Points to Consider: Ethical, Legal, and Psychosocial Implications of Genetic Testing in Children and Adolescents

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In 1995, the American Society of Human Genetics (ASHG) and American College of Medical Genetics and Genomics (ACMG) jointly published a statement on genetic testing in children and adolescents. In the past 20 years, much has changed in the field of genetics, including the development of powerful new technologies, new data from genetic research on children and adolescents, and substantial clinical experience. This statement represents current opinion by the ASHG on the ethical, legal, and social issues concerning genetic testing in children. These recommendations are relevant to families, clinicians, and investigators. After a brief review of the 1995 statement and major changes in genetic technologies in recent years, this statement offers points to consider on a broad range of test technologies and their applications in clinical medicine and research. Recommendations are also made for record and communication issues in this domain and for professional education.

Introduction

In 1995, the American Society of Human Genetics (ASHG) and American College of Medical Genetics and Genomics (ACMG) published a joint statement titled "Points to Consider: Ethical, Legal, and Psychosocial Implications of Genetic Testing in Children and Adolescents."[1] This publication was influential in guiding clinicians and families during an era in which a number of new genetic tests, particularly predictive or predispositional testing, were being introduced into clinical medicine. Since 1995, clinicians have gained substantial experience with genetic testing in a number of clinical contexts, and research has improved the evidence on which professional recommendations can be developed. The ASHG determined that a new statement addressing genetic testing in children was timely, both because of the continuing evolution of genetic testing and because of the special considerations raised in the care of children. The purpose of this statement is to provide guidance on a variety of different genetic testing approaches for children in both the research and clinical contexts.

The ethical, legal, and social issues in genetic and genomic testing have been subject to special scrutiny for several reasons. First, for some heritable conditions, genetic testing can provide powerfully predictive information about the individual's future health status. Professionals, and society more broadly, have been concerned about the impacts of such predictive power on the psychological well-being of those found to be at increased risk, as well as concerns about stigma and discrimination. Second, genetic information about one individual provides presumptive information about other "blood" relatives. The family or kindred nature of genetic information poses ethical, legal, and social challenges for the appropriate management of that information in clinical and research contexts. Third, genetic and genomic information is complex, and health risks associated with this information are often probabilistic. This means that special care and expertise are important in ordering and interpreting many genetic tests. Finally, genetics has a troubled history, evident during the first half of the twentieth century, when genetic concepts were misunderstood and misused to the detriment of vulnerable groups in society. Genetic and genomic tests are not uniquely challenging with respect to ethical, legal, or psychosocial considerations, but these features justify careful thought and an element of caution as we assess the benefits and risks of these evolving technologies.

This statement is focused on the use of these technologies with children. Children also warrant special consideration for several reasons. Informed consent to genetic and genomic testing is a core principle for which there are few exceptions. Young children lack decision-making capacity, so decisions about testing must be conducted through surrogates, usually the parents, and must be done with the child's best interest at heart. The notion of "best interest" is intended to place the child's welfare foremost in medical decision making. However, given the

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subjective nature of the interests of those who cannot speak for themselves, defining an individual child's "best interest" is often complex and controversial, particularly in medical circumstances involving burdensome treatments and profound disabilities. Surrogate decision making is also an ethically freighted concept, because although parents are the appropriate surrogates for their children in almost all cases, controversies arise when parents make decisions that seem contrary to the best interest of their child.

As children age, they gain decision-making capacity and experience with health conditions. Therefore, including children to various degrees as they age in genetic- and genomic-testing decisions and responses is important but challenging. Finally, because children are young, decisions for them, and by them, might have implications for the course of their lives.

As genetic and genomic tests become more accurate and their use becomes more common, these ethical, legal, and psychosocial challenges will become more familiar and less worthy of statements of this sort. In many contexts, genetic and genomic tests are no different than other forms of testing. But in the contexts outlined below, the ASHG believes that these recommendations will assist families, clinicians, investigators, and policy makers in maximizing the benefits offered by these evolving forms of genetic and genomic testing.

A Summary of the 1995 ASHG Report

In 1995, the ASHG and ACMG issued a joint report that offered points to consider for genetic testing in children. The clinical context of that report focused on decisions about testing for single-gene disorders in response to either a family history or within-population screening programs. The social context of that report included limited data about the psychosocial impact of such testing in children. The ASHG and ACMG recommended that clinicians and parents consider timely medical benefits related to diagnosis, prognosis, and interventions as the best justification for testing in the child. Additionally, the report recommended that the potential psychological benefits to adolescents who request such testing also be considered. The report suggested that in the absence of timely medical benefits to the child, or the expressed wishes of adolescents, testing should be deferred until adulthood, particularly for adult-onset conditions or for carrier status for reproductive decision making. However, the report acknowledged that there was limited information about the benefits and risks of genetic testing in children. The report recommended deferral of testing in the face of this uncertainty, yet it also recommended deference to parents in some circumstances. The report has been influential in encouraging caution and reflection regarding testing children but often has been over-interpreted as a stricter prohibition of predictive testing in children for adult-onset conditions than was intended.

Recent Changes in Genetic and Genomic Technologies

Cytogenetics and molecular diagnostics have both undergone several revolutions since the fields began in 1959 and in 1976, respectively.[2,3] Cytogenetics started with chromosome analysis and matured with increasingly detailed banding and then fluorescence in situ hybridization. Most recently, the field has seen the introduction of chromosomal microarray analysis (CMA) for deletions and duplications (formerly done by cytogenetics). Molecular diagnostics has transitioned from hybridization-based techniques to Sanger sequencing with the increasingly common utilization of next-generation-sequencing-based techniques. In both fields, the increased coverage and increased resolution of the current technologies confer high analytic validity, but both platforms create problems with interpretation. First, a significant challenge is the difficulty in distinguishing between pathogenic variants and rare polymorphisms, resulting in the identification of "variants of uncertain significance." Second, there are difficulties in interpreting variants and copy-number alterations whose significance is incompletely understood because of reduced penetrance or a lack of sufficient data on clinical associations. Third, these technologies result in the identification of variants unrelated to the indication for testing (secondary or incidental findings). These challenges arise from our evolving understanding of the fine structure and variation in the human genome. At the present time, the contrast between our ability to identify genetic variants and our ability to fully interpret the information gives rise to many of the ethical issues in this domain.

