

UNDERSTANDING ETHICAL DILEMMAS IN PEDIATRIC LIPIDOLOGY - GENETIC TESTING IN YOUTH

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ABSTRACT

Over the past 25 years there has been an increasing focus on early identification of individuals at-risk of premature cardiovascular disease (CVD), with the goal of improving outcomes and reducing premature CVD-related events such as myocardial infarction and stroke. In 2011, a National Heart, Lung and Blood Institute (NHLBI) Expert Panel recommended universal cholesterol screening of all children, irrespective of health status and family history, beginning at 10 years-of-age (range 9-11) and, if normal, repeated once between 17 and 20 years-of-age (1). Children found to have significant hypercholesterolemia are encouraged to adopt a heart-healthy lifestyle and, when appropriate, offered treatment with lipid-lowering medication, starting at 8 years-of-age and older. Research studies have convincingly demonstrated the safety and effectiveness of lipid-lowering medications in reducing risk and improving outcomes in adults, providing indirect support for universally cholesterol screening of children. Data from individuals with familial hypercholesterolemia (FH), treated for 20 years with pravastatin starting at a young age, have shown no adverse effects of growth, development, or

reproductive function during adulthood. Shared decision-making in this population, however, is complex. Unlike most adults who are capable of making informed healthcare decisions, children have a wide range of developmentally-related intellectual and cognitive function, creating unique challenges in their ability to 1) understand long-term risk and benefit; and 2) make informed decisions regarding testing and medical management. In addition, some children have mental health and developmental disabilities that limit their cognitive abilities and judgement. Furthermore, legal guardians have the moral responsibility and legal right to make decisions on behalf of a minor. In this article, we will discuss 1) privacy, discrimination, and the legal rights of children; 2) ethical considerations and concerns and 3) recommendations for clinicians when providing medical care of children with disorders of lipid and lipoprotein metabolism.

OVERVIEW OF LIPID AND LIPOPROTEIN DISORDERS IN YOUTH

Children with abnormal levels of lipids and lipoproteins are generally identified as result of targeted, universal or occasionally, coincidental

testing. Current recommendations for lipid screening of children are listed below.

1. Targeted screening in all children ≥ 2 years of age in whom:
 - a. One or both biologic parents are known to have hypercholesterolemia or are receiving lipid-lowering medications
 - b. Who have a family history of premature cardiovascular disease (men < 55 years of age and women < 65 years of age)
 - c. Whose family history is unknown (e.g., children who were adopted)
2. Universal screening of all children 10 years of age (range 9-11), regardless of general health or the presence/absence of CVD risk factors. If normal, repeat screening is recommended at 17-20 years-of-age.

Since hypercholesterolemia is often caused by an underlying genetic mutation, such as in FH, cascade screening of biologic relatives is also recommended. Cascade screening involves systematic testing of all first-degree relatives (parents and siblings) of a child with FH, followed by testing of second- and third-degree relatives if any of the first-degree relatives are affected. The most practical approach to cascade screening is biochemical testing of cholesterol, which is inexpensive, readily available and can be performed without the need for fasting. However, up to 25% of family members may be misdiagnosed as being either affected or unaffected when screening is based on cholesterol levels alone. Testing for a known genetic mutation in the family combined with fasting or non-fasting LDL-C levels will yield the most definitive information. While helpful if known, the child's family history is often unknown, incomplete, or inaccurate. Reliance upon family history alone fails to identify as many as 30-60% of children with significant hypercholesterolemia. For additional information see the Endotext chapters entitled "Guidelines for Screening, Prevention, Diagnosis, and Treatment of Dyslipidemia in Children and

Adolescents" and "Principles of Genetic Testing for Dyslipidemia in Children".

Abnormalities of lipids and lipoproteins in youth may be caused by genetic mutations, acquired conditions, or both. Those with acquired conditions, such as obesity and insulin resistance, are encouraged to adopt a heart-healthy lifestyle, which includes a low-fat, calorically appropriate carbohydrate diet, weight loss if overweight or obese, participation in 30-60 minutes of moderate-to-vigorous physical activity per day and smoking avoidance or cessation. Those suspected of having a genetic mutation are generally diagnosed based upon clinical criteria with or without genetic testing.

Genetic mutations that cause lipid and lipoprotein abnormalities vary depending upon the mode of inheritance (autosomal co-dominant vs autosomal recessive), the type of mutation present (slice vs missense), the number of genes involved (monogenic vs polygenic) and their phenotypic expression. When a genetic mutation is present, its expression may potentially be modified by other gene abnormalities (often small effect mutations) and environmental factors (e.g., obesity, insulin resistance, medications). For additional information see the Endotext chapter entitled "Genetics and Dyslipidemia".

