is never a good reason to avoid returning individual research findings, and that there is value in offering the information regardless of whether the news is good or bad.³⁵ Focus groups of research participants also show that both adolescents and parents feel that medically important information should be disclosed to parents and their children simultaneously. Even nonmedical information of a more private nature, such as high blood alcohol levels, was deemed by adolescents to be important for the researchers to disclose if severe enough to affect the child's health.³⁶

Although the desires of the subject and family in receiving incidental findings are important to take into account, parents may not be fully aware of the psychological and social risks associated with the receipt of genetic information. Studies of children in Australia who had undergone predictive genetic testing for adult-onset conditions reveal the complexity of emotions that such information can produce. These studies found that psychosocial harms are associated with both gene-positive and gene-negative tests and suggested that reactions to genetic information are difficult to anticipate.²⁹ Short-term anxiety was common, and was brought on by the testing process itself as well as familial disputes regarding the decision to be tested. Few subjects, however, ultimately regretted knowing this information^{30,37}; and both pediatric subjects and their families generally want to know the results of research, whether those results will positively or negatively affect their health status.³⁵ This evidence suggests that decisions about whether to disclose, or to receive, genetic information are complicated, involving both risks and potential benefits to children and their families; and it provides some support for disclosure of

incidental findings from pediatric genomic research in at least some specific cases.

A FRAMEWORK FOR THE LIMITED DISCLOSURE OF INCIDENTAL FINDINGS

Building on existing models for disclosure of incidental findings, we propose a tiered approach for limited disclosure as a framework to be applied in the case of pediatric genomic research (Table 1). Our approach is grounded in concerns about depriving participants of information that could help avoid or prevent significant harm, aligned with the principles of beneficence and a duty to warn.^{16,22,25,38} It is also grounded in a desire to respect the child's developing autonomy, preserving the child's ability to exercise his or her right not to learn nonurgent genetic information as an adult. This limited disclosure framework rejects the claim that parents have right to know all information about their children, and instead attempts to balance the need to fulfill these ethical duties (beneficence, duty to warn, and respect for developing autonomy) to return select incidental findings without placing an undue burden on the researchers or the study as a whole.

Criteria for Clinical Utility and Severity

This limited disclosure framework suggests that investigators should, at a minimum, disclose incidental findings of genetic variants with known, urgent clinical significance for the children enrolled in the study. We propose the following criteria for evaluating whether a finding has "known, urgent clinical significance":

1. Knowledge of the finding must have a clear and direct benefit that could be lost if the disclosure was postponed until the child reaches the age of majority, such as information that could substantially alter medical decisions in the short term.

TABLE 1 Recommendations for a Limited Disclosure of Pediatric Incidental Findings

When do findings have known, urgent clinical significance?	Knowledge of the finding must have a clear and direct benefit that could be lost if the diagnosis was postponed until the age of majority, such as information that could substantially alter medical decisions in the short term. The potential benefit of knowing a genetic disorder exists must clearly outweigh the potential risks of anxiety and other psychosocial harms that could result from this knowledge. Genetic variants related to multifactorial conditions that also have strong environmental components, such as heart disease or diabetes, should be disclosed only if they indicate a substantial increase in risk.
Who will decide?	The decision to notify or not notify will be made by the study investigators, in consultation with relevant experts and the institutional review board, based on knowledge at the time of data analysis. A review committee, including expertise in clinical genetics, genetic counseling, biostatistics/bioinformatics, and ethics, may be employed to assist with these decisions.
Who is informed?	If possible, results should be disclosed, with consent, to: 1. the subject's pediatrician or 2. if the pediatrician is not available, the participant (or the parents, if the participant is a minor). If results are disclosed directly to the participant or his or her parents, efforts should be made to refer participants to local medical genetics professionals.

2. The potential benefit of knowing the information must clearly outweigh the potential risks of anxiety and other psychosocial harms that could result from this knowledge.
3. Genetic variants related to multifactorial conditions that also have strong environmental components, such as heart disease or diabetes, should be disclosed only if they indicate a substantial increase in risk.

These criteria provide a starting point for determining which variants should and should not be disclosed, as well as instances where disclosure is permissible but not obligatory. For example, the

discovery of a mutation at the *VHL* locus associated with Von Hippel-Lindau syndrome,³⁹ which could lead to the early detection and removal of tumors and prevent or minimize secondary deficits, such as hearing loss, vision loss, and neurologic symptoms, would likely meet the criteria for disclosure. Similarly, a finding in a pediatric subject of a germ-line mutation in the *ATM* gene, which has been linked to radiosensitivity, could lead to a decision to avoid future radiation treatments for that child and would also be potentially reportable.⁴⁰ These criteria would rule out disclosure of findings in a pediatric subject related to APOE4, Huntington disease, and other late-onset conditions with no available interventions known to improve health outcomes associated with the condition. Such findings would not helpfully alter medical decisions for affected children before their reaching the age of majority, yet could cause harm to those children and their families by providing distressing information in the absence of mechanisms to ameliorate the identified risks.^{41,42}

