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Role of Family Medical History Information in Pediatric Primary Care and Public Health: Introduction

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

In February 2006, the Centers for Disease Control and Prevention sponsored a workgroup meeting in Atlanta, Georgia, on the use of family medical history information in pediatric primary care and public health. The meeting focused on pediatric topics as part of the Centers for Disease Control and Prevention Family History Public Health Initiative. One outcome of the meeting was a series of published articles that summarized the proceedings and explored 4 topics that emerged as leading issues from the meeting: (1) optimizing use of family history in primary care; (2) linking obstetric and pediatric clinicians through preconception health care; (3) assessing potential campaigns to prevent chronic disease, starting with family history assessment in childhood; and (4) using birth defect family histories for prevention efforts. In this introduction we highlight each article and preview existing efforts in preconception health care and birth defects prevention that use family history.
PEDiatric clinicians are well acquainted with many aspects of family medical histories, starting with medical conditions during pregnancy that can affect the health of infants who they might see first in the delivery room. Individuals who work in some pediatric areas of public health (such as professionals who are involved with newborn screening programs and counsel parents about carrier status for certain conditions identified at birth) are also familiar with family histories. How can these histories be better used for prevention and improving the lives of families? To address primary care and public health issues, the Centers for Disease Control and Prevention (CDC) sponsored a pediatric family history workgroup meeting in Atlanta, Georgia, in February 2006. This supplemental issue of Pediatrics is devoted to the proceedings of that meeting and more-in-depth articles about salient issues that were raised by the workgroup.

The roots of this project at the CDC go back to 2002, when what is now the National Office of Public Health Genomics launched the Family History Public Health Initiative. The purpose of the initiative was to evaluate the use of family history in assessing people’s risks for common diseases and developing more effective early detection and prevention strategies. The initiative has featured a new Web-based family history tool (Family Healthware) that currently focuses on 6 chronic diseases that primarily affect adults and research activities to assess the use of family medical histories as a public health strategy. The initiative also has included collaborative campaigns to increase public awareness about the importance of one’s family history and improve and facilitate the use of family history information by health professionals. One of the most visible products of these collaborations has been the development of the US Surgeon General’s online family history tool.

The primary purpose of the pediatric workgroup’s meeting in Atlanta was to discuss extending the scope of the CDC’s initiative to children and their families. Because pediatric clinicians are on the front line of gathering family history information, the opening session of the workshop focused on primary care issues. Many of the topics discussed, such as competing priorities, reimbursement issues, and other barriers to pediatric family history taking, are summarized in depth by Trotter and Martin (p S60). Their article also contains a summary of practical points for primary care clinicians and lists useful Web sites that include electronic and downloadable paper tools that can be used by families, clinicians, and public health practitioners.

The focus of the Surgeon General’s campaign, a family history tool known as My Family Health Portrait, is likely to be one of the most widely used instruments for collecting family history. Mirroring the emphasis of the CDC’s Web-based tool, My Family Health Portrait can be used to record family history and draw a family pedigree for heart disease, stroke, diabetes, colon cancer, breast cancer, and ovarian cancer. How might awareness of such conditions that primarily affect adult family members be useful for prevention and health-promotion campaigns that start in childhood? The article by Valdez et al (p S78) explores this question and will be of particular interest to public health practitioners and researchers.

Given the lack of emphasis in many existing tools on single-gene and common complex conditions that affect children in particular, the workgroup thoroughly examined the family history aspects of 5 exemplary conditions: cystic fibrosis, fragile X syndrome, autosomal-dominant polycystic kidney disease, coronary artery disease, and birth defects. Participants at the meeting agreed that family history information about these types of conditions is useful and is already gathered by pediatric clinicians to assist with diagnosis, treatment, and carrier testing. With the exception of the existing “tracking” of heart disease in electronic tools, there was less consensus about going forward with adding these disorders to tools such as Family Healthware, which uses well-established algorithms to produce individualized risk assessments based on family history. Nevertheless, steps toward making family history information more widely used in pediatric settings might easily be taken through 2 existing efforts: preconception health care and birth defects—recurrence prevention.

Dolan and Moore (p S66) discuss the use of family history information in preconception settings, which in the pediatric arena includes interconception counseling of families. Provision of preconception health care is a major multidisciplinary public health initiative that includes the development of tools with family history components for clinical use. The First Page family history tool was designed specifically for using family history information about genetic conditions and birth defects in clinical settings, and Dolan and Moore explain how algorithms for clinical decision-making are part of this paper-based tool.

The summary by Fisk Green at the end of this supplement (p S87) provides an overview for grasping the breadth of the workgroup’s discussions and the theoretical underpinnings to the meeting discussions. The criteria for selecting conditions for discussion at the meeting are outlined in the article by Fisk Green and explored in more depth with the example of birth defects in the article by Romitti (p S71). Romitti also discusses how family history information has been used for intervention to prevent birth defects in Irish families. This effort is another example of how family history information can be integrated into existing perinatal public health and family-counseling programs, such as promotion of folic acid intake to reduce the occurrence and recurrence of neural tube defects. Romitti concludes in his article that additional research is necessary before the tracking of birth defects becomes a standard component of family history tools in pediatric settings. Support for testing and
evaluation of family history–ascertainment efforts is indeed necessary, particularly for pediatric issues that have been less of a focus in early initiatives. In the meantime, the articles in this supplement provide in-depth discussion of many strategies that are available already for assisting pediatric clinicians and public health practitioners to benefit families through their histories.

REFERENCES

Family History in Pediatric Primary Care

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ABSTRACT

The family history is a critical element in pediatric medicine and represents the gateway to the molecular age of medicine for both pediatric clinicians and their patients. The pediatric clinician has several opportunities to obtain a family history and multiple clinical and educational uses for that information. Available methods include paper and digital forms, classical pedigrees, online programs, and focused family history at the time of a new diagnosis or problem. Numerous barriers impede the application of family history information to primary pediatric practice. The most common barrier is the limited amount of time the typical primary care encounter allows for its collection. The family history can be used in many facets of pediatric practice: (1) as a diagnostic tool and guide to testing and evaluation; (2) to identify patterns of inheritance; and (3) as a patient-education tool. The most exciting future use of family history is as a tool for public health and preventive medicine. More accurately identifying children at risk for common chronic conditions such as diabetes, asthma, and cardiovascular disease could change the primary care clinician’s approach to pediatric medicine.
As clinicians, we are living and practicing in the molecular age of medicine. To use the exciting products of the Human Genome Project, pediatric clinicians must be able to identify those patients or families for whom testing or intervention would be beneficial. An accurate family history represents the gateway to the molecular age of medicine for primary care pediatrics. In this review we summarize current practices, current and future uses for this information, barriers to collection of this information, and possible solutions for achieving the goal of having a pedigree in every chart.

The family history represents the most traditional diagnostic tool in clinical genetics and remains an inexpensive approach to identifying individuals at risk for genetic disorders. Also, family history information is increasingly being used for complex common conditions for which the genetic etiology is unknown. The family history is defined as the description of the genetic relationships and medical history of a family; when it is represented in diagram form using standard symbols and terms, it is referred to as a pedigree. As the recognition of the importance of genetic factors in the causation of human disease grows, the family history becomes not only a tool for providing appropriate care for specific diseases but also a tool for public health and preventive medicine.

The goal of universal inclusion of family history in the medical chart is formidable. As the director of the National Human Genome Research Institute, Francis Collins, MD, PhD, noted, "This 'next revolution of medicine' will fall on the shoulders of physicians who provide primary care." Although many primary care clinicians already incorporate genetic screening into their routine services, the demands on clinicians are increasing substantially with the growing need to provide information on new genetic tests to their patients, help interpret test results, and consider prescribing new genetic therapies as they become available. To illustrate why the clinician must become the point person in this genetic information revolution, we need only to review the 2003 survey of the American Board of Medical Genetics, which addressed the state of the medical geneticist workforce. The survey identified 882 clinical geneticists in the United States who reported devoting an average of 30% of their professional time to direct patient care. There are additionally 1399 certified genetic counselors who devote an average of 70% of their time to direct patient care. Because "all patients have genes," it becomes obvious that although medical geneticists and genetic counselors are the experts in the clinical use of genetic tests for the diagnosis and management of heritable disorders, it is clearly the primary care clinician who must identify and guide those patients who will benefit from their expertise.

Current Practices

Family history has always been important in health care. Families share genetic susceptibilities, environments, and behaviors, all of which interact to cause different levels of health and disease. Family history can help identify conditions that are predominantly genetic, as well as those that might be the result of gene-environment interactions. The opportunity to use family history to focus on prevention and earlier intervention has grown with the expanding genetic knowledge gleaned from the mapping of the human genome. Pediatricians (physicians, nurse practitioners, and physician’s assistants) are particularly well positioned to use this knowledge, because they provide primary care to an individual from birth to adulthood, the period during which most genetic disorders will become manifest. Also, medical genetics has traditionally been incorporated into their overall practice. The challenge is to make the collection of a family history with annual updates as standard as collecting and updating information on a child’s immunizations.

In general, clinicians do ask about family history in the context of routine physical examinations, but they need to do a better job collecting an initial family history and updating the history annually. Clinicians use family history for a variety of purposes: to establish patterns of inheritance, assist with medical diagnoses, identify risk, provide appropriate screening, target educational and preventive efforts, and inform counseling for preconception health care. The family history also helps to establish rapport with patients and families, understand familial relationships, and identify shared environments that may predispose one to risk.