Early identification and treatment of children with clinically suspected or genetically confirmed FH has become increasingly common. However long-term outcome studies demonstrating the safety and efficacy of this approach are lacking. Since lifestyles and therapeutic options are likely to change over the extended period of time that would be necessary to reach "hard" end points in children with FH, such as myocardial infarction and stroke, outcome studies are unlikely to be forthcoming. Given the significant benefit statins have shown in reducing CVD-related mortality in adults, it has been suggested that withholding effective treatment in moderate-to-high

risk children would be unethical (2). For additional information see the Endotext chapter entitled “Familial Hypercholesterolemia”.

A novel approach has been suggested to potentially lower costs and avoid prolonged exposure of at-risk children to lipid-lowering medication, while offering timely and presumably effective intervention. Rather than continuous treatment implemented at an early age, Robinson and Gidding proposed intermittent lipid-lowering medication guided by noninvasive measures of atherosclerosis, such as carotid intima-media thickness (3). As with conventional approaches, the goal of such therapy would be regression of atherosclerotic lesions, with retreatment periodically throughout adulthood as needed. While intriguing, the benefits of this recommendation have not been proven.

To date recommendations for early identification and treatment of children with hypercholesterolemia have focused primarily on the potential benefits. Fortunately, no significant physical or psychological harms have been shown in children who have undergone early screening and treatment. However, healthcare providers who advocate screening, genetic testing and treatment of children should carefully consider potential ethical issues, including the rights of the child to participate in clinical decision-making, the presumed benefits to the child and the family, as well as potential harms.

PRIVACY, DISCRIMINATION AND THE LEGAL RIGHTS OF CHILDREN

Over the last 50 years, in the U.S. Congress has passed a variety of laws to assure the privacy of an individual's health information and eliminate discrimination based upon an individual's health status. While most clinicians have an awareness of these laws, it is unclear how clinicians use this information in clinical decision-making, particularly as it relates to the current or future interests of the child.

Privacy

In 1996, Congress passed the Health Insurance Portability and Accountability Act or HIPAA. This law mandates the protection and confidential handling of protected health information, including genetic information. Furthermore, HIPAA states that genetic information in the absence of a diagnosis (e.g., predictive genetic test results) cannot be considered a pre-existing condition. Since children with heterozygous FH are rarely affected by their hypercholesterolemia during childhood, genetic testing would be considered “predictive” of adult-onset disease. Children found to have a pathogenic or presumed pathogenic mutation, therefore, are afforded privacy under HIPAA and are not considered to have a pre-existing condition.

The Genetic Information Nondiscrimination Act (GINA), passed in 2008, adds to HIPAA by prohibiting health insurers and employers from asking or requiring a person to take a genetic test and using genetic information in 1) setting insurance rates and 2) making employment decisions.

Discrimination and Pre-existing Medical Conditions

Prior to 2014, insurance companies based eligibility for and the cost of health insurance on the presence or absence of pre-existing medical conditions. A pre-existing condition is typically one for which an individual has received treatment or a diagnosis before being enrolled in a health plan. Because they were determined by insurance providers, criteria defining pre-existing conditions varied widely. This meant that when applying for health insurance individuals, including children, previously diagnosed with and/or treated for hypercholesterolemia were considered to have a pre-existing condition.

Since 2014, with the passage of the Affordable Care Act, insurance companies can no longer deny coverage or discriminate against individuals due to a pre-existing condition. Nor can individuals be charged significantly higher premiums, subjected to an extended waiting period, or have their benefits curtailed or coverage withdrawn because of a pre-existing condition. However, this protection does not extend to an individual's ability to obtain nor the rates charged for life, disability, and long-term care insurance.

Despite these reassurances, in some cases exemptions may apply, particularly for members of the United States military, veterans obtaining healthcare through the Veterans Administration (VA), and individuals who receive services through the Indian Health Service.

Children's Rights

A child's rights can be considered in two parts 1) nurturance rights, i.e., the right to care and protection and 2) self-determination rights, i.e., the right to have some measure of control over their own lives. Historically, society has focused on the former. Increasingly there is a growing emphasis on shared decision-making in medicine that recognizes children have the right to take an active part in many of the decisions regarding their own lives. While such efforts are commendable, the ability of children to become actively and willfully involved in the decision process is complicated by normal, and sometimes abnormal, growth and development. This raises an important question about a child's ability to understand their rights in a reasonable and meaningful way (4). It also assumes that healthcare providers are trained, capable of and willing to provide developmentally-appropriate information to children in a comprehensible and non-threatening way.