Predictive Genetic Testing in High-Risk Families

In the 20 years since the first ASHG-ACMG pediatric-testing statement, there has been a modest volume of clinical research about the impact of predictive testing in high-risk families. To date, this limited research has not found evidence of significant psychosocial harms in children.[4] Perhaps the most significant finding is that, even without testing, children and many families create narratives about a child's genetic status. That is, some families simply assume that their children are destined to have, or not have, the familial condition. Further, the baseline uncertainty about risk status can cause psychosocial distress in the absence of genetic testing. Over the last two decades, there has been a general shift toward greater parental discretion in the face of clinical uncertainty about the best interests of the child.[5] This broad shift is not exclusive to genetics but has implications for genetic testing.

As parents consider the best course of action regarding genetic testing of their children, it remains important for parents to be aware that informed adults make a range of choices about predictive and reproductive testing, and thus many adults decline such testing. Deferring testing to adulthood allows children the opportunity to make their own decisions. This is especially important for the small subset of conditions where a minority of at-risk adults opt

for genetic testing, such as for Huntington disease. Approaching parents (and children, when appropriate) with respectful but directive recommendations, along with acknowledging flexibility, might be an effective approach to forging a therapeutic alliance with families. Encouraging families to consider such decisions over a period of time might convince some families that testing will be helpful in their particular context, or it might become clear that it will be most appropriate to defer testing until adulthood. The ASHG offers the following recommendations:

- Unless there is a clinical intervention appropriate in childhood, parents should be encouraged to defer predictive or pre-dispositional testing for adult-onset conditions until adulthood or at least until the child is an older adolescent who can participate in decision making in a relatively mature manner.
- Adolescents should be encouraged to defer predictive or pre-dispositional testing for adult-onset conditions until adulthood because of the complexity of the potential impact of the information at formative life stages.
- Providers should offer to explore the reasons why parents or adolescents are interested in predictive or pre-dispositional testing for adult-onset conditions. Providers can acknowledge that, in some cases, testing might be a reasonable decision, but decisions should follow thorough deliberation.

Adolescents should be provided the opportunity to discuss these issues without the presence of their parents, although parents should be involved in, and supportive of, any final decisions for testing. A referral to genetic counselors and mental-health professionals is appropriate if the clinician and family need additional support for decision making or in assessing the psychosocial dynamics.

- Facilitating predictive or pre-dispositional testing of children for adult-onset conditions can be justified in certain circumstances. For example, after careful deliberations with the family and older child, testing can be justified to alleviate substantial psychosocial distress or to facilitate specific life-planning decisions. The impact of predictive testing on children and families remains uncertain and therefore can be justified in specific cases when it is requested by families after informed deliberations and when the testing is not clearly inconsistent with the welfare of the child.
- Empirical research on the psychosocial impact of predictive or pre-dispositional testing in children is necessary for future policy recommendations. Genetic testing of children for adult-onset conditions in the research context can be ethically justified because of its social importance and when risks are minimized by appropriate counseling and support and when appropriate parental permission and child assent are obtained.

Genome-Scale Sequencing in Children

The technology to enable whole-exome sequencing and whole-genome sequencing has become more accurate, more efficient, and less expensive. For the purposes of this statement, we use the term "genome-scale sequencing" to mean either whole-genome or whole-exome sequencing. The cost of genome-scale sequencing is coming down progressively, and there is some confidence that "the $1,000 genome" will be achieved in the next few years. These cost estimates are for the generation of sequence data and do not include the clinical interpretation of the information. Given these technical improvements, genome-scale sequencing can be considered in a variety of clinical and research contexts. These include diagnostic testing, predictive testing for childhood-onset conditions, pharmacogenetic testing, and testing in children with cancer to inform diagnosis or therapy.

Genome-scale sequencing creates a tension between the need to generate a comprehensive analysis of an individual's genome to address a clinical challenge and the need to limit problems created by a wealth of data, including secondary findings and findings of uncertain clinical significance. Yet, the improving coverage, accuracy, sensitivity, and cost effectiveness of genome-scale sequencing will eventually equal that of testing a single gene or performing targeted gene panels, meaning that genome-scale sequencing might become an attractive choice for interrogating a single gene or targeted set of genes. The ASHG recognizes the current debate regarding the obligation, if any, to search for selected variants with high clinical validity and clinical utility when conducting genome-scale sequencing.[6] The ASHG makes an important distinction between using genome-scale sequencing as the method of choice for searching broadly for a diagnosis and choosing genome-scale sequencing with analysis restricted to a limited number of genes when a more targeted strategy is indicated. The recommendations below reflect ASHG's assessment that targeted tests, or selective sequence analysis, is usually preferable to less-discriminate data acquisition when the clinical challenge can be addressed through a targeted approach.

- When clinically indicated, the scope of genetic testing should be limited to single-gene analysis or targeted gene panels based on the clinical presentation of the patient.
- Targeted testing using genome-scale sequencing, but restricting analysis to a limited set of genes relevant to the clinical indication, is an acceptable alternative to a single-gene analysis or targeted gene panel in certain circumstances. When genome-scale sequencing is performed but the analysis is restricted to a limited set of targeted genes, ASHG finds it ethically acceptable for the laboratory to limit the analysis to the genes of clinical interest.
- ASHG recommends that, in the context of diagnostic testing for a child with a most likely genetic disorder, genome-scale sequencing is appropriate when prior,

more limited genetic testing failed to identify a causative mutation. Depending on the clinical presentation and on the quality and availability of appropriate targeted testing, comprehensive testing such as genome-scale sequencing might also be indicated in certain circumstances, even in the absence of prior, more limited genetic testing.

- At the present time, genome-scale sequencing is not indicated for screening in healthy children. Accordingly, genome-scale sequencing is not indicated for the purposes of clinical newborn screening at this time. In the research setting, genome-scale sequencing in newborns for screening purposes can be justified as part of carefully developed protocols for better understanding the potential benefits and risks of this technology in this context.