Family history information is considered one of the key elements in a new or return patient visit for a complete physical examination and must be collected to warrant billing for that encounter. Pediatric and adolescent medicine textbooks provide varying recommendations for the collection of family history information from the very general to the specific. The Genetics in Primary Care Family History Working Group, a program that is funded by the Health Resources and Services Administration and has been ongoing since 1998, has created an easy-to-use mnemonic for family history collection for the clinical setting entitled SCREEN (Table 1). If there were significant findings from this initial screen, more in-depth information or a family pedigree could then be obtained. As a mnemonic, its main benefit is to remind the clinician to collect some limited, key family history information; it is not intended to be used as a tool for collection of a complete family history.

The pedigree, the gold standard for the collection of family history, is a visual way to enhance recognition of patterns of inheritance. Pedigrees have the advantage of standardized nomenclature and structure, but their use might not be feasible for many primary care prac-
Parents can facilitate the collection of family history information through the use of Internet sites such as the US Surgeon General’s My Family Health Portrait. This site allows a user to create a simple pedigree that is kept on the user’s computer and is not part of any central database. Web-based tools are becoming more popular and reflect the trend toward electronic medical charts as well as consumer-driven preferences. Computer-savvy children could work with their parents to create their own pedigree to bring to their preventive visit. Families can be encouraged to collect family history information from relatives on Thanksgiving Day, which was designated as Family History Day by former Surgeon General Richard Carmona because it is a day when families repeatedly come together in a multigenerational manner.

**EXAMPLES OF CURRENT USES OF FAMILY HISTORY INFORMATION**

The family history is a critical factor in many facets of pediatric practice. It has traditionally been used as a diagnostic tool and as a guide to evaluation and treatment in single-gene disorders, and it is increasingly becoming important in the arenas of patient education, public health, and preventive medicine.

A recent case from Dr Trotter’s pediatric practice illustrates the power of the family history to direct medical evaluations and genetic testing, aid in diagnosis, and

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>The SCREEN Mnemonic for Family History Collection</th>
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<tbody>
<tr>
<td>S</td>
<td>Some concerns</td>
</tr>
<tr>
<td>C</td>
<td>“Do you have any (some) concerns about diseases or conditions that run in the family?”</td>
</tr>
<tr>
<td>R</td>
<td>Reproduction</td>
</tr>
<tr>
<td>E</td>
<td>Early disease, death, or disability</td>
</tr>
<tr>
<td>N</td>
<td>Nongenetic</td>
</tr>
<tr>
<td></td>
<td>“Have there been any problems with pregnancy, infertility, or birth defects in your family?”</td>
</tr>
<tr>
<td></td>
<td>“Have any members of your family died or become sick at an early age?”</td>
</tr>
<tr>
<td></td>
<td>“How would you describe your ethnicity?” or “Where were your parents born?”</td>
</tr>
<tr>
<td></td>
<td>“Are there any other risk factors or nonmedical conditions that run in your family?”</td>
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...and some clinicians might not feel capable of creating or accurately interpreting a pedigree. As one approach, genetic counselors often start the history collection over the telephone, before the initial appointment, so that they and the families can begin the research needed for a complete pedigree. Although this approach might be less practical for primary care because of the time involved, the content of a 3-generation family history remains the important factor regardless of whether an actual pedigree is drawn.

No matter which tool or form a practice uses, clinicians have limited time to collect family history in the context of a preventive care visit. The average duration of time spent with a patient during a visit is 15.2 minutes for pediatricians and 17.9 minutes for family practitioners. According to a study by Acheson et al, the amount of time spent by family physicians on family history discussions averaged 2.6 minutes for a new patient and 1.8 minutes for a return patient. The challenge for clinicians is to collect a useful family history in a brief period of time.

Pediatric clinicians have an advantage over adult clinicians in that children are seen more frequently for preventive care visits, especially in the first 2 years of life. If the periodicity recommended by the American Academy of Pediatrics is followed, a child will be seen for 10 visits in that time period, which provides multiple opportunities to obtain and expand a family history. An extensive family history is recommended at the first visit, and an assessment of interval change is recommended at each subsequent visit.

The conditions that are the focus of interest can shift depending on the developmental stage of the child. For example, a family history of developmental delay might be the focus during the infant stage, but interest might shift to a family history of depression when the child is an adolescent. Creation of a 3-generation pedigree for a child and his or her family could provide years of prevention, risk reduction, and early identification if the pedigree were updated regularly and shared with the family. A recent survey of people with a family history of cancer suggests that detailed family histories of younger patients (starting at 18 years of age) might detect those at higher risk for a hereditary cancer syndrome. When a particular condition or syndrome is identified or suspected, disease-specific family history tools are available to direct and extend collection of family history information.
provide appropriate counseling for a family. The case involved a 4-year-old girl who had been diagnosed with autism spectrum disorder at 18 months of age. When she was seen by her primary care pediatrician for her 4-year well-child visit, her family history was updated, as recommended by the American Academy of Pediatrics. At that time, her mother related that in the previous 6 months her sister’s 2 sons had been diagnosed with fragile X syndrome. This new history prompted molecular genetic testing specific for FMR1, the gene that is responsible for fragile X syndrome, which led to the subsequent diagnosis of fragile X syndrome for this patient. Additional testing of the family revealed both the mother and an older sister as premutation carriers. For this family, the family history focused the evaluation and ultimately led to the correct diagnosis and provided a basis for both prognostic and reproductive counseling.

Additional clinical scenarios commonly dealt with by pediatric clinicians further illustrate use of the family history as a diagnostic tool. For instance, in evaluating an infant with several café-au-lait spots, the knowledge that one of the child’s parents has neurofibromatosis will clarify screening tests and follow-up for the infant. Likewise, awareness that a young adolescent girl with severe or prolonged vaginal bleeding at menarche has a father with von Willebrand disease will substantially guide the workup.11

A family history also helps to identify patterns of inheritance and can aid in a diagnostic workup, such as the evaluation of a boy with mental retardation in a family with a pattern of X-linked recessive mental retardation, even when no other family members carry a known diagnosis. The extension of this information is to use inheritance patterns to counsel other family members, quantify risk assessment for other relatives, and assess reproductive options.3 Inheritance patterns can be explained visually by using a standard pedigree, and the variability of expression can be similarly demonstrated. This is especially useful when making a diagnosis or presumptive diagnosis at an early age. It would be important for parents to know that their toddler with presumed neurofibromatosis might have only a dozen café-au-lait spots and a few neurofibromas like her father or might develop an optic nerve glioma and severe scoliosis like her aunt.

Another major use of a 3-generation family history is as a patient-education tool. Collection of family history information can demonstrate to patients the need for medical documentation of relatives’ histories and sharing of family history information with relatives. For example, did your uncle die of a myocardial infarction or of a fatal arrhythmia? Accurate documentation could be vital to a possible diagnosis of long QT syndrome in the family. Once a diagnosis of long QT syndrome is confirmed, parents can then be educated regarding signs and symptoms to be aware of in family members, such as near-sudden infant death syndrome, syncope, and aborted cardiac arrest, and can be counseled regarding their child’s participation in athletics or exercise programs that might increase the risk of an event.

The family history can also be used to clarify misconceptions that families have. Commonly, families erroneously assume that certain genetic diseases affect only one gender, because thus far, for example, only men have been affected in their family. Another common misconception is that a disease “skips” generations. This is often a result of incomplete penetrance, variability of expression, or misdiagnosis. Correcting these misunderstandings by using a simple pedigree can be invaluable to all the family members and often leads to expanded opportunities to explore levels of understanding and facilitate patient and family education.

FUTURE USES

The newest and potentially most exciting use of the family history is as a tool for public health and preventive medicine. In 2002, the Office of Genomics and Disease Prevention at the Centers for Disease Control and Prevention formed a multidisciplinary working group and developed a research initiative to explore these possible uses for family history information.7 This cause was further advanced in 2004 when US Surgeon General Dr Richard Carmona announced the inaugural National Family History Day in the November 25, 2004, edition of the New England Journal of Medicine.11

Most diseases are the result of the interactions of genes and environmental factors. Although these interactions are complex, almost every patient today has access to a free, well-proven, personalized genomic tool that captures many of these interactions and can serve as the cornerstone for individualized disease prevention. This valuable tool is the family history.10,11,13 The Valdez et al article (p S78) more completely explores this exciting and valuable use of the family history for identifying children at risk of common chronic conditions such as diabetes and cardiovascular disease.

STRATEGIES: PRACTICAL CLINICIAN POINTS

● Choose a family history tool that works for you, your patient, and your setting.

● The National Coalition for Health Professional Education in Genetics has a summary of available family history tools listed at www.nchpeg.org/newsletter/inpracticespr05.pdf.

● The March of Dimes has developed a preconception/prenatal family history questionnaire that is available at www.marchofdimes.com/pnhec/4439_1109.asp.

● Families can create their own simple pedigree with the US Surgeon General’s My Family Health Portrait, which is available at https://familyhistory.hhs.gov.
• Introduce families to resources during their first visit.
• Add family history links to your office or clinic Web site, if available.
• Provide handouts with resource information.
• Print out fact sheets from Web sites.
• Publicize Thanksgiving Day as Family History Day.
• Take advantage of frequent well-child visits to complete a family history.
• Post reminders or create slogans for clinicians and families, such as “Five Minutes for Family History” or “Don’t Forget Family History.”
• Involve the kids by using a computer.
• Involve the parents by obtaining a maternal prenatal family history.
• Review and update family history annually.

CONCLUSIONS
All pediatric primary care practitioners should have the basic competencies to collect and interpret a family medical history. Obtaining a family history remains an inexpensive and basic approach to identifying individuals at risk for genetic disorders. For adults, family history has also been shown to be an accurate way to approach risk identification for common complex disorders such as cardiovascular disease, diabetes, several cancers, asthma, and stroke. Family history is a way to reach those at higher risk and to target resources to get them into screening. A family history can establish patterns of inheritance and serve as a guide to diagnostic, therapeutic, and preventive approaches.