In the 1980s, Melton (5, 6) suggested that children progress through three distinct stage-like levels of reasoning about rights: Level 1, children exhibit an egocentric orientation where they perceive rights in terms of privileges that are bestowed or withdrawn on the whims of an authority figure. Level 2 children see rights as being based on fairness, maintaining social order and obeying rules. Finally, in Level 3 rights are seen in terms of abstract universal principles. Subsequent models favored the gradual acquisition of context specific knowledge (7-9). When and how well a child progresses from limited to abstract reasoning presents challenges for physicians who strive to involve children in decisions regarding early screening and intervention for CVD risk prevention.

MIGHT EARLY DIAGNOSIS AND TREATMENT OF HYPERCHOLESTEROLEMIA COMPROMISE A CHILD'S FUTURE RIGHTS?

Laws such as HIPPA, the Affordable Care Act, and GINA protect privacy and prohibit health insurance companies from denying coverage or discriminating against individuals due to a pre-existing condition, including hypercholesterolemia. Nonetheless, current laws do not preclude an individual being denied other forms of coverage, such as life, disability, or long-term care insurance. Furthermore, laws governing privacy, healthcare, and insurance coverage are subject to change over the course of the child's lifetime. This potential vulnerability needs to be considered by clinicians who provide care to children and fully disclosed to the family prior to diagnostic evaluation and treatment of children with hypercholesterolemia. To the extent that they can participate in such conversations, children should be included in the clinical decision-making. The accelerated risk of atherosclerosis beginning in young adults notwithstanding, the urgency of screening and early treatment of children needs to be considered in the context of the child's overall best interest and, ideally, with their approval.

ETHICAL CONSIDERATIONS AND CONCERNS

Since 1953, there has been an impressive increase in new technology and expanded uses of genetic testing and screening. Application of these diagnostic tools in minors has increasingly become commonplace, raising concerns about ethical issues. While pediatric screening and genetic testing are much less common outside of newborn screening, universal screening and increased use of genetic testing has been advocated by many national professional organizations and societies. Justification for such recommendations cite early identification of a child with an underlying genetic abnormality as an opportunity to initiate treatment that may prevent or reduce morbidity or mortality.

Over the past 50 years, genetic testing has increasingly played an important role in helping to understand the basis of many disorders of lipid and lipoprotein metabolism, identifying those who are affected and aiding our understanding of an individual's risk. While only a minority of individuals with hypercholesterolemia who undergo genetic testing are found to have a pathogenic mutation, epidemiologic and Medallion randomization studies suggest these individuals are at significantly higher risk of premature ASCVD-related morbidity and mortality than the general population.

Genetic testing of an asymptomatic child based upon an abnormal blood test and/or positive family history for a specific genetic condition, such as FH, has also been proposed, particularly if early treatment may affect future morbidity or mortality. Some genetic tests can reasonably predict disease which only manifest in adults.

Ultimately, decisions about whether to offer genetic testing and screening should be driven by the best interest of the child. This, perhaps, is best determined by a thoughtful discussion between the child's healthcare provider, the parents, and, when

appropriate, the child. Current recommendations and guidelines suggest early intervention to achieve the best outcomes. Yet, there is no clear definition as to the optimum age at which intervention should be recommended, nor clear understanding about a child's ability to understand and make a rational decision regarding testing and/or treatment.

The genetic testing of children raises specific considerations. Because of the need to respect a children's rights, caution has been advised in performing genetic tests during childhood. Newborn genetic testing is now ubiquitous, yet it is not always seen as routine for older children despite specific indications. Testing for drug responsiveness or disease susceptibility is supported by the ethical principle of beneficence when the benefit/risk ratio is in favor of discovering these results during childhood. Possible harms are seen when such knowledge may impact a child negatively, or foreclose future autonomy about the decision to accept the consequences of such testing. Therefore, there is a difference between genetic confirmation in symptomatic children, and that of pre-symptomatic children in which the benefit may accrue later, but the risks may occur in childhood. Such immediate risks potentially include stigmatization by the disease, depression, or decreased self-esteem. Conversely, altered family dynamics may result in parental favoritism, and survivor's guilt in siblings who test negative. This limitation on future autonomy is not confined to just refusing or allowing an adult decision for testing, but also dealing with the impact on future employment, education, and social relationships when the diagnosis is made at an early age.