Secondary Findings

The move from targeted genetic testing to genome-scale sequencing has led to a vigorous debate about the ethics of managing massive amounts of individual-level genetic data.[7] (It should also be noted that although secondary findings are a significant problem for genomic medicine, they are by no means unique to this field; other disciplines, particularly radiology and pathology, have been grappling with similar concerns for decades. See, e.g., Berland et al.[8] and Orme et al.[9]) The generation of a patient's genomic sequence data radically increases the probability of discovering incidental or secondary findings.[10] For consistency, throughout this statement we use "secondary findings," defined as clinically relevant information unrelated to the condition for which the sequencing was originally ordered.

Secondary findings might have a clinical utility for a child or his or her family members. Therefore, there will be cases in which it is acceptable to return Clinical Laboratory Improvement Amendments (CLIA)-validated information derived from a child's sequence when such information has important clinical implications for the child or someone in the child's family.

Parents or guardians should have a clear understanding of when secondary findings might be generated and of the circumstances, if any, under which they can expect to be offered results. Children should be included in the informed-assent or -consent process to the extent that they are capable.

- ASHG recommends that clinicians offer to disclose secondary findings for a child to the child's parents or guardians only when the information has clear clinical utility for the child and/or his or her family members.
- In any clinical genomic endeavor that has a substantial likelihood of generating clinically relevant secondary findings, ASHG recommends that there should be a robust informed-consent process.
- If genome-scale sequencing is performed in somatic tissue, such as in tumor tissue in children with cancer, it is usually necessary to also conduct germline sequencing on the patient to adequately interpret the tumor sequence.[11] Therefore, ASHG recommends that the same considerations in the management of secondary findings be undertaken for both somatic-tissue sequencing and germline genome-scale sequencing.

Parents have wide decision-making authority, but in cases where the clinical response to a secondary finding will most likely prevent serious morbidity or mortality for the child, it can be appropriate to override a parental decision not to receive this information.

- ASHG recommends that, in general, parents should be able to decline to receive secondary findings in advance of genetic testing.
- However, when there is strong evidence that a secondary finding has urgent and serious implications for a child's health or welfare, and effective action can be taken to mitigate that threat, ASHG recommends that the clinician communicate those findings to parents or guardians regardless of the general preferences stated by the parents regarding secondary findings.

There is an ongoing debate about the extent to which researchers are obligated to disclose secondary findings to research participants. Research and clinical care have distinct characteristics, and the responsibility of a clinician necessarily differs from that of a researcher.[12] Clinicians have a primary obligation to act in the best interest of their patient; researchers must protect the welfare of subjects but are primarily charged with the production of generalizable knowledge. Although they are generally distinct, the line between research and clinical care is often blurry, particularly in the context of genomics.[13] Institutional review boards (IRBs), perhaps with expert consultation, are in the best position to determine whether and how to disclose secondary findings in a given research setting.

- When secondary findings are likely to be generated in the conduct of pediatric research, ASHG recommends that investigators develop and follow an IRB-approved plan to manage such findings.

Questions about whether there is a duty to look for secondary findings have been actively debated.[6] As analytic tools make searching for a limited list of high-value variants more efficient, the benefits of actively searching for such variants in the clinical context are likely to outweigh the costs and adverse consequences. However, more data, experience, and debate are necessary for defining the most ethically appropriate approach in the clinical pediatric context regarding an obligation to look for secondary findings. In the research context, the ethical responsibilities and risk-benefit considerations differ from the clinical

context. Therefore, actively searching for secondary findings in research involving genome-scale sequencing might be ethically acceptable in certain circumstances (with the informed consent of parents) but should not be considered ethically required at the present time.[7,14]

- In the clinical and research contexts, ASHG recommends that it be considered ethically acceptable, but not required, to search for secondary findings that are not relevant to the clinical or research indication for sequencing.

CMA

The transition from chromosome analysis by karyotype to the utilization of CMA has transformed genetic diagnostics.[15] CMA is now a standard diagnostic test for a wide variety of conditions, including developmental delay with and without dysmorphic features, autism spectrum disorders, and multiple congenital anomalies, in the pediatric population.[16] Use of these arrays has increased the utility of cytogenetic testing by increasing the rate of positive diagnoses (allowing the identification of much smaller deletions and duplications than cytogenetics alone), and with increasingly precise definition of breakpoints and gene content for deletions and duplications, it has allowed the identification of many new syndromes.[17] However, these tests also allow the identification of copy-number alteration of disease-associated genes unrelated to the initial reason for study, allow the identification of excessive homozygosity indicating potential consanguinity or incest, and have a significant likelihood of identifying a variant of uncertain significance. CMA also has the potential to identify secondary findings. Therefore, CMA, like sequencing, raises ethical considerations that warrant obtaining informed consent from the child's parents, a practice that has not been routine for traditional chromosome analysis.

- The ASHG recommends that work be conducted for assembling a list of genes in which duplications or deletions are clearly associated with clinically important diseases. This list could function as a secondary-findings list with implications for what should and should not be reported back to families.
- Clinicians and parents should be adequately informed about the complexities of CMA testing before CMA testing is ordered and results are provided to patients. Clinicians should understand the concepts of variants of uncertain significance, variable expressivity, and reduced penetrance and the potential need to consider testing of other family members.
- The ASHG recommends that practice guidelines be established for using CMA testing.