Pediatric clinicians are familiar with genetics in their patient population and have the advantage of frequent well-child visits for collecting and updating family history. A variety of tools exist to assist clinicians and patients in improved collection of these data. Pediatric clinicians will need to tailor the family history tool they choose to the strengths and challenges of their practice setting and their patient population. Numerous barriers impede the application of family history information to primary pediatric practice. New tools will be required to assist pediatric clinicians with the efficient collection and application of family history information in the era of genomic medicine.

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ABSTRACT

Family history captures the collective influence of shared genetic susceptibility, shared environmental factors, and common behaviors within families. Throughout the reproductive continuum, pediatricians, obstetricians, family practitioners, genetic counselors, and other clinicians can work with families to elicit relevant family history information and factor it into risk-assessment calculations and, when appropriate, decision-making. Current screening tools have focused on understanding the risk for single-gene disorders, chromosomal conditions, and teratogen exposures during the preconception, prenatal, and interconception periods. More research and data are needed to understand how family history influences risk for a wide variety of complex birth outcomes such as preterm birth, stillbirth, and many birth defects. With a better understanding of the impact of family history on many adverse birth outcomes, tools for the collection of a broader set of pertinent family history information must be developed.
When seeing a child for pediatric care, a pediatrician will compile a family history that includes not only the complete medical history of the child but also that of first-degree relatives (ie, siblings and parents), as well as more distant relatives such as aunts, uncles, and grandparents. Although a family history of birth defects or genetic conditions is of obvious particular relevance, more subtle medical conditions such as premature ovarian failure or multiple miscarriages can also be risk factors. Linking pediatric information with family medical history during the preconception (before pregnancy) or interconception (between pregnancies) period will provide the most comprehensive assessment of risk and provides a valuable supplement to information that is gathered routinely by obstetricians during prenatal visits.

The importance of preconception care has been emphasized for women by their health care clinicians. Pediatricians serve an important role in identifying family history information that is relevant to future pregnancies and making families aware of the need to discuss that information with the mother’s clinician during the interconception period to enhance continuity of care. Because pediatricians see children and their families frequently during the first year of a child’s life, they are likely to detect abnormalities that become important aspects of the family history for the mother in the preconception period should she choose to have a subsequent pregnancy. In addition, the father’s family history is important and may be captured in a pediatric visit.

Family history includes shared genetic susceptibility, shared environmental factors, and common behaviors within families. Although for most traditionally defined genetic conditions the prenatal influence of environmental factors and behaviors on infant outcome is largely unknown, these risks are increasingly being defined for a number of birth defects such as neural tube defects (NTDs) and orofacial clefts. Identifying family history of a condition during the preconception or interconception period provides the physician with a unique opportunity to raise familial awareness of increased risk and motivate behavior modification and decision-making to reduce risk and improve obstetric and subsequent pediatric outcome. Family history can also lead to early diagnosis during pregnancy, which allows for secondary interventions in decision-making during pregnancy, including location and mode of delivery and tertiary interventions in medical care during the newborn period and childhood.

An emerging challenge is the collection, translation, and transfer of family history information among the many health care professionals who will assist the family in using the information during these times of potentially unique opportunities for intervention. Electronic medical records may provide improved mechanisms to link information between family members, while still respecting their privacy. To enhance communication and continuity of care, pediatricians play a key role in conveying information about a child to his or her family and emphasizing the importance of sharing such information with the appropriate family members and clinicians to assist in health care and reproductive planning.

Advances in genetics and genomics are broadening the scope of conditions that can be screened or tested for during the preconception, prenatal, interconception, and early childhood periods. Here we examine several pediatric conditions for which a family history might warrant a number of screening and testing options.

**ROLE OF THE PEDIATRICIAN IN TRANSLATING FAMILY HISTORY**

Family medical history belongs to the entire family and should reflect as broad a picture of the nuclear and extended families as is feasible. Genetic conditions and birth defects may have implications for the parents’ own health as well as their reproductive planning. Pediatricians serve a critical role in interpreting for the parents the clinical findings that pertain to a child’s health and the implications for the parents’ own health and that of their subsequent pregnancies.

An autosomal recessive condition diagnosed in a child will often reveal for the first time that parents are asymptomatic carriers of the condition. Parents with a child who tragically dies of sudden infant death syndrome and whose workup reveals medium-chain acylcoenzyme A dehydrogenase deficiency should receive counseling about the possible implications for their older children, who might also have the condition. This could include anticipatory guidance regarding the importance of intervening early in the event of infection or febrile illness. In addition, reproductive planning for future children might include identifying the parents’ mutations to facilitate prenatal diagnosis.

Because pediatricians often see women more frequently than their obstetricians do between pregnancies, pediatricians can be important purveyors of family history information and counseling during the interconception period and can bridge the gap between a family’s pediatric and obstetric care. However, mechanisms to transfer family history information between pediatricians and obstetricians are not well established and often rely on the family with the potential inherent problems of miscommunication and inaccuracy. By linking a family’s health care, all of a family’s health clinicians can help facilitate the transfer of accurate and reliable information and thereby enhance continuity of care.

**TOOLS FOR SCREENING**

The role of family history as a marker for shared genetic susceptibility is growing as more is known about the genetic basis of many pediatric conditions. Several tools are commonly used during the prenatal period that can also be used during the preconception and interconcep-
tion periods to screen for increased risk on the basis of family medical history. One example is First Page, a screening tool developed by the Foundation for Blood Research.7 The simple 1-page tool inquires about personal or family history of many single-gene and chromosomal conditions as well as structural birth defects, teratogen exposures, and recurrent miscarriages. The First Page tool assesses risk for single-gene disorders that affect children, such as sickle cell disease and cystic fibrosis (CF), and provides detailed algorithms for appropriate counseling and testing. It also screens for complex pediatric conditions such as developmental delay, for which varying genetic and environmental causes exist.

The American College of Obstetricians and Gynecologists dedicates one section of its antepartum record8 to genetic screening and teratology counseling. The tool can be used to screen the patient, the infant’s father, or anyone in either family for increased risk for thalassemia (of Italian, Greek, Mediterranean, or Asian ancestry or with a mean corpuscular volume of <80), NTDs, congenital heart defects, Down syndrome, Tay-Sachs disease, Canavan disease, familial dysautonomia, sickle cell disease or trait, hemophilia or other blood disorders, muscular dystrophy, CF, Huntington’s disease, mental retardation/autism (specifically fragile X syndrome), other inherited genetic or chromosomal disorders, and maternal metabolic disorders (specifically type 1 diabetes or phenylketonuria) and find out about a previous child with a birth defect, recurrent pregnancy loss or stillbirth, and medications (including supplements, vitamins, herbs, over-the-counter drugs, illicit or recreational drugs, and alcohol).8

The American College of Obstetricians and Gynecologists also provides an obstetric medical history form,9 which the patient fills out by answering questions about personal health history, exposures affecting health, gynecologic health history, family history and genetic screening, and psychosocial screening. In the family history and genetic screening section, the patient is asked to identify her ethnicity and the ethnicity of the father. Subsequent questions ask whether she or the father has ever had a child born with a birth defect or whether they have birth defects themselves. The patient is then asked to describe any abnormalities that have occurred in children within her family or the father’s family, including mental retardation, birth defects, early infant death, deformities, or inherited diseases such as hemophilia, muscular dystrophy, or CF. A history of pregnancy losses (miscarriages or stillbirths) is then asked with follow-up information regarding previous genetic or chromosomal testing for the losses. The form also asks the patient whether she or the father is of an ethnic group that is at increased carrier risk for thalassemias (of Mediterranean or Southeast Asian ancestry or with a mean corpuscular volume of <80), NTDs, congenital heart disease. In the case of CF, a child born with meconium ileus might be tested for CF; if the child were affected, the test would reveal that both parents are obligate carriers. Prenatal testing would be recommended in any subsequent pregnancies and could be performed after identifying the specific mutations that the parents carry. Whereas family history was previously the sole indicator for carrier screening, population-based screening programs such as newborn screening are, in many states, now identifying newborns affected with CF well before they exhibit symptoms. In addition, preconception, prenatal, and interconception carrier-screening recommendations are broadening the scope of carrier testing,10 thereby providing more information to families whose members are CF carriers.

Families of certain ethnicities are encouraged to undergo carrier testing on the basis of increased carrier frequency among their ethnic group. For instance, all women with an Ashkenazi Jewish family background should be offered carrier screening during the preconception or prenatal period for Tay-Sachs disease, Canavan disease, CF, familial dysautonomia, mucolipidosis IV, Niemann-Pick disease type A, Fanconi anemia group C, Bloom syndrome, and Gaucher’s disease.11,12 Likewise, patients of Southeast Asian or Mediterranean background should be screened for abnormal hemoglobin variants,13 because thalassemias are more common in these regions. Individuals of African ancestry are offered screening for hemoglobinopathies, as well, because of the increased risk for being carriers of sickle cell disease or a-thalassemia.

FAMILY HISTORY OF SINGLE-GENE DISORDERS

Traditionally, family history has revealed increased risk for single-gene disorders such as sickle cell disease and CF. These conditions follow autosomal recessive–inheritance patterns, and a positive family history suggests that unaffected, at-risk family members should undergo carrier testing. In the case of CF, a child born with meconium ileus might be tested for CF; if the child were affected, the test would reveal that both parents are obligate carriers. Prenatal testing would be recommended in any subsequent pregnancies and could be performed after identifying the specific mutations that the parents carry. Whereas family history was previously the sole indicator for carrier screening, population-based screening programs such as newborn screening are, in many states, now identifying newborns affected with CF well before they exhibit symptoms. In addition, preconception, prenatal, and interconception carrier-screening recommendations are broadening the scope of carrier testing,10 thereby providing more information to families whose members are CF carriers.