Tests which help diagnose an ongoing, treatable condition that could affect current and future manifestations and complications clearly can be in the child's best interest. However, when a child is asymptomatic and the disorder is late-onset, it is no longer obvious that such a diagnosis during childhood is in the child's best interest. Therefore, it is

advised the children only undergo genetic testing when there is immediate medical benefit in childhood, either through diagnosis and treatment of a disease manifesting in the pediatric age range, or a disease whose prevention is possible and should not be delayed. Under these circumstances, informed decision-making is essential, with *parental permission* being linked to the *child's assent* whenever possible.

CHOLESTEROL SCREENING AND TREATMENT

Currently, universally cholesterol testing is recommended for all children in the U.S., starting at 10 years-of-age (range 9-11). The primary purpose of cholesterol screening is to identify individuals with familial hypercholesterolemia. For those found to have a significant elevation of cholesterol a low-fat diet is recommended. Lipid-lowering medications, such as a statin, are recommended for children with a persistently elevated LDL-C, starting at approximately 8-10 years-of-age.

Genetic Testing

Genetic testing of all children suspected of having FH has been recommended (10). The purported benefits of genetic testing are 1) to assist in clinical decision-making regarding the need for lipid-lowering medication, 2) to help determine the appropriate on-treatment goal of LCL cholesterol; and 3) facilitate cascade screening of biologic relatives.

To help better understand the complexities of genetic testing and provide guidance, in 2013 both the American Academy Pediatrics (AAP) and the American College of Medical Genetics (ACMG) published recommendations for genetic testing of children. These guidelines are particularly relevant for those providing care for children with lipid and lipoprotein disorders since, with the exception of homozygous disease, children with heterozygous FH are asymptomatic. Hence, genetic testing in this

unique population would be considered “predictive” of adult disease.

However, although there is much emphasis on early screening and genetic testing of children for FH, children have a variety of genetic conditions that affect other lipids and lipoproteins as well, such as triglycerides. The infantile form of lysosomal acid lipase deficiency, for example, is generally fatal in the absence of early diagnosis and enzyme replacement therapy. Thus, biochemical screening and genetic testing in this condition becomes imperative in order to reduce early morbidity and prevent premature mortality. Examples of other conditions in which there is a sense of urgency include familial chylomicronemia syndrome (FCS), cerebrotendinous xanthomatosis (CTX), and homozygous mutations of MTTP (abetalipoproteinemia), APOB (familial hypobetalipoproteinemia), and SAR1 (chylomicron retention disease). When considering screening and genetic testing of children with lipid and lipoprotein disorders, therefore, “one size” clearly does not fit all circumstances. Clinicians must consider each child and condition as unique, carefully weighing the presumed benefits and potential harms individually, before making diagnostic and therapeutic recommendations.

In deciding whether a child should undergo predictive genetic testing, the AAP and ACMG emphasize that the focus must be on the child’s medical best interest. Both organizations concluded that unless ameliorative interventions are available during childhood, children should not undergo testing for predispositions to adult-onset conditions and clinicians should generally decline to order testing. With the exception of those with homozygous FH, this suggests that children with heterozygous disease could defer treatment until adulthood. There is convincing evidence using noninvasive techniques, however, that early initiation of lipid-lowering medication can significantly reduce subclinical atherosclerosis. It is presumed that as a

consequence of early and persistent LDL-cholesterol lowering that ASCVD-related events will be prevented or delayed. Yet proof of improved outcomes is currently limited and generally inferred from adult data.

The AAP and ACMG did recognize that the potential psychosocial benefits and harms to the child and the extended family also need to be carefully considered. Extending consideration beyond the child's medical best interest not only acknowledges the traditional deference given to parents about how they raise their children, but also recognizes that the interest of a child is embedded in and dependent on the interests of the family unit.

Predictive genetic testing for adult-onset conditions generally should be deferred unless an intervention initiated in childhood may reduce morbidity or mortality. In some families, the psychosocial burden of ambiguity may be so great as to justify testing during childhood, particularly when parents and mature adolescents jointly express interest in doing so.

AAP AND ACMG RECOMMENDATIONS

Genetic testing performed in children can be considered either as diagnostic or predictive (11).

1. Diagnostic Genetic Testing - Is performed on a child with physical, developmental, or behavioral features consistent with a potential genetic syndrome or for pharmacogenetic drug selection and dosing decisions. Medical benefits include the possibility of preventive or therapeutic interventions, decisions about surveillance, the clarification of diagnosis and prognosis, and recurrence risks. If the medical benefits of a test are uncertain, will not be realized until a later time, or do not clearly outweigh the medical risks, the justification for testing is less compelling.