Carrier Testing of Adolescents

Carrier testing of adolescents has historically been controversial, and professional statements generally do not support routine carrier testing of adolescents outside of pregnancy or reproductive planning.[18,19] Hypothetical concerns include stigma, discrimination, and potential confusion over affected versus carrier status.[4] It is notable that a significant body of literature addresses carrier screening in adults. Outside of some specific populations (e.g., Orthodox Jewish individuals), there is little documentation of discrimination around carrier status in recent years, and most adult carriers without a family history do not appear to have significant short- or long-term differences in anxiety. In contrast, adult siblings of individuals affected by recessive or X-linked conditions often have strong views on whether or not they wish to know their carrier status and how it might affect their reproductive decision making. Some studies have reported that siblings show transient anxiety and depression after carrier testing.[20–23]

Most studies assessing adolescent or childhood carrier testing are small and address individuals with a family history of X-linked conditions (e.g., Duchenne muscular dystrophy, hemophilia, and fragile X syndrome) and autosomal-recessive conditions; Borry et al. provide a summary of some of the early literature in this area.[18,24] These small studies documented high short-term recall and a number of potentially beneficial psychosocial outcomes, including relief in those who are non-carriers, relief from uncertainty in both carriers and non-carriers, and positive reappraisal of self-esteem and self-image. Additionally, these studies also suggested that adolescents found to be carriers felt able to plan for future parenthood and that most were open about the condition and their carrier status, sharing with family, and planning to tell partners.[25–29]

- On the basis of the evidence indicating potential benefits and a low risk of harm, ASHG neither recommends nor discourages offering carrier testing to adolescents who desire such testing in the setting of a positive family history. Adolescent assent and parental consent should be obtained for carrier testing, and genetic counseling might be appropriate in some circumstances.

Carrier testing could be performed on children in other less well-studied settings, including institutional settings such as high school, college, or athletic programs. Outcome studies in this area are somewhat limited and generally describe carrier testing offered in high schools in Canada, Australia, and the Netherlands. These studies, performed over 20 years, have shown high uptake rates and have not demonstrated adverse psychological consequences.[30,31] Ross summarizes many of these early studies and discusses potential concerns—including those about potential coercion, confidentiality, and the informed-consent process—with similar implementation in the US.[32]

- ASHG recommends that carrier testing in children and adolescents not be performed through institutional or population-based approaches at this time.

Research projects to further evaluate adolescent carrier testing in institutional contexts is appropriate with carefully drafted protocols.

Direct-to-Consumer Testing

Direct-to-consumer genetic testing (DTC GT) refers to genetic testing that bypasses the involvement of healthcare providers and is sold directly to consumers. DTC GT is marketed to consumers primarily via the internet and was initially limited to paternity and ancestry testing. However, DTC GT has in recent years been expanded to offer testing for potential health-related claims.[33] Several concerns have been raised about DTC GT, and they include the lack of high-quality pre-test and post-test counseling and clinical interpretation of test results, the lack of adequate validation of some tests, and the testing of children for adult-onset conditions.

DTC GT offers individuals the opportunity to have access to personal genetic information.[34] Yet, there is a strong tradition in genetics that in many clinical circumstances, testing involves pre- and post-test counseling from a qualified health-care provider, meaning a genetic counselor or a medical geneticist.[35] It is clear that some clinicians who provide genetic-risk assessment of DTC GT results to patients lack the knowledge or background for appropriate interpretation. In one study of interviews conducted with clinicians who offered genomic-risk assessment to patients, the clinicians appeared to have learned most of what they know about genomics directly from the commercial laboratories.[36] In the absence of professional counseling and interpretation, there are concerns that consumers might make misguided changes in their health care or lifestyle.[37] Fortunately, empiric studies of DTC GT to date have shown little or no evidence of inappropriate changes in lifestyle or health-related behaviors.[38–46]

DTC GT provides information of variable accuracy and clinical validity.[47] Some companies that offer DTC GT have made poorly validated claims regarding the health impact of their testing. In response to such marketing claims, the FDA prohibited 23andMe from selling its personal-genome service in November 2013.[48] However, this does not prevent overseas companies from marketing or providing services or US-based companies from moving overseas.[49] It also does not prevent companies from offering genetic testing services without associated clinical interpretation. Other countries have passed legislation that regulates DTC GT.[50]

DTC GT has additional implications in children, given that many of these tests are intended to diagnose or identify risk for adult-onset disorders, such as breast cancer, ovarian cancer, and Huntington disease. One study surveyed companies that offer DTC GT, and only 13 responded. Ten of those 13 companies performed testing of minors in response to requests from parents or legal guardians. Three companies would consider testing if it was requested by a minor.[51]

Finally, there is no consistency regarding the information provided on DTC GT websites regarding consent for testing. Information on DTC GT websites might not be balanced with regard to how they present risks and benefits. Users of the test might consent to testing without understanding the full consequences of the results.[52,53]

- The ASHG recommends that DTC GT be discouraged in children until such a time when companies that provide DTC GT can assure quality, accuracy, and validity of their testing and assure that there is adequate pre- and post-testing counseling.
- The ASHG recommends that DTC GT in children be performed with the appropriate informed permission from a parent or legal guardian and the assent of the child when appropriate.
- The ASHG recommends that DTC GT not be performed in children for genetic conditions that have onset in adulthood or require surveillance beginning in adulthood.

Pharmacogenomic Testing

Pharmacogenetic testing in adults and in children has the potential to improve drug efficacy and reduce adverse events.[54] Testing might be indicated prior to the first use of a medication in order to guide drug choice and initial dosing or to evaluate adverse effects or non-responsiveness to prior drug treatments. However, research on pharmacogenetic testing in children has been limited, so there is little current evidence on the potential benefits and harms associated with this type of genetic testing. Further, pharmacogenetic data can account for some, but not all, variability in drug response and therefore should be considered in conjunction with other factors in clinical pharmacologic decision making. In particular, some enzymes known to have significant pharmacogenetic variability can be "metabolically immature" in newborns and infants.[55,56] This can result in clinical outcomes that are different from those predicted by genotype alone. CYP2C19, an enzyme that is involved in a number of commonly prescribed drugs, is one example in which genotypically predicted extensive (normal) metabolizers can have a poor metabolizer phenotype in the first few months of life.[57]

Clinical pharmacogenetic testing in children is strongly supported by evidence in some areas, such as TPMT testing in association with thiopurine therapy for childhood leukemia. Pharmacogenetic testing has been proposed for clinical use and is supported by varying levels of evidence in many medical specialties, including but not limited to oncology, rheumatology, psychiatry, HIV treatment, immunosuppression, and anticoagulation.[54–56,58–62]

- ASHG recommends that when there is a clear evidence base in the literature for clinical utility, pharmacogenetic testing in children might be appropriate.

- ASHG recommends additional evaluation of pharmacogenetic testing opportunities in the pediatric population in order to better demonstrate the utility and limitations of this form of testing.