FAMILY HISTORY OF BIRTH DEFECTS: NTDs

The prevention of NTDs has been quite successful with the implementation of public health messages encouraging folic acid supplementation and fortification of the food supply with folic acid.5 Family history serves a role in preventing NTDs during the preconception and interconception periods by providing a targeted recommendation for women at increased risk for NTD on the basis
of their personal or family histories. The general recommendation for all women of childbearing age is to take a multivitamin containing 400 μg of folic acid daily in addition to eating a healthy, well-balanced diet. The targeted recommendation is that women who have a personal history of an NTD or who have had a pregnancy or child affected by an NTD take 4 mg of folic acid starting 1 month before conception and continuing through the first 3 months of pregnancy. Screening for a family history of NTDs can have direct implications on preconception and interconception care by invoking targeted recommendations for prevention.

FAMILY HISTORY OF DEVELOPMENTAL DELAY

Fragile X Syndrome
Global developmental delay is a challenging pediatric diagnosis with a complex etiology that includes genetic and environmental factors and gene-environment interactions. One example of a single-gene condition that presents as a global developmental delay is fragile X syndrome, which is passed on through a triplet repeat expansion in a premutation state with ramifications for the entire family. For instance, a 32-year-old woman with fragile X syndrome during any subsequent pregnancy would be warranted. If this finding occurred before the mother desired a subsequent pregnancy, testing to determine premutation carrier status of the mother would be indicated during the interconception period. The prenatal implications are clear: a child affected with fragile X syndrome is likely to have a premutation carrier mother; thus, prenatal testing for fragile X syndrome during any subsequent pregnancy would be warranted.

In the scenarios presented here, establishing the diagnosis in one member of a family has implications for the entire family. Furthermore, the conditions that can affect premutation carriers provide expanded opportunities for screening. Whereas screening for a family history of developmental delay or autism currently occurs during preconception and prenatal care, screening for a sister with premature ovarian failure or a father with ataxia does not. Screening tools for use during the preconception and prenatal periods could be expanded to include other aspects of family history that can identify a family at risk. This would offer increased opportunities for a family to understand its risk earlier, which is generally desirable. A 2003 study showed that 55.5% of families with at least 1 child diagnosed with fragile X syndrome reported having another child before they found out about the fragile X syndrome diagnosis in their first child.

Chromosomal and Genomic Etiologies
Global developmental delay can also result from chromosomal abnormalities, including an unbalanced translocation (exchange of material between 2 chromosomes). For example, Down syndrome can result from an unbalanced translocation involving chromosome 21. A parent with a balanced translocation and, thus, a full complement of chromosomes can pass on an unbalanced translocation to his or her child, which leads to developmental delay and other abnormalities. The family history might reveal a history of recurrent miscarriages in the individual carrying the balanced translocation. If a known balanced translocation carrier becomes pregnant, prenatal testing should be undertaken via chorionic villus sampling during the first trimester or by amniocentesis during the second trimester to determine the chromosomal complement of the fetus. Thus, a family history of Down syndrome, developmental delay, or multiple miscarriages could indicate the need for karyotype analysis of the mother to test for a balanced translocation.

Technology is moving forward rapidly and expanding our ability to test for more conditions. Array-based comparative genomic hybridization, also known as chromosomal microarray analysis (CMA), offers simultaneous testing for an increase or loss of genetic material on all 23 pairs of chromosomes. The role of family history as an indicator for such testing remains an interesting future research subject. When a child with developmental delay or congenital anomalies is tested in childhood and found to have a chromosomal abnormality, the finding becomes part of the family history. With this family history, prenatal testing during subsequent pregnancies could then be undertaken via CMA. Furthermore, perhaps a woman in a family with a deceased member with unexplained mental retardation or developmental delay would consider undergoing CMA testing during her pregnancy. Whether testing is warranted remains unclear, and research is needed to understand the performance and role of CMA testing.

COMPLEX CONDITIONS: ADVERSE BIRTH OUTCOMES

Family history might also be relevant to the assessment of risk for complex conditions and adverse birth outcomes such as placental abruption or preeclampsia. The factor V Leiden mutation imparts an increased risk for clotting abnormalities, which can lead to miscarriage during the first trimester or increase the risk for placental abruption and subsequent poor birth outcomes during the second and third trimesters. A woman with a sister or mother who had a deep venous thrombosis at a young age while taking oral contraceptives, a history that is consistent with factor V Leiden heterozygosity,
might consider factor V Leiden mutation testing when anticipating pregnancy. The factor V Leiden carriage rate is ~5.3% among white Americans, 2.2% among Hispanic Americans, 1.3% among Native Americans, 1.2% among black Americans, and ~0.5% among Asian Americans. Women in whom the factor V Leiden mutation is detected can be managed with aspirin or low molecular weight heparin during the preconception, prenatal, and interconception periods with improved birth outcomes. Because clotting abnormalities are implicated in outcomes such as abrupton that lead to preterm birth with potentially lifelong sequelae, such screening and testing for complex birth outcomes represents the future direction of preconception and interconception screening.

CONCLUSIONS
Although risk reduction through the elimination of environmental risk factors remains an important aspect of preconception, prenatal, and interconception care, research in the genomic era is in the process of translating the vast information found in the genome sequence into information that will improve health. Family history helps to capture the information that is contained within each individual child’s genome and currently holds much promise to raise awareness of individual risk and motivate interventions and behavior change to minimize that risk.

Current screening tools have focused on understanding the risk for single-gene disorders, chromosomal conditions, and teratogen exposures during the preconception, prenatal, and interconception periods. More research and data are needed to understand how family history influences risk for a wide variety of complex birth outcomes such as preterm birth, stillbirth, and many birth defects. With a better understanding of the impact of family history on many adverse birth outcomes, tools for the collection of a broader set of pertinent family history information must be developed.

Pediatricians can facilitate the linking of pediatric, preconception, and interconception care by working with families and their obstetricians, family practitioners, and other health care clinicians to enhance communication and knowledge about risk as well as provide guidance on how to minimize that risk and improve pregnancy outcomes.

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Utility of Family History Reports of Major Birth Defects as a Public Health Strategy

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ABSTRACT

A major birth defect is an abnormality that can affect the structure or function of an organ. In the United States, major birth defects are the leading cause of infant mortality and contribute substantially to childhood disability and morbidity. Globally, these conditions lead to the death of millions of infants and children annually. Patients with 1 or more affected family members may be at increased risk for having a child with a major birth defect; thus, accurate knowledge of these conditions among family members of their patients gives the clinician the ability to provide improved risk assessment and reproductive planning. Such knowledge can also serve as motivation for patients to adhere to healthy behaviors such as folic acid use or smoking cessation. To evaluate the utility of collecting family history reports of major birth defects as a public health strategy, 6 key criteria were examined by reviewing the relevant published literature. Overall, the review showed that major birth defects satisfied several of the criteria. Additional research is needed, however, regarding the awareness of parent reports of the occurrence of these conditions among relatives and how knowledge of birth defect diagnoses and related risk factors are transmitted among relatives. Such research needs to encompass not only immediate family members but also other first-degree and second-degree relatives. In summary, routine collection of family history reports of birth defects in pediatric practice holds promise as a public health strategy to reduce the burden of morbidity, mortality, and disability associated with major birth defects.
A positive family history of disease has often been ascribed to an underlying genetic susceptibility. In recent years, our understanding of specific genetic predispositions to the risk of disease has been enhanced through information provided by the Human Genome Project and related endeavors such as the International Haplotype Mapping Project. To date, gene discovery using such information has accounted for a small proportion of the total burden of a particular disease (eg, BRCA1 mutations for breast cancer prevention). Less well understood is the contribution of a positive family history as a predictor of common chronic diseases that encompass both genetic and partial genetic origins (ie, multifactorial conditions). Birth defects can be grouped into 2 broad categories: major and minor defects. A major defect is an abnormality of an organ structure or function that results in physical disability, mental disability, or death, whereas a minor defect does not produce significant health consequences. Both major and minor defects can occur as isolated entities, affecting 1 organ system, or as multiple defects, affecting 1 or several organ systems. Alone, minor defects are not considered to have significant health consequences, although their presentation with 1 or more major defects can provide clues to an underlying genetic or teratogenic etiology. Conservatively, estimates suggest that a causal gene or teratogen accounts for <30% of defects that occur. For the remainder, the most likely explanation is a confluence of genetic and teratogenic exposures and, to a lesser degree, factors such as intrauterine constraint and amniotic bands that can lead to deformations and disruptions, respectively, of otherwise normally developed structures.

As with many common chronic diseases, multiple etiologies for major birth defects present challenges in disentangling risk associated with a reported family history of these conditions. Approaches to inferring risk of common chronic diseases on the basis of family history information have been attempted through calculation of quantitative family history scores or classification of risk into qualitative categories. Most recently, Yoon et al proposed development of a public health–oriented family history tool to identify risks for common chronic diseases. To be most effective across diverse populations, they recommended that the tool be simple, easily applied, and inexpensive and that a disease to be included in such a tool (1) contributes to a substantial public health burden, (2) has a well-defined case definition, (3) generates awareness among relatives, (4) is accurately reported by family members, (5) has family history as an established risk factor, and (6) has established and effective interventions for prevention.