This limited disclosure framework describes a minimum obligation for disclosure of genomic research findings. In some cases, however, it is permissible, and perhaps desirable, to disclose research findings that go beyond this framework. (It may also be permissible not to disclose any results in some cases, such as when biobanks do not maintain identifiers that would enable researchers to re-contact participants.) For example, although a *BRCA1* variant in a pediatric research subject would not be immediately relevant to that child, it is a finding of potentially urgent significance to the parent from whom the variant was inherited, indicating a need to pursue further screening. Accordingly, although investigators would not be obliged to disclose such a result under the framework described above,

a decision to disclose it to a parent, with the intention of providing potential benefit to that parent (rather than the child), could nonetheless be ethically desirable. In this scenario, parents who receive *BRCA1* results may independently decide to disclose them to their children.⁴³ These decisions may be more common when the subject is a teenager who is determined by the parents to be mature enough to understand the information and its implications. This decision potentially pushes against concerns about the future autonomy of the child, providing a potential justification for overriding that future autonomy in favor of the parent's interests. In other instances, the investigator may have a more formal relationship with a child's parents as participants in genetic studies, which might indicate a higher level of obligation to additional members of the family based on this relationship.

Moreover, some variants, such as a *BRCA1* mutation, may be important to the child once he or she reaches adulthood. According to the framework we outlined previously, there is no duty to disclose such information for the child's benefit because it does not have immediate relevance to the child; however, it might nonetheless be ethically desirable for the researcher to ensure that the child can have access to this information once he or she becomes an adult. The researcher could disclose the information to the child's parents, who could then inform their child at an appropriate time in the future. Alternatively, the researcher could endeavor to disclose the information directly to the research subject once he or she reaches adulthood, although this entails a long-term commitment that may go well beyond the duration of the research itself.

The disclosure of recessive mutations continues to be an open area of debate. Although there is a clearer duty to return findings of direct clinical significance to

the participant, the significance of carrier status is less certain. Knowledge of carrier status may have an impact on reproductive decision making for the child; however, depending on his or her age, such decisions may not occur for many years. Carrier status information is likely to be more beneficial to the parents of an affected child, who may find the information useful in exploring their own future reproductive options. However, according to the framework described previously, the investigator's responsibility to disclose such information does not extend to information that is only beneficial to the parents. Disclosure of carrier status for purposes of facilitating future reproductive decision making does not advance the goal of identifying a clear net benefit for the child enrolled in a given study. It is also difficult to determine a threshold of prevalence that would rise to the level of urgency severe enough to warrant disclosure. Although we acknowledge the interest that parents may have in knowing carrier status, we believe that reproductive decision making does not meet the criteria for known, urgent clinical significance and is outside the scope of an investigator's limited duty to disclose. Again, it may be morally praiseworthy for investigators to decide to disclose this information to parents in some cases if the benefits of the information outweigh potential harms to the child associated with loss of autonomy.

How Should Subjects Be Informed?

Parents (and adolescents when appropriate) should be informed of the plan for disclosing incidental findings during the consent process. In addition, having a mechanism to contact pediatric participants when they reach the age of majority, especially for biobanks and other longitudinal studies, will ensure that they have an opportunity to

review and consent to the disclosure plan as adults. Ideally, a genetic counselor should be available to assist the researchers during both the consent and disclosure processes to ensure that research participants and their parents understand the implications of incidental research findings. In addition, to help ensure that information can be used in a way that improves clinical care/outcomes, incidental findings can also (or alternatively) be disclosed to the subject's pediatrician or pediatric specialist, with the permission of the parents or legal guardians, who can then be prepared to discuss the information with the participant. If results are disclosed directly to the participant (or his or her parents, if the participant is still a minor), efforts should be made to provide a referral to local medical genetics professionals.

DISCUSSION

The management and disclosure of incidental pediatric genomic research findings are increasingly pressing issues. Investigators are looking to IRBs and research ethics consultants for guidance,⁴⁴ yet disagreements persist about this complicated set of issues. As NGS becomes increasingly widespread, excessive IRB variation may lead to decisional inconsistencies.^{45,46} More uniform guidelines on how to address the disclosure of incidental findings can serve as a framework to guide IRB decisions, and additional investigation is needed to identify the most effective methodological approach to interrogating and interpreting data, the types of incidental findings being discovered, how decisions are being made on what is appropriate to disclose, and the impact of producing this information over time.