Newborn Screening

Newborn screening (NBS) is one of the most effective public-health programs of the last century. The ASHG strongly supports NBS programs and encourages genetic professionals to support NBS in their communication with patients, colleagues, and policy makers.

NBS is conducted by state-based public-health programs in the US. For the first four decades of the programs, there was substantial variability between states on the conditions targeted.[63] In 2005, the ACMG published recommendations for a uniform panel composed of 29 primary conditions and a number of secondary conditions that will be identified through targeting the primary conditions.[64] These recommendations were supported by the American Academy of Pediatrics and the newly formed Secretary's Advisory Committee on Heritable Diseases in Newborns and Children (SACHDNC).

The SACHDNC was established in 2004 through federal legislation with the primary goal of establishing an evidence-review process to make recommendations for conditions on a uniform screening panel.[65] Although states determine the nature of their screening programs, currently all states screen for all conditions on the ACMG list.

Given the low prevalence of most conditions targeted by NBS, making informed policy decisions regarding the introduction of new tests is challenging. For this reason, the ASHG supports robust evidence-review processes, at the state and/or federal level, as an essential element to a state health department's policies and procedures for NBS programs.

- The ASHG recommends that state programs only introduce new conditions on a mandated NBS panel after a thorough review of the evidence on the benefits and harms, the impacts on systems of care, resources, and capacity, and input from relevant stakeholders.

State NBS programs are designed to both enable affected children to receive a prompt, accurate diagnosis and coordinate short-term clinical care for the condition. However, health departments do not typically collect data on the longer-term outcomes for children or their families. Further, the low prevalence of many conditions targeted through NBS makes it difficult to conduct outcomes research without large, multicenter projects. Therefore, data on the clinical outcomes of affected children, with or without NBS, is often limited.

- The ASHG supports conducting outcomes research on NBS and developing infrastructures for conducting outcomes research on these rare conditions. Such infrastructures would support the ability to assess outcomes and to conduct controlled trials of therapeutic options and evaluate support systems required for affected children and their families.

NBS is conducted on dried bloodspots collected from the infant within the first few days of life. Although all state programs provide information to parents about NBS, usually in the form of a brochure, the literature shows that most parents do not read this information. Accordingly, most parents have little awareness and understanding of NBS.[66] The literature also demonstrates that many primary-care physicians (PCPs) have a limited understanding of NBS and often feel poorly prepared to manage screen-positive infants and provide guidance to their parents.[67] Adequate information and education of parents and PCPs is important for maximizing the effectiveness of these programs. The literature demonstrates that parents want to be informed, but most only want basic facts about NBS programs.[66] However, research has been limited on how to effectively deliver information to parents about NBS. Public surveys, the American Academy of Pediatrics, the American College of Obstetrics and Gynecology, and commentators support NBS education in the prenatal time period.[68]

- The ASHG recommends additional research for improving the quality, delivery, and effectiveness of parental, public, and professional education regarding NBS.

NBS is conducted under state mandates in all but two US states or territories (Wyoming and the District of Columbia). However, 43 states permit parents to refuse NBS for either religious or philosophical reasons. The number of parents who opt out of NBS is exceedingly small.[69,70]

The role of parental permission in the conduct of NBS has been a topic of debate since the inception of the programs in the 1960s. State programs typically are strongly supportive of the current opt-out approach because a formal permission process is cumbersome, particularly if signed consent forms are required, and could increase the risk that newborns will not be screened. Nevertheless, a number of professional statements over the years support a parental permission process (an "opt-in" approach).[19,71] Surveys of public and professional attitudes regarding parental permission demonstrate that the public is evenly split on the appropriateness of opt-in versus opt-out approaches.[72,73] However, the public expects to be informed about NBS regardless of the permission model.

Obtaining truly informed permission for NBS during the postnatal period is challenging because of the hectic environment, the short hospitalization for many newborns, and the many competing priorities for parents and newborn-care providers. Further, signatures to document permission can be obtained in a perfunctory fashion, so

requiring signatures per se does not assure a meaningful informed-permission process. Under the assumption that parents are reasonably informed about the program and their rights under state law, both opt-in and opt-out approaches to NBS are ethically acceptable.

- Although the ASHG supports improved parental education about NBS, it does not advocate a change in most state programs that mandate screening but permit parental refusals.

When screening is conducted, programs obtain sufficient blood from infants to perform all testing and to conduct repeat testing when warranted. This means that most infants will have extra blood on the filter cards after screening. Traditionally, many states have saved these residual dried bloodspots (DBSs) for several purposes, including quality assurance (QA) for NBS laboratory services, forensic uses, and biomedical research.[63] The DBSs are particularly useful for research because they represent a tissue set on the entire population of newborns and can be used for genetic epidemiology and for exposure to prenatal infectious diseases and environmental toxins, among other applications. Although many states discard the DBSs after screening is complete, many states retain these DBSs for various lengths of time. The retention of DBSs became controversial in recent years when two state programs, those of Minnesota and Texas, were sued by parent groups for the lack of parental permission for this practice.

In the US and Canada, research on public attitudes regarding the management of DBSs demonstrates broad public support for the retention of DBSs for QA and biomedical research, contingent on parental education and choice.[72,74] Consistent with public and professional opinions on this issue, the ASHG supports the retention and research uses of residual DBSs under carefully developed, transparent public policies and practices. Prior to 2015, when used for biomedical research, residual DBSs were typically de-identified, or research was conducted under a waiver of parental permission. However, in late 2014, the Newborn Screening Saves Lives Reauthorization Act of 2014 (public law no. 113-240) was passed to require informed consent from parents for all Department of Health and Human Services-funded research using DBSs and to prohibit the waiver of consent. The impact of this law on NBS-related research remains to be determined. However, the ASHG considers the retention of DBSs strictly for quality-improvement activities for the NBS programs to be covered under the state mandate for screening. Therefore, parental permission should not be necessary for the use of DBSs for QA purposes.