To date, the work by Yoon et al has encompassed evaluation of family history information for several common chronic diseases. This article uses the framework established by Yoon et al to evaluate the utility of collecting family history reports of major birth defects as a pediatric public health strategy. Specifically, it attempts to summarize the relevant published literature to assess each criterion for inclusion.

Substantial public health burden

In the United States, major birth defects, including structural defects and chromosome anomalies, are estimated to affect 3% of all live births. Major birth defects also continue to be the leading cause of infant mortality in the United States, and costs for care and treatment of children with major birth defects annually totals millions of dollars. Canfield et al used pooled data from 11 states with active case finding to calculate national birth prevalence estimates for 18 selected defects. Rates calculated ranged from 0.82 per 10 000 live births for truncus arteriosus to 13.65 per 10 000 live births for Down syndrome, and these estimates varied according to race and ethnicity. Compared with the rates for children of non-Hispanic white mothers, rates were significantly higher for tetralogy of Fallot, lower-limb–reduction defects, and trisomy 18 among children of non-Hispanic black mothers and significantly higher for anencephalus, spina bifida, encephalocele, gastrochisis, and Down syndrome among children of Hispanic mothers.

Major birth defects also represent a global public health burden. A recent report by the March of Dimes showed that, worldwide, an estimated 6% of births or 7.9 million children are born annually with a major birth defect of genetic or partially genetic origin. Among the most common disorders identified were congenital heart defects, neural tube defects, thalassemia, sickle cell disease, Down syndrome, and glucose-6-phosphate dehydrogenase deficiency. The report also cited that, annually, hundreds of thousands more children are born with defects resulting from in utero exposure to teratogenic agents, such as alcohol or infectious disease, and that at least 3.3 million children <5 years old die as a result of major birth defects. The highest totals of occurrence (94%) and deaths (95%) that resulted from major birth defects were found in middle- and low-income countries.

Well-defined case definition

Detailed clinical descriptions or definitions are available for individual major birth defects. For example, a cleft lip (CL) can be defined as an incomplete closure of the lip that is often accompanied by a maxillary alveolar defect (gum), cleft palate (CP), or both. The maxillary alveolar defect can be a complete cleft that is continuous with the CP, or it can be limited to a notch on the gum. The CL can show unilateral, bilateral, or median presentation and can be further specified as a complete CL, in which the defect extends through the entirety of the lip and the...
nasal floor and is often associated with a more-severe nasal deformation, or an incomplete CL, in which the defect does not extend into the nasal floor. In clinical practice, major birth defects are usually documented by using the World Health Organization’s International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Birth defect monitoring systems, such as the Metropolitan Atlanta Congenital Defects Program, use an expanded version of the ICD-9-CM that is based on the British Paediatric Association (BPA) Classification of Diseases. These modified BPA codes retain the original ICD-9-CM code for a particular defect and expand the code to include reference to location. For example, a unilateral complete CL could be further specified as a right, unilateral complete CL.

**Awareness of Birth Defects Among Relatives**

Although well-defined case definitions exist for major birth defects, the awareness of a diagnosis among relatives or even self-awareness of a diagnosis is variable. Romitti evaluated family history reports of birth defects provided by telephone interview from a sample of mothers (case mothers, n = 28; control mothers, n = 29) who participated in a population-based study of orofacial clefts in Iowa. Responses for specific birth defects reported by these mothers were reviewed by a board-certified clinical geneticist and classified as definite; possible, but more information needed; or excluded (ie, not a birth defect). Of the 84 defects reported for relatives, 38 (45.2%) were classified as definite, 6 (7.1%) were classified as possible, and 40 (47.6%) were excluded. Examples of excluded defects were single-gene conditions that manifested later in childhood such as cystic fibrosis and multifactorial traits such as asthma. Using this sample, Romitti requested permission from mothers to contact first- and second-degree relatives to obtain self-reports of birth defects. Overall, 345 (66%) case and 380 (69%) control adult relatives provided self-reports and reports for 299 offspring. These reports recorded 147 birth defects among relatives, and review by a clinical geneticist classified 68 (47.0%) as definite and 27 (15.1%) as possible; the remaining 52 (37.9%) reports were excluded.

More recently, family history reports provided by telephone interview from case (n = 9331) and control (n = 3390) mothers who participated in the National Birth Defects Prevention Study were evaluated (R. Fisk Green, PhD, R. S. Olney, MD, J. Reelhuis, PhD, L. D. Botto, MD, P.A.R., National Birth Defects Prevention Study, unpublished data, 2007). Maternal reports of birth defects were classified initially according to the type of condition (eg, birth defect, genetic disorder, or developmental disability), and reports coded as birth defects or genetic disorders were subsequently assigned a level of detail (high, medium, or low) that corresponded to the terminology used by the mothers. For example, a maternal report that provided the specific medical terminology to describe the defect (eg, ventricular septal defect) was coded as having a high level of detail; a report that provided a positional or conformational description (eg, hole in heart) was coded as having a medium level of detail; and a report that provided a nonspecific description or mentioned only the organ group (eg, heart defect) was coded as having a low level of detail. Using this coding system, they found that mothers most often tended to provide a high level of detail for defects that were phenotypically evident (eg, neural tube defects and orofacial clefts), whereas a medium or low level of detail tended to be reported for defects that were less phenotypically evident (eg, heart defects) (R. Fisk Green, PhD, R. S. Olney, MD, J. Reelhuis, PhD, L. D. Botto, MD, P.A.R., National Birth Defects Prevention Study, unpublished data, 2007).

Fisk Green et al also noted that reports were influenced by case status and maternal demographic factors; mothers who were non-Hispanic white, aged ≥25 years, had more than a high school education, and had an annual income greater than $20 000 were more likely to provide reports of affected relatives.

**Accurate Reporting of Birth Defects Among Relatives**

Four published studies were identified that have examined the accuracy of reporting of birth defects among relatives: 3 that examined maternal reports for offspring only and 1 that examined maternal reports for offspring and first- and second-degree relatives. Axelsson and Rylander compared questionnaire reports of birth defects among offspring provided by 745 mothers with information recorded in the Swedish Register of Congenital Malformations. They found that mothers failed to identify 10 of the 38 children recorded in the register as having a defect and also listed 24 defects that were not ascertained by the register. Although not reported by the authors, sensitivity and specificity estimates computed by using these data would have been 74% and 97%, respectively. In a similar comparison of maternal interview reports from the Atlanta Births Defects Case-Control Study and records from the Metropolitan Atlanta Congenital Defects Program, Rasmussen et al found that 3024 of 4929 case mothers reported that their child had a major birth defect (yes/no for presence of a defect), for a sensitivity estimate of 61%; 67 of 3029 control mothers gave responses that indicated that their child had a major birth defect, which produced a specificity estimate of 98%. The authors also reported that maternal age of ≥25 years, college education, and non-Hispanic white race were independently associated with the sensitivity of interview responses. More recently, Chessa et al used a modified Leuven knowledge questionnaire to survey parents of patients with congenital heart defects at a university pediatric cardiology department in Italy. The investigators surveyed parents in 148...
families and found that 91% of them were able to correctly name the heart defect diagnosed for their children, and 55% were able to indicate on a diagram where the heart defect was located, but only 10% correctly identified their risk of having another child with congenital heart disease.20

Using the relative self-reports described previously as a gold standard, Romitti et al21 evaluated maternal interview reports of family history information. For all relatives combined, sensitivity for presence (yes/no) of a birth defect was 31% for case mothers and 9% for control mothers; specificity was 98% and 97%, respectively. Mothers who correctly identified a relative who recorded a birth defect also often showed agreement for the specific defect group. In addition, the authors found that the sensitivity of interview responses was higher when the child was first in the birth order and mothers were <30 years old and participated in family genealogy.21

Taken together, these studies showed that the sensitivity of maternal reports for presence of a defect was high for offspring but considerably lower for other first-degree and second-degree relatives. For all relatives, the accuracy of reports varied according to the type of defect.

FAMILY HISTORY AS AN ESTABLISHED RISK FACTOR
For several major defects, an affected parent has an increased risk of delivering a child with the same malformation compared with an unaffected parent. Also, parents with 1 or more affected children have a higher risk of having a subsequent affected pregnancy. Using isolated CL plus CP as an example, unaffected parents with no family history of CL plus CP have a risk of ~0.1% for delivering a child with CL plus CP. If 1 of these parents is affected with CL plus CP, the risk increases to 2% to 5%. In addition, parents who have 1 affected pregnancy have a 3% to 7% risk for recurrence in a subsequent pregnancy (sibling), and those with 2 affected pregnancies have an 8% to 14% risk. It is important to note that these estimates might vary depending on characteristics of the underlying population (eg, race or ethnicity) and location of the defect (eg, bilateral versus unilateral). In addition, recurrence risk for CL plus CP with an underlying genetic origin might be as high as 25% for unaffected parents.22

Several researchers have also investigated the risk of major birth defects associated with a reported family history of a defect in combination with other factors. Although a detailed review of these studies is beyond the scope of this discussion, use of selected examples highlights their commonalities. Hwang et al23 examined the risk of clefting associated with a family history of birth defects, maternal smoking, and variants in the transforming growth factor α gene (TGFA) among case and control children delivered in Maryland from 1984 through 1992. They found a significantly higher frequency of family history of birth defects among case children compared with control children. In addition, they reported a significantly increased risk of CP associated with the potential interaction between mothers who smoked during pregnancy and infants who carried the rarer C2 allele at the TGFA Taq1 site (odds ratio [OR]: 8.69; 95% confidence interval [CI]: 1.57–47.8).23 Findings from this study were replicated in an investigation in California24 but not in investigations in Iowa25 or Denmark.26 In these latter studies, however, a family history of clefting was found more frequently among case than among control children.