Although ethics consultants, investigators, and IRBs should avoid leaning on one-size-fits-all solutions regarding incidental genetic research findings,

especially given that our understanding of such findings is in a state of flux and will require constant updating, we have identified a core set of questions that should be addressed in all cases to determine an appropriate disclosure mechanism for a given context (Table 2). At a minimum, we recommend first that investigators engaging in NGS clearly define the threshold for disclosure both in protocols and consent forms. Simply stating that clinically significant and actionable findings will be returned is insufficient; the terms need to be explicitly defined, both to guide investigators' actions and to help manage parents' and adolescents' expectations about the kinds of information that will or will not be disclosed. Second, care must be taken to articulate clearly who will have responsibility for determining what information will be disclosed. Investigators can assume this responsibility for themselves, but we are increasingly seeing thoughtful proposals to convene deliberative bodies (composed, for example, of medical geneticists, bioethicists, genetic counselors, bioinformaticians) to help provide counsel about which results to offer for disclosure. Third, a clear plan must be outlined that provides for the responsible disclosure of information. It is an ethical requirement that the disclosure of genetic information be done by a clinical professional with the requisite training and experience, in a manner that helps the subject understand the implications of the finding and

positions them to seek a referral for appropriate follow-up care. Finally, realistic attention needs to be paid to the logistics and cost to researchers of a plan for managing incidental findings. The effort involved in re-identification, analysis, and interpretation of samples and reaching out to participants to deliver incidental results can be dramatically resource-intensive and could potentially draw away from funds dedicated to the conduct of research.²⁴ Researchers should not promise more than they can reasonably deliver.

These guidelines are intended to establish a baseline for the information investigators have an ethical obligation to provide to their pediatric research subjects. We recognize, however, that some investigators may wish to go beyond the limitations we have outlined. Investigators may be justified in going above and beyond these guidelines, such as in cases in which information may be of benefit to the parents of an affected child. Studies will differ in their design, subject population, resources, and infrastructure, all of which might reasonably have an impact on the extent of their obligation to disclose incidental findings. Researchers cannot rely solely on the precedent set by other studies; they will have to justify a realistic approach that works best for the specific characteristics of their own research.

Furthermore, procedures for returning incidental findings cannot be static. As genomic sequencing and analytic technology evolves, and barriers to finding and disclosing genetic findings are reduced, the ethically appropriate level of obligation is likely to change.³⁷ Recent efforts by Green and colleagues⁴⁷ have shown some promise in determining which genetic disorders are believed by experts to rise to a level of clinical significance that warrants disclosure. There were 4 candidate disorders affecting children that 100% of the medical geneticists surveyed agreed

TABLE 2 Core Requirements of an Appropriate Plan for Managing Incidental Genomic Research Findings

1. Define the threshold for disclosure.
2. Articulate who will have responsibility for determining what information will be disclosed.
3. Outline a plan for the responsible disclosure of information, including the involvement of professionals with relevant expertise.
4. Address logistics and cost to researchers of a plan for managing incidental findings.

should be disclosed: phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome, retinoblastoma, Von Hippel-Lindau, and Romano-Ward (long QT syndrome). However, the panel's variability regarding 78 other pediatric and adult genetic conditions underscores the difficulty of developing policies in a dynamic environment. Guidance needs to be flexible as more is learned about genetic associations, and better technology for analyzing genomic data becomes widely available. Procedures for returning incidental findings will also have to be flexible, given that we do not yet fully understand the effect that disclosure will have on the participants and their families.

The proposed framework serves as a starting point for thinking about the kinds of incidental results that should be disclosed in the pediatric genomic research setting. Each of these determinations is dependent on the state of the medical literature and practice guidelines, clinical judgments about whether findings correlate with available phenotypic information about individuals and their family members,

and subjective determinations about the urgency and significance of each potential finding. Decisions about disclosure are still further complicated by general considerations that are beyond the scope of our analysis. In particular, scholars have raised concerns about potentially staggering costs associated with returning incidental findings.⁴⁸ An obligation to disclose incidental findings might require investigators to build from scratch the infrastructure necessary for analyzing genomic data, verifying possible findings, and returning information with sufficient support and counseling.⁴⁹ Although the availability of ongoing resources to support disclosure efforts needs to be acknowledged and explored further, we believe that cost alone is an insufficient reason for discounting disclosure of incidental findings when such disclosure is ethically required. As the research ethics field further delineates the contours of the duty to return incidental findings, investigators, research institutions, and funders will have to figure out who should have to bear the burden of this new obligation. In the meantime, we

have endeavored to construct an approach that reasonably constrains the obligation such that it is not so resource intensive that the research enterprise will be impaired.

It is important for pediatric researchers to think through the complicated ethical issues raised by advances in genomic technology prospectively, before embarking on research that incorporates these new developments. Current NGS methodologies are foreshadowing future ethical issues and therefore place the pediatric research community within a narrow window of opportunity to anticipate them. This article proposes a flexible strategy to address incidental findings that we hope will allow disclosure policies to keep pace with this rapidly emerging technology.

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