2. Predictive Genetic Testing - Is performed on an asymptomatic child with a positive family history for a specific genetic condition, particularly if early surveillance or treatment may affect morbidity or mortality. When there is uncertainty that the presence of a genetic mutation will give rise to clinical manifestations, testing is referred to as "pre-dispositional" testing. Most predictive genetic testing for adult-onset conditions is pre-dispositional.

Recommendations for Genetic Testing of Children

1. General

A) Decisions about whether to offer genetic testing and screening should be driven by the best interest of the child.

B) Genetic testing is best offered in the context of genetic counseling.

2. Diagnostic Testing

A) In a child with symptoms of a genetic condition:

i. Parents or guardians should be informed about the risks and benefits of testing, and their permission should be obtained.

ii. Ideally and when appropriate, the assent of the child should be obtained.

B) When performed for therapeutic purposes:

i. Pharmacogenetic testing of children is acceptable, with permission of parents or guardians and, when appropriate, the child's assent.

ii. If a pharmacogenetic test result carries implications beyond drug targeting or dose-responsiveness, the broader implications should be discussed before testing.

3. Newborn Screening

A) The AAP and ACMG support the mandatory offering of newborn screening for all children. Parents should have the option of refusing the procedure, and an informed refusal should be respected.

4. Carrier Testing

A) The AAP and ACMG do not support routine carrier testing in minors when such testing does not provide health benefits in childhood. This recommendation accords with previous statements supporting the future decisional autonomy of the minor, who will be able to make an informed choice about testing once he or she reaches the age of majority.

B) For pregnant adolescents or for adolescents considering reproduction, genetic testing and screening should be offered as clinically indicated, and the risks and benefits should be clearly explained.

5. Predictive Genetic Testing

A) Parents or guardians may authorize predictive genetic testing for asymptomatic children at risk of childhood onset conditions.

B) Ideally, the assent of the child should be obtained.

C) Predictive genetic testing for adult-onset conditions generally should be deferred unless an intervention initiated in childhood may reduce morbidity or mortality.

D) An exception might be made for families in whom diagnostic uncertainty poses a significant psychosocial burden, particularly when an adolescent and his or her parents concur in their interest in predictive testing.

E) For ethical and legal reasons, health care providers should be cautious about providing predictive genetic testing to minors without the involvement of their parents or guardians, even if a minor is mature. Results of such tests may have significant medical, psychological, and social implications, not only for the minor, but also for other family members.

Potential Benefits and Harms of Predictive Genetic Testing of Children. Adapted from (11)	
Medical	
Benefits	Possibility of evolving therapeutic interventions, targeted surveillance, refinement of prognosis and clarification of diagnosis
Harms	Misdiagnosis to the extent that genotype does not correlate with phenotype, ambiguous results in which a specific phenotype cannot be predicted and use of ineffective or harmful preventive or therapeutic interventions.
Psychosocial	
Benefits	Reduction of uncertainty and anxiety, the opportunity for psychological adjustment, the ability to make realistic life plans and sharing the information with family members.
Harms	Alteration of self-image, distortion of parental perception of the child, increased anxiety and guilt, altered expectation by self and others, familial stress related to identification of other at-risk family members, difficulty obtaining life and/or disability insurance, and the detection of misattributed parentage.
Reproductive	
Benefits	Avoiding the birth of a child with genetic disease or having time to prepare for the birth of a child with genetic disease.

Harms	Changing family-planning decisions on the basis of social pressures.
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It is essential that parents, guardians and maturing minors receive genetic counseling before undergoing predictive testing, which includes a discussion of the limits of genetic knowledge and treatment capabilities as well as the potential for psychological harm, stigmatization, and discrimination (12).

If an adolescent declines genetic testing, and the benefits of knowing will not be relevant for years to decades, the adolescent's decision should be final. If a minor is young or immature, genetic testing should be delayed until the minor can actively participate.

If predictive testing of conditions for which childhood interventions will ameliorate future harm, this may

favor early testing. In such cases, parental authority to determine medical treatment supersedes the minor's preferences with regard to liberty and privacy.

CONCLUSION

Although recommended for all individuals, including children, with clinically suspected familial hypercholesterolemia, genetic testing should be approached with caution. Parents and, when appropriate, children should be provided with a comprehensive discussion of the pros and cons of genetic testing, and informed about out-of-pocket costs prior to testing.

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