Using data from the Atlanta Birth Defects Case-Control Study, Honein et al27 examined the association of family history of clubfoot and maternal smoking on the occurrence of clubfoot in offspring. They found elevated risk estimates for the independent effects of family history of clubfoot (OR: 6.52; CI: 2.95–14.41) and smoking (OR: 1.34; 95%; CI: 1.04–1.72) and for the joint effects of each exposure (OR: 20.30; CI: 7.90–52.17).27 An investigation of similar risk factors in Washington State tended to support the findings of an elevated risk of clubfoot associated with maternal smoking and an increased occurrence of clubfoot among relatives of case children compared with relatives of control children.28

In the studies mentioned previously, reports of birth defects among relatives were provided by the mother through an interview or self-administered questionnaire, and birth defect reports for relatives tended to be higher among mothers of case children than mothers of control children. Selected environmental agents also affected the risk estimates reported, which supports the suspected multifactorial inheritance for these defects. The magnitude of risk observed could reflect a true difference in occurrence of defects between case and control relatives, true differences in exposure to deleterious environmental agents, reporting bias between case and control mothers, or, most likely, some combination of these explanations.

EFFECTIVE INTERVENTIONS FOR PREVENTION
The myriad risk factors for major birth defects present numerous approaches for reducing the occurrence of these conditions. Among the approaches are avoidance of selected medications during pregnancy,29 vaccinations against infectious disease,30 and cessation of cigarette smoking31 and alcohol consumption32 to reduce risk. Perhaps one of the biggest success stories in birth defects prevention has been the identification of the benefits of folic acid. Randomized clinical trials have demonstrated the benefits of periconceptional supplementation of folic acid and a reduced risk of neural tube defects,33,34 which prompted public health recommendations for daily folic acid supplementation for reproductive-aged women and, since 1998, folic acid fortification of grain products in the United States. Evaluation of population preva-
Prevention programs have been developed to reduce the recurrence of neural tube defects by targeting families with an affected child. Collection of family history reports among these families provides an opportunity to target additional relatives who might benefit from directed interventions to reduce the occurrence of these defects. To date, limited published information exists about the utility of such an approach. Byrne et al examined folic acid knowledge and use among aunts of children with neural tube defects in Ireland to identify the success of prevention approaches in high-risk families. They found 57.9% of pregnancies reported by aunts to have been supplemented before pregnancy and 89.5% of pregnancies to have been supplemented during pregnancy. Byrne also examined the effect of distributing a folic acid–intervention pack to the aunts and female first cousins of children who were affected with neural tube defects. Although 73% of the aunts and cousins had knowledge of the benefits of folic acid, only 8.8% used folic acid before the intervention; the rate of use increased to 19% after intervention.

CONCLUSIONS

Major birth defects satisfy many of the criteria outlined by Yoon et al for use of family history reports as a public health strategy. These defects represent a substantial public health burden both in the United States and worldwide. There also exist well-defined case definitions for major birth defects, including systematic criteria for diagnosis of recognizable patterns of defects that may have an underlying genetic or teratogenic etiology. In addition, family history is a risk factor for birth defects, although the magnitude of risks observed could also reflect differences in exposure to deleterious environmental agents, reporting bias, or a combination of these factors. Last, effective interventions exist for reduction of major birth defects, including folic acid supplementation and fortification, which may be especially important in families with a family history of folate-sensitive birth defects.

Less clear and less well studied, however, are the awareness of major birth defects among relatives and the accuracy of reporting these defects. Additional research is needed regarding the awareness of these conditions among relatives, including self-awareness, and the accuracy of parent reports for these conditions among relatives. In particular, research to date has largely focused on defects that occurred among offspring and needs to be extended to other relatives. Also, such research needs to encompass all pregnancy outcomes for an individual, because major birth defects contribute to miscarriage, intrauterine death, and stillbirth. For example, the occurrence of CL, CP, or both, is thought to be 3 times higher among pregnancies that end in miscarriage or stillbirth compared with live births. In addition, future research should target how knowledge of birth defect diagnosis and shared risk is transmitted among immediate family members and more distant relatives.

To improve awareness of birth defects among relatives, classification schemes developed for surveillance projects might be useful. For their work with the Antiretroviral Pregnancy Registry, Scheuerle and Tilson condensed and rearranged the BPA code list to create a classification scheme that combined defects with common general diagnoses and some degree of common pathogenesis to classify affected pregnancies among mothers who took antiretroviral medications during pregnancy. As an example, they reduced the numerous available codes for CL plus CP to CL of any type without CP, CL of any type with CP, and CP alone. A related approach was developed by the Iowa Registry for Congenital and Inherited Disorders (IRCID) to notify birth parents of an affected live-born child that their child has been identified by the IRCID. This notification is made by mail and includes a letter describing the IRCID and the defect diagnosis(es) of the child. So that parents recognize the terms used to describe a defect, the letter includes both the medical term (BPA definition) and a lay term for the defect that was developed by a group of clinical geneticists, genetic counselors, and IRCID staff.

To improve the accuracy of reporting of birth defects among relatives, attention should be paid to the mode of information request and the types of items used. Cole et al designed a mailed, self-administered family history questionnaire for patients who were attending a medical genetics clinic to replace collection of pedigree information at the time of the clinic visit. Comparing family history information collected in the clinic setting with that collected by the self-administered questionnaire, Cole et al found that the questionnaire provided patients with the opportunity to consult with other family members, increased their awareness regarding reasons for their clinic visit, reduced clinic time, and increased standardization of family history data collection. Romitti et al concurred with Cole et al on the use of a self-administered questionnaire and recommended that attention be given to the type of birth defect items used. The authors found that less-specific items (eg, born with an eye defect) tended to encourage the recording of defects (eg, farsighted) that were neither classified as definite nor possible birth defects and produced reports of unspecified defects (eg, limb defects) in excess of expected prevalence rates. As such, Romitti et al recommended that family history questionnaires for investigations of birth defects contain only specific, closed-ended items.

In summary, accurate knowledge of family history of
birth defects is important for making informed decisions regarding clinical care, risk assessment, and reproductive planning. Before implementing a routine family history tool for birth defects in the pediatric visit, further research is needed in how best to collect and evaluate the accuracy of birth defect reports and how knowledge of birth defect diagnosis and related risk factors is transmitted among relatives. As recommended by Yoon et al, improved understanding of these factors will allow for evaluation of the analytic and clinical validity of the tool developed, as well as the clinical utility of such knowledge in reducing the public health burden of birth defects.

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Is Family History a Useful Tool for Detecting Children at Risk for Diabetes and Cardiovascular Diseases? A Public Health Perspective

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ABSTRACT

Several studies indicate that the risk for type 2 diabetes or cardiovascular disease is detectable in childhood, although these disorders may not emerge until adulthood. In addition, type 2 diabetes and cardiovascular disease seem to share risk factors, including obesity and dyslipidemia, and might even share etiology, which has important implications for screening and prevention strategies for both diseases. Primary prevention, in particular, has gained importance because the results of major randomized, controlled trials strongly suggest that, at least in high-risk adult groups, type 2 diabetes can be prevented or delayed. Furthermore, some intervention studies indicate that the risk factors for diabetes and cardiovascular disease can be reduced in children. A simple way to detect risk for either diabetes or cardiovascular disease is to examine the family history. Numerous studies have shown that adults who have 1 or more first- or second-degree relatives affected with diabetes or cardiovascular disease are at high risk of having or developing these diseases. Currently, there are no overall screening strategies recommended for either diabetes or cardiovascular disease among children and adolescents. The evidence is strong, however, that youth with a positive family history already show signs of increased risk for these conditions. Family history can be part of the approach to screening for children at risk of diabetes and cardiovascular disease and should be part of prevention campaigns aimed at reducing the burden of these diseases and their risk factors in children.
A COMMON ASSUMPTION in the epidemiology of chronic disease is that there will be a long time between exposure and expression of the disease. A challenge to this assumption is the increasing appearance of children with type 2 diabetes or distinctly elevated risk for cardiovascular disease (CVD). Explanations for such accelerated development include increased frequency and intensity of environmental risk factors, greater numbers of genetically susceptible people exposed early to risk factors for chronic disease as a result of urbanization and industrialization, and, most likely, a combination of these circumstances. The appearance of signs of adult chronic diseases in children indicates that genetic factors are important, because the environment has had only a short time to act. However, environmental risk factors are also at work, with drastic deteriorations of diet and physical activity patterns in the past several decades. The foods consumed, the frequency with which we eat, and the amounts we ingest have been affected by major shifts in the way we produce, process, and distribute food. Changes in physical activity have been prompted, mostly, by modifications to our built environment and the technology we have come to depend on in our daily lives.

Distinguishing genetic from environmental causes is difficult in chronic, multifactorial diseases. Fortunately, there is a simple way to explore simultaneously the influence of genetic and environmental factors on a condition: the use of family history. There is no standard operational definition of family history, but having 1 or more first- or second-degree relatives who are affected with a condition is often considered a positive family history for an individual person. In this article we discuss the use of a family history of type 2 diabetes or CVD as both an indicator of risk and a tool for disease prevention in public health practice.

THE BURDEN OF DIABETES AND CVD AND THEIR RISK FACTORS

In the United States there are ~21 million adults (aged >20 years) and 180 000 young people (aged ≤20 years) with diabetes, and there are ~1.5 million new cases of diabetes diagnosed every year. Most adult cases are of type 2 diabetes, and most cases in youth (aged ≤20 years) are type 1. Type 2 diabetes, however, seems to be increasing rapidly among children and adolescents.