- The ASHG encourages states to retain DBSs for QA purposes. Retention for QA purposes should be considered integral to the NBS program and should not require specific permission from parents.
- The ASHG encourages states to retain DBSs and to make specimens available to investigators and to public-health programs under carefully developed guidelines.
- Parents should be informed of state policy and practices regarding the retention and use of DBSs.[75]
- Parents should be offered a choice regarding the retention and use of their child's DBSs for purposes beyond the clinical NBS program and QA uses. This choice ought to be clearly separated from the decision to participate in NBS.

NBS can also provide benefits to a newborn's family by alerting parents to their reproductive risk for future pregnancies and can benefit society more broadly by advancing the understanding of disease. Information relevant to reproductive risk is also provided by the generation of results related to carrier status. Disclosure of carrier status through NBS raises challenges because this information is not typically available without informed consent and is not usually provided to minors.[76–78] However, recent guidelines and studies have suggested that reproductive benefits might represent an important goal of NBS because carrier detection can inform family planning.[79–82] Many NBS programs disclose carrier results to families. However, there is limited evidence to support the utility and impact of disclosing carrier results to families. A stronger evidentiary base is required to inform evidence-based decision making and recommendations.

- The ASHG recommends additional research for assessing the utility of disclosing carrier results generated from NBS for reproductive decision making and cascade testing, as well as the impacts on systems of care and resources in the context of engagement with relevant stakeholders

Adoption, Consanguinity, and Paternity

Adoption

In the US, approximately 2% of children are adopted, and many children are living in foster care. Prospective adoptive parents might want genetic information about a child to inform their decision on whether or not to adopt. But previous consensus statements of the ASHG and ACMG have advocated that indications for pre-adoption testing closely parallel the indications applied to children living with their biological parents.[83] The rationale for these recommendations rests on concerns that harms might come to the child without sufficient benefit to balance the scales. If such concerns are valid for children living with their biological parents, then the standards for genetic testing should be the same for all children. The "principle of equity" articulates the idea that prospective adoptive parents are entitled to no more information at the time of taking custody of a child than the child's birth parents could obtain.[84]

A countervailing argument has been raised to the principle of equity. It has been suggested that it is in the interest of the child to be placed with families who are optimally capable of taking care of their medical needs.[85] Adoptive parents are already subjected to additional scrutiny to ensure that they have the capability to serve as suitable parents.[86] To some extent, the child's background might also influence these decisions. A commonly held view is that it would disadvantage the child to be placed with some adoptive parents and that even factors such as cultural and ancestral education should be considered.

It is possible that a child with an untreatable genetic disorder would be better off with parents specifically chosen because of their ability to deal with this difficult circumstance. An obvious objection is that knowledge of the disorder might so restrict the pool of willing parents that the child is made "unadoptable." Another concern is that adults responsible for the placement of adoptive children most likely do not have the specialized genetics knowledge that would be required for assigning children to "matched" families.

Another argument for matching is that prospective, adoptive parents' interests would be harmed by failure of the adoption agency to make the best possible choice of home on the basis of the full range of relevant information about the child. However, there is no assertion of a parallel responsibility of the prospective parents to undergo genetic testing themselves. The argument of matching creates the possibility that some parents might find themselves to be genetically unsuitable to adopt.

- The ASHG recommends that both children awaiting adoption and adopted children be given the same consideration in genetic testing as children living with their biological parents. We endorse and affirm the previous recommendations of the ASHG.
- All genetic testing of newborns and children in the adoption process should be consistent with the tests performed on all children of a similar age for the purposes of diagnosis or of identifying appropriate prevention strategies.
- Because the primary justification for genetic testing of any child is a timely medical benefit to the child, genetic testing of newborns and children in the adoption process should be limited to testing for conditions that manifest themselves during childhood or for which preventive measures or therapies can be undertaken during childhood.

Consanguinity

Inbreeding, including first-degree relative relationships, could be detected in genome-wide assays including but not restricted to SNP genotyping, whole-exome sequencing, and whole-genome sequencing.[87] It is possible to find long segments of chromosomes lacking expected heterozygous variation—called runs of homozygosity or absence of heterozygosity (AOH). If AOH is confined to a single chromosome, the cause could be a chromosome replication or segregation abnormality (uniparental isodisomy [UPD]). In UPD, the person undergoing testing has received identical copies of one parental homolog for part or all of a chromosome. The length of the homozygous segment will usually distinguish UPD from autozygosity—identical chromosome segments inherited from the mother and father as a result of a recent shared ancestor. In contrast, if there are multiple long AOH segments with AOH involving many or all of the chromosomes, the most likely explanation is that the parents are close biological relatives. The ACMG has published guidelines for diagnostic laboratories to distinguish UPD from consanguinity.[88] With the accumulation of extensive genomic data in diverse human populations, we can expect further refinement and improved specificity in methods of interpreting tests.[89]

In some ways, detection of extensive AOH is a secondary finding. The motivation for genetic testing might be to detect a diagnostically important DNA copy-number abnormality or single-gene disorder. But the finding of AOH cannot be considered purely incidental because UPD detection is a formal reason for diagnostic testing. UPD or autozygosity can be a necessary condition for imprinting defects or homozygous recessive disorders. Disclosure of the results should, therefore, be guided by the same principles as those for other diagnostic testing.

The detection of extensive long segments of AOH is most consistent with reproduction between close relatives. In the absence of a history of assisted reproduction, this implies incest. The central concern for practitioners is the possibility of sexual abuse of a minor. Sexual relations between close relatives are illegal in most jurisdictions, but the specifics of the laws vary in how relatedness is specified.[90] The detection of a consanguineous relationship by itself does not engender a duty to report it to the authorities. Physician-patient confidentiality must be respected in most circumstances. An important exception is the circumstance in which the health-care provider suspects that a child is being abused. Physicians are obligated to report suspected child abuse without exception.

It does not necessarily follow that the possibility of discovering information that could lead to a suspicion of child abuse should be presented in pre-test counseling. For most patients, this information will be irrelevant but could cause unnecessary anxiety and could even lead to the refusal to allow a diagnostic test.

- The ASHG recommends that laboratories adopt data standards and analytical methods that allow reliable detection of incest. Practitioners should develop procedures for case management when genetic laboratory results are consistent with incest involving a minor. Practitioners have a duty to report suspected child abuse. Health-care providers do not have a responsibility to report incest involving consenting adults, even though this might be illegal in their jurisdiction.