CVD includes heart disease and stroke, the first and third leading causes of death in the United States. It was estimated recently that some 71 million or 35% of US adults have some form of CVD (ie, heart disease, stroke, heart failure, high blood pressure [BP], and congenital cardiovascular defects). Approximately 10% of adolescents aged 12 to 19 years have total cholesterol concentrations that exceed 200 mg/dL, which is an important risk factor for CVD. High BP in children and adolescents is defined as a systolic BP (SBP) and/or a diastolic BP (DBP) at or above the 95th percentile for the youth’s age, gender, and height. In youth, a BP between the 90th and 95th percentiles is considered prehypertension (ie, an above-normal BP that is just below the threshold for hypertension); this is associated with an increased risk of developing hypertension. Elevated BP in childhood and adolescence is considered a predictor of elevated BP later in life.

A major public health concern is that diabetes and CVD share risk factors. In the pediatric age group, both overweight (BMI ≥ 95th percentile according to age and gender) and impaired glucose metabolism are now relatively common and have been increasing among both children and adolescents. A recent report estimated that among US children aged 2 to 19 years, 17.1% are overweight, and another 16.5% are at risk of overweight. In addition, among adolescents, 1 in 10 boys and 1 in 25 girls have impaired fasting glucose; these figures double among overweight adolescents. Compared with their peers with normal fasting glucose, adolescents with impaired fasting glucose have an unfavorable cardiovascular profile, with significantly higher levels of glycated hemoglobin, total and low-density lipoprotein (LDL) cholesterol levels, fasting triglyceride levels, SBP, and fasting insulin, as well as lower concentrations of high-density lipoprotein (HDL) cholesterol.

FAMILY HISTORY AS AN INDEPENDENT RISK FACTOR FOR TYPE 2 DIABETES AND CVD

Numerous epidemiologic studies have shown that people with 1 or more first-degree relatives who are affected with diabetes are 2 to 6 times as likely to have the disease compared with people who have no affected relatives. Some studies have suggested that the contribution of family history to this excess risk is actually independent of that conferred by other common risk factors. For example, in a recent study that tested the effectiveness of the screening guidelines from the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus using a US national sample, having at least 1 first-degree relative with diabetes doubled a person’s risk of having undiagnosed diabetes even after adjusting for age, ethnicity, BMI, hypertension, HDL-cholesterol level, high triglyceride level, and gestational diabetes.

In support of the consistent epidemiologic findings about family history, a wide range of metabolic studies have reported early signs of abnormalities among otherwise healthy people who have a family history of diabetes. Persons with a positive family history of diabetes, including children, might show early signs of defective insulin actions, glucose intolerance, lipid abnormalities, high BP, large weight gains, reduced β-cell function, impaired endothelial function, and altered energy (mitochondrial) metabolism.

The epidemiologic evidence for the familial aggregation of CVD is also strong. For example, a US study...
found that 14% of the families had a positive family history of coronary heart disease (CHD), but this group contained 72% of the cases of early CHD (at <55 years of age). Similarly, 11% of the families had a positive family history for stroke, but 86% of the cases of early stroke (at <55 years of age) occurred in this group. Researchers from the Framingham Study, who used prospective data and consistently validated CVD events in parents, offspring, and siblings, reported that having CVD in at least 1 parent doubled the 8-year risk of CVD among men and increased (albeit nonsignificantly) the risk among women by 70%. The excess risk was independent of other risk factors such as age, ratio of total/HDL-cholesterol level, SBP, antihypertensive therapy, diabetes, BMI, and current smoking status. Furthermore, having at least 1 sibling with CVD was associated with an increased risk independent of the usual risk factors and the premature occurrence of CVD in the parents.

Although family history has been found to contribute independently to the risk of both diabetes and CVD, it is rarely used quantitatively to assess such risk. When it is, family history is mostly used to rank subgroups within a population according to the excess prevalence in 1 group relative to another (relative risk). More often, family history is used in concert with other well-known risk factors to predict disease in individual people in a given period (absolute risk). Guidelines from the American Diabetes Association, the American Heart Association, and the National Cholesterol Education Program include family history as a factor that should be considered to assess risk and make decisions about treatment. In addition, in several major studies, family history has shown significant contributions to risk scores even after accounting for other well-established risk factors.

Because diabetes and CVD share risk factors such as obesity and dyslipidemia and might even share etiology, people with a family history of diabetes show increased risk for CVD. Conversely, people with a family history of CVD might show early signs of insulin resistance and impaired glucose metabolism and, ultimately, risk of diabetes. This sharing of risk factors, and possibly of etiology, has important implications regarding joint screening and prevention strategies for the 2 diseases.

**EVIDENCE THAT DIABETES AND CVD START EARLY IN LIFE**

Several studies have highlighted the presence of insulin resistance and CVD risk factors among children. For example, the Bogalusa Heart Study, in a series of cross-sectional studies, demonstrated conclusively that cardiovascular risk factors are detectable in childhood and that signs of adult heart disease, including atherosclerotic lesions, are evident as early as the second and third decades of life. Other studies that have demonstrated the presence and development of risk factors in children and adolescents include the Pathobiological Determinants of Atherosclerosis in Youth Study, the Muscatine Study, Project HeartBeat!, and the Cardiovascular Risk in Young Finns Study. A different line of argument, which began with detailed geographic studies in the United Kingdom and Wales, is that infants who are malnourished during their fetal life and early infancy are more susceptible to CVD and diabetes as adults.

**EVIDENCE THAT TYPE 2 DIABETES AND CVD ARE PREVENTABLE**

Results of 3 major randomized, controlled trials from China, Finland, and the United States indicate that, at least in high-risk adult groups, the incidence of type 2 diabetes can be significantly reduced with lifestyle interventions involving diet, exercise, or a combination of both. In the study from the United States, the reduction in risk was similar across all racial/ethnic groups and was significant in all age and BMI subgroups.

In the pediatric population, there have been some attempts to lessen the risk factors for diabetes in children from high-risk groups. For example, the Bienestar Health Program is a school-based intervention that was designed to reduce the risk of diabetes in preadolescent Mexican Americans. This 7- to 8-month program used 50 training sessions with 3 major messages: decrease dietary intake of saturated fat, increase dietary intake of fiber, and increase physical activity. At the end of the program, children in the intervention group had decreased blood glucose concentrations and increased fitness and intake of dietary fiber when compared with the control group. There were no differences between the control and intervention groups regarding the percentage of total body fat and intake of saturated fat.

In adults, reducing or controlling risk factors for heart disease and stroke can reduce the risk of cardiovascular deaths and events. For example, studies conducted in Veterans Administration hospitals in the 1960s demonstrated that lowering DBP by medication resulted in fewer cases of stroke, cardiac failure, and worsening hypertension. More recently, an average reduction of 12 to 13 mm Hg in SBP over 4 years of follow-up was reported to be associated with reductions of 21% in CHD, 37% in stroke, 25% in total cardiovascular mortality, and 13% in all-cause mortality. Others have estimated that a 10% reduction in serum cholesterol concentrations may reduce the incidence of coronary events by 30%. With regard to the prevention of CVD in children, the evidence from well-designed school-based interventions indicates that health-related knowledge, attitudes, and behaviors in children can be changed significantly and positively in a relatively short time. In addition, several randomized, controlled trials have shown that risk factors in children and adolescents can be modified outside the school setting. Overall, these changes are usu-
ally modest, but they might prove to be of importance when translated to the general population of pediatric age and to high-risk children in particular. For example, in a 3-year intervention, the Child and Adolescent Trial for Cardiovascular Health demonstrated that the percentage of calories from fat could be significantly reduced in school lunches (from 38.7% to 31.9%) and that the amount of vigorous physical activity could be significantly increased during physical education classes (from 37% to 52%). However, total cholesterol level, SBP and DBP, and BMI did not differ significantly between those in the intervention and control schools at the end of the study.71,72

As an example of an investigation in a non–school setting, the Dietary Intervention Study in Children was a randomized, controlled trial in children aged 8 to 10 years with elevated LDL-cholesterol levels.73 The children were recruited from schools, a health maintenance organization, and several pediatric practices. The dietary intervention, which followed recommendations of the National Cholesterol Education Program, reduced the percentage of energy intake from total fat from 33.4% to 28.5% during the intervention, and this percentage remained virtually unchanged at a later follow-up (5 years later). Meanwhile, LDL-cholesterol levels decreased from 130.6 to 109.8 mg/dL and then increased to 114.1 mg/dL 5 years later.

Weight loss in overweight adolescents has been found to be associated with a decrease in BP.74 A meta-analysis of 12 randomized trials suggested that increased physical activity resulted in a small but not statistically significant decrease in BP.75

SCREENING STRATEGIES FOR DIABETES AND CVD

No overall screening strategies have been recommended for either diabetes or CVD among children and adolescents. The American Diabetes Association recommends that children should be tested every 2 years for diabetes and to high-risk children in particular. For example, in a 3-year intervention, the Child and Adolescent Trial for Cardiovascular Health demonstrated that the percentage of calories from fat could be significantly reduced in school lunches (from 38.7% to 31.9%) and that the amount of vigorous physical activity could be significantly increased during physical education classes (from 37% to 52%). However, total cholesterol level, SBP and DBP, and BMI did not differ significantly between those in the intervention and control schools at the end of the study.71,72

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IMPORTANCE OF FAMILY HISTORY IN ASSESSING RISK

Familial health risk does not remain constant throughout life. It changes as families grow, as family members age and increase their exposure to the environment, and as the status of their health evolves. Accordingly, a person’s family history needs to be updated regularly, which might make this history an excellent tool for increasing awareness of risk among people as they age. Family history assessment is probably not as useful when the risk of those persons compared is too low or high according to risk factors other than family history. For example, in the selection of participants for the Diabetes Prevention Program, a family history of diabetes did not increase the yield of high-risk participants.79

Among persons whose risk factors are intermediate, however, family history could play a role in discriminating levels of risk. More importantly, health risks are more likely to be reversible for those in this group.

Findings from family history studies may lead not only to an understanding of how inherited factors interact with the environment to cause disease in some families but also to assessing how this interaction works in the population at large. Long-term follow-up of persons at high familial risk may help us understand the natural course of some diseases and identify the life stages at
which people would benefit the most from interventions such as screening, early detection, prevention, and genetic counseling. Although it is possible that just a modest proportion of all cases of a disease in the population emerge from people who are genetically susceptible, such as those with a strong family history, this is still an important question, because it might be the first to show, at a population level, the effects of adverse environmental changes. An example of the application of these principles is the identification of several gene variants associated with diabetes and CVD in studies in which family history was an important criterion for selecting high-risk persons. Incidentally, those who are assessing for cases of diabetes and CVD in families should know that the pattern of inheritance of these diseases is not always complex. For example, maturity-onset diabetes of the young is inherited as an autosomal-dominant trait. There are many other examples of rare cases in which a well-defined genetic component has been identified. In a recent search of the Online Mendelian Inheritance in Man database, a large catalog of human genes and genetic disorders, a total of 2592 entries were reviewed for common chronic conditions related to cancer, diabetes, and CVD. In all, 188 entries for these diseases were reported in >1 family and displayed a discernible pattern of inheritance, mostly autosomal dominant. Of those entries, a subgroup of 156 referred to CVD or diabetes; interestingly, 74 of them included combinations of at least 2 traits from 1 or both diseases.

**FAMILY HISTORY AS A SCREENING TOOL**

Screening is the systematic search for precursors or preclinical signs of a condition in apparently healthy people and entails health risks and costs. For example, it might increase the cost and length of treatments; it might also cause unnecessary anxiety among those who are wrongly assigned to high-risk categories or give a false sense of security to those who are wrongly assigned to low-risk categories. Therefore, the World Health Organization has issued criteria to screen for a condition: the condition must be of public health importance, the diagnostic tests must be safe and reliable, adequate treatments or interventions must be available, and finding, diagnosing, and treating people with the condition should be affordable. Diabetes and CVD meet most of the World Health Organization criteria. It is not clear, however, what the best strategy or combination of strategies might be to provide routine screening for diabetes or CVD (whole population, high-risk persons, opportunistic) and how cost-effective these strategies might be.

Family history has the potential to become a screening tool to identify people at increased risk of chronic diseases such as diabetes and CVD, but several conditions will need to be met. First, family history should be a demonstrable, independent risk factor for the diseases. Second, the methodology used to determine risk according to family history must be valid and reliable. Third, people must be aware of the disease status of their relatives and willing to report it. Finally, the time and resources required to collect and interpret the data on family history should be comparable to those needed for alternative screening tools.

Family history is an independent risk factor for diabetes and CVD, but the tools and methodologies for collecting and assessing familial risk for these and other chronic diseases are not well developed. Family history of diabetes and major CVD events are reported fairly accurately, because each has a good case definition, both are serious enough to be of concern to relatives, and there is little stigma associated with them. Even so, diabetes, in particular, is likely to be underreported; approximately one third of the people with diabetes have not had it diagnosed.

In addition to primary care, schools and national or state surveys are settings in which family history could be used as a screening tool to identify children who are at increased risk of chronic diseases. For example, there are states in which BMI is a required measurement for schoolchildren, and parents are notified of the weight status of their children. If family history of diabetes and CVD is collected from overweight children, it may be possible to identify a subgroup of children who, because of their greater risk, would benefit the most from personalized and family-based efforts at prevention. As for surveys, Hariri et al recently used a national survey to compare obesity and self-reported family history of diabetes as screening tools to identify adults with undiagnosed diabetes. The authors found that a positive family history identified 73% of all respondents with diabetes, compared with obesity, which identified only 40%. In addition, the 2 risk factors combined had a larger positive predictive value for diabetes than family history or obesity alone.

Other features to be considered when collecting family history of diabetes and CVD include early age at disease onset; presence of related conditions (hypercholesterolemia and CHD); the existence of 2 or more closely related affected relatives; and a history of 2 or more generations with affected relatives. Algorithms for stratifying risk that incorporate these features of family history to rank individual people are being evaluated in adult populations. Algorithms to predict the risk of chronic conditions in susceptible children may have to be modified to account for the potentially prolonged period between exposure and outcomes. Ideally, the algorithm should identify children at increased risk who would benefit the most from early preventive measures and children at very high risk, who may be referred to a specialist.

Even if family history is properly validated as a screening tool, it would still need to face the question of
clinical utility; how does this tool influence early detection and the prevention of disease in populations? Will parents be more motivated to engage their children in healthy behaviors if they are aware of the familial risk of disease? Will adolescents make healthier choices for themselves if they know about a preventable disease that “runs in the family?” There are some indications that the answer to these questions is affirmative. We note that family-based lifestyle interventions with parents as coaches may be more effective than individual approaches.94

Several ethical and legal issues need to be considered before family history can be used as a screening tool in children. For example, what are the consequences of labeling children at risk for diseases that will not emerge for years to come? How will the labeling affect their present and future medical insurability? Is there a potential for fatalism, impairment of self-image, depression, or blame associated with assessment of familial risk? These issues have been examined in more detail for single-gene disorders than for common chronic diseases.95,96 Legal issues associated with collecting family histories include informed consent, ownership of the data, obligation to disclose, and requirements for reporting. These vary with the setting, but clinical settings already have guidelines and regulations (eg, Health Insurance Portability and Accountability Act regulations) that protect medical information.

If family history improves the risk assessment for both diabetes and CVD, and if the evidence shows that screening and early behavioral changes help prevent these diseases, clinicians and parents may be more receptive to considering family history as a legitimate risk factor in children and start intervening earlier rather than later.

CONCLUSIONS

Diabetes and CVD are common and costly health problems, the public health impact of which could be eradicated or greatly ameliorated by early detection and interventions in the population at risk. The evidence is clear that type 2 diabetes and CVD start early in life and that both can be prevented or delayed, at least among adult, high-risk men and women. In addition, family history has been found to be an established, independent risk factor for both diseases as well as for some precursors of these diseases. A next step that would not add much expense would be to make family history part of mass-awareness strategies and prevention campaigns aimed at reducing the burden of diabetes and CVD and their risk factors. Much research needs to be done, however, on the most effective ways to incorporate family history in those strategies and campaigns, particularly for children and young adults.

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ABSTRACT

A workgroup meeting on the use of family history information in pediatric primary care and public health sponsored by the National Center on Birth Defects and Developmental Disabilities at the Centers for Disease Control and Prevention was held February 24 to 25, 2006. The workgroup participants met to discuss how to improve the use of family history information in pediatric settings. Topics addressed at the meeting included current practices, needs, and barriers for use of family history information in pediatric primary care and public health. Other considerations included how available family history tools might be applicable to pediatric settings and which areas require additional research. Specific model conditions were presented that illustrated issues involved in the use of family history information in pediatric settings, including cystic fibrosis, fragile X syndrome, polycystic kidney disease, hyperlipidemia and coronary artery disease, and birth defects. Ethical, economic, and technologic concerns involved in integration of family history information into pediatric settings were discussed also.
Family history is an important risk factor for both common complex conditions and single-gene disorders, and it incorporates not only shared genetic susceptibilities but also shared environmental, behavioral, and cultural factors. The use of family history information to determine risk of disease and promote prevention on the basis of this risk is a key public health initiative. Currently, much of the focus has been on the use of family history information in prenatal and adult health care. Although aspects of each may be applicable to pediatric settings, pediatric health care has its own unique characteristics and needs. To address these issues, the National Center on Birth Defects and Developmental Disabilities at the Centers for Disease Control and Prevention (CDC) sponsored a workgroup meeting (February 24–25, 2006, in Atlanta, GA) on the use of family history information in pediatric primary care and public health. The workgroup brought together primary care practitioners and public health workers along with experts in economics, ethics, bioinformatics, and selected disorders. The goals of the workshop were to assess the current use of family history information in pediatric settings and evaluate different conditions that could act as models for use of family history information in pediatric settings by addressing the following questions:

1. How can ascertainment and use of relevant family history information in pediatric primary care and public health settings be improved?
2. What barriers need to be overcome in pediatric settings to facilitate the use of family history information?
3. How can lessons learned from the development of current tools be applied to pediatrics?
4. What public health and pediatric research topics should be addressed in the development of pediatric family history tools?
5. What types of disorders and which specific model conditions applicable to children could be incorporated into existing or new family history tools?
6. How should the ACCE (analytic and clinical validity, clinical utility, and ethical, legal and social issues) criteria be prioritized to select these conditions? (“Analytic validity” refers to how accurately family histories can be ascertained; “clinical validity” addresses how well these family histories predict risks for children; and “clinical utility” deals with the utility of this information for prevention.)
7. What ethical and economic issues need to be considered?
8. How can we anticipate future needs for tool development?

The meeting agenda, selected presentations, and a reference list are available on the CDC Web site (www.cdc.gov/ncbddd/bd/family_history.htm). This article provides a summary of the presentations and key concepts discussed at the meeting.

USE OF FAMILY HISTORY IN PRIMARY CARE

Current Practices, Barriers, and Needs: Presentations by Trotter, LoPresti