Parentage

Misattributed parentage could be detected when biological relatives undergo genetic testing. Genetic testing, and especially genomic testing, of children and their parents can lead to results inconsistent with the assumed social inheritance relationships. The most commonly encountered problem is misattributed paternity. With estimated rates of 1%–10% from various studies, non-paternity is relatively common and is therefore highly likely to be encountered in routine practice and in research.[91–93] However, with the increased use of assisted reproduction, rare occurrences of misattributed maternity have been described. Misattributed parentage (where neither the mother nor the father is biologically related to the child), albeit very rare, would be quickly recognized with many forms of modern genetic testing. Clarifying the pattern of inheritance of pathogenic variants is a key goal of genetic testing; therefore, it is recommended in all cases that evidence of segregation of potentially disease-causing alleles and parental test results be examined to conclusively demonstrate de novo mutation.

Arguments in favor of full disclosure of paternity findings center on issues of a patient's right to know, avoiding paternalism, and the duty of physicians to be truthful. A broad answer to these concerns is that it is not possible for either mothers or fathers to truly exercise their autonomy if the options are not presented before testing has taken place. Given the intuition that there could be extensive harm, health-care providers following a plan of non-disclosure could be exercising prudence in avoiding interference in the family relationships.

Specific recommendations for the disclosure of misattributed parentage have been made, but opinions expressed in the literature are diverse and unsettled.[94] Although the mother and father (both social and biological) have an undoubted stake in the outcome of parentage information, there is an asymmetry of risk. Only the fidelity of the mother is at stake in the test result. For this reason, it is common practice to disclose only to the mother. For example, the Institute of Medicine produced a report advocating disclosure of misattributed paternity only to the biological mother.[71] This has been countered with arguments pointing out that both the integrity of the physician-patient relationship and professional responsibility involve both the mother and father.[95] Intentional deception is contrary to fundamental values in medical practice. In her critique, Ross strongly advocated for full disclosure to both parents. Although the risk is asymmetric prior to testing, the post-test results involve both the mother and father. Lack of disclosure to the father could involve either misleading interpretations with consequent misleading counseling or outright deception. These are departures from standards of full disclosure, non-directiveness, and respect for autonomy.

More recently, it has been suggested that information about parentage should not be part of routine genetic test reporting and counseling unless it is specifically requested by the parents in advance of the test. Arguing in favor of such an approach, Palmor and Fiester conclude that health-care professionals have no legitimate right to decide about a matter with such high potential for harm to so many individuals in both the close and extended family.[96] They suggest that providers inform clients that although misattributed parentage could be detected in the testing, it will not be disclosed to either the mother or the father. They further argue that parents wishing to investigate parentage should pursue specific testing.

Given the unsettled nature of the debate, it is essential that health-care providers develop a consistent plan for dealing with parentage and ancestry questions of all types. Parents should be informed before the test is performed about the risk of detection of misattributed parentage, and as with other forms of incidental findings, pre-test counseling should be provided. Because the risk in misattributed paternity is asymmetric, an approach for pre-test counseling could include confidentially informing the mother of the potential detection of non-paternity.

- The ASHG recommends that parents be given information about the possibility of detecting misattributed parentage during pre-test counseling. While honoring their broad responsibility to be truthful with patients and their families, we recommend that health-care providers avoid disclosure of misattributed parentage unless there is a clear medical benefit that outweighs the potential harms.

Record and Communication Issues

Quality clinical genetics practice begins and ends with good communication, and evidence indicates that patients value clear communication from medical providers. Because of the complexity of the information, genetic test results have the potential to be misunderstood and to cause harm. Examples include NBS false-positive results, over-interpretation of carrier status or variants of uncertain significance, and the nuances of "negative" results in the face of a suspected genetic disorder.

- The ASHG recommends that providers of pediatric genetic testing have appropriate training and expertise in the interpretation and communication of genetic information.
- The ASHG recommends that diagnostic laboratories develop reports that are detailed and accurate but also facilitate comprehension by providers.

Communication of genetic test results in the pediatric setting is complicated by the potentially long timeline of transition from childhood to adulthood, during which parents act as decision makers on behalf of the child, and the differing capacity of individual children at different development stages to participate in such decisions and to contemplate the meaning of the results. Genetic

information can also have important implications for siblings and other family members.

- The ASHG recommends that genetic testing in children should include a long-term communication plan for all results, including consideration of who should be involved in the communication of information and the staging of information sharing on the basis of age, maturity, and capacity to understand.

Unlike medical tests that measure temporary aspects of an individual's anatomy or physiology, genetic tests provide information of a permanent nature about an individual and potentially their family members. However, maintaining knowledge of genetic results over long periods of time can be challenging. Even though basic information might be recalled (such as the fact that a genetic work-up was performed), the specific details about childhood genetic test results and their implications might not be accurately remembered many years later. This loss of retention severely impairs their subsequent utilization by clinicians, patients, or patients' family members and can lead to unnecessary repeat genetic testing and thus a waste of resources. Modern electronic medical records have the potential to maintain information with much greater fidelity over the lifespan of the individual.

- The ASHG recommends that standards be developed for permanent storage of genetic data in electronic health records or other secure electronic systems to facilitate the provision of genetic information in patient portals.
- The ASHG also recommends the development of mechanisms for sharing family history and genetic results with family members.

As genetic testing modalities become more comprehensive and generate large amounts of raw data, genetic test results will challenge the current model of storing laboratory results. Most genetic variation will be of unclear clinical significance but might become interpretable over time with continual advances in medical science. However, current electronic medical records are not typically designed to manage storage or re-analysis of genome-scale information, and it is not clear whether it would be desirable for them to do so. Recent federal regulations provide for laboratory results to be the property of the patient, raising questions about how much genomic information should be placed in the medical record, particularly in the case of genetic variation that does not have well-established clinical implications. Furthermore, with some notable exceptions, a key limitation of the typical interface between the clinical laboratory and the medical record is that it involves a single instance of data transfer that does not permit re-interpretation of genetic results over time.

- The ASHG recommends the development of uniform guidelines to standardize medical-record capabilities and management of interpreted results and raw genetic sequence data.
- The ASHG also recommends developing novel models for molecular laboratory and interpretive services on the basis of prospects for the re-analysis of genetic information over time.

Professional Education

If health-care providers are to adhere successfully to the recommendations in this report, they must have appropriate knowledge and skills related to genetic and genomic testing, interpretation of test results, communication of results to patients and families, and basic genetic counseling. In addition, the health-care system will require adequate numbers of trained medical geneticists and genetic counselors to assist in the role of specialty testing and interpretation of results. With the expected expansion of genetic and genomic testing, all health-care providers will need (1) educational programs that target relevant scientific, clinical, ethical, legal, and social topics and (2) support systems that address structural and systemic barriers to the integration of genetic medicine into clinical practice.

Providers' Understanding of Genetic Medicine

Previous studies have clearly documented that health-care providers have knowledge gaps that constitute a rate-limiting step in the incorporation of genetics and genomics into mainstream health care.[97–99] Guttmacher et al.[97] and McInerney et al.[98] summarized some of the central deficiencies related to clinicians' understanding of genetic medicine as follows:

> Misconceptions about genetics: many health-care providers still believe that genetic medicine is defined by rare, Mendelian disorders and circumscribed by pediatrics and obstetrics, when in fact genetics increasingly is concerned with the common, chronic diseases that are the daily focus for most health professionals.
>
> Lack of knowledge and confidence about genetics: surveys of practicing health professionals demonstrate a lack of basic knowledge about genetics and, often, a lack of confidence to deal with genetics-related issues that arise in the clinical setting.

Deficiencies in genetics education extend from the preservice training of most health-care professionals to postgraduate internships, residency and fellowship training, and continuing medical and professional education for actively practicing health-care professionals. Notable efforts exist in various organizations across the US to integrate genetics and genomics into formal education and to increase the genetics content of certifying exams.[100–104] Many of those efforts are driven by the development of competencies that focus on content knowledge and related clinical skills.

Equally important is the challenge of training those health-care providers currently in practice. A 2012 report from the UK's Human Genomics Strategy Group[105] captures the situation concisely:

> Ensuring that genomics is an integral part of initial medical/health education and training will be an important step towards developing the work force. But for the next 15 years at least, the majority of staff who will have to cope with the movement of genomics into mainstream clinical work will be those who are already trained and accredited. That is why the bigger educational challenge is to close the skills gap within the existing work force, via continuing professional development (CPD) arrangement.

The highly diverse disciplines, clinical settings, and motivations reflected in this vast health-care work force will require equally diverse educational approaches, all of which must involve the end user from the initial planning through implementation and evaluation.[98] Again, some good models for CPD are in place or in development in the US, but implementation, evaluation, and scaling from local to broader application remain as significant challenges, and addressing them will require material and personnel resources.[106–108]

Structural and Systemic Barriers

The practice model in health care evolves constantly, and just as the development of antibiotics in the twentieth century and medical imaging in the late twentieth and early twenty-first centuries changed the practice of medicine, genetics and genomics are changing medical practice today. Education of practicing clinicians and the application of new knowledge and skills highlight some of the systemic challenges to incorporating genetic medicine into health management, for example:

> Lack of management and referral guidelines in genetics and genomics: the paucity of evidence-based guidelines related to genetic medicine, and the slow dissemination of those that do exist, impede clinicians' attention to genetics and raise questions about clinical utility.
>
> A dearth of genetics professionals: the low numbers of medical geneticists and genetic counselors in the USA and elsewhere limit the provision of genetic services directly and, furthermore, limit the extent to which other providers have formal and informal access to genetics expertise.[109]

Haga et al. reported that in a survey of US PCPs, "more than half (53%) of respondents indicated they do not have access to genetics expertise." The authors of the study suggest "a hybrid model of education and support for PCPs and access to specialist consultation when needed."[110] Hamilton et al., using diffusion of innovation theory and focusing on clinical genetic services in the Veterans' Administration, have elaborated some of the factors that promote or impede the integration of genetics into various types of primary and specialist practice.[111] In assessing factors such as complexity, compatibility with existing services, and relative advantage ("added value … when compared to existing practice"), the authors found that study participants "indicated that benefits did not outweigh the costs of genetic services," and they conclude that uptake of genetic services "by simple diffusion" will not work. "Instead," they assert, "adoption of clinical genetic services will require development of targeted organizational supports to strengthen the likelihood of adoption and implementation."

Even these few examples demonstrate the complexity of the challenges facing the education of health professionals and the subsequent integration of genetics and genomics into practice. Information does not equal education, especially when the objective is to change clinical behaviors and improve patient outcomes.

Although it is not ASHG's responsibility to direct change in this complex system of formal and informal education from pre-clinical training to continuing education, it can help to promote change by supporting the recommendations below.

- ASHG recommends that the genetics community work closely with appropriate educational institutions, governing bodies, and professional societies to develop and deliver programs that provide the knowledge and skills health-care providers need to apply the recommendations herein in their own practices.
- ASHG recommends that the introduction of genetics-related content and case examples should emphasize the extension of existing knowledge and skills and should not portray genetics as a discipline that requires wholly new approaches to clinical care.
- ASHG recommends that those developing educational programs be cognizant of the structural barriers that impede the integration of genetic medicine—or any other clinical innovation—into routine practice and attempt to address those barriers in program content and implementation strategies.
- ASHG recommends that no educational program for health-care providers include well-designed evaluation plans that assess the efficacy of content, instructional approaches, and implementation strategies. Evaluation plans should be in place before program development begins and should reflect carefully developed educational objectives and outcomes.
- Because a well-informed public presumably will make better individual and collective decisions about the issues elaborated in this report, the genetics community should support efforts to improve public genetic literacy and scientific literacy in general.
- The inevitable and significant increase in the number and use of genetic tests will require more genetic

counselors and more genetically competent nurses, physician assistants, and physicians. The ASHG recommends an increase in the number and size of training programs and the provision of funds to support this expanding training infrastructure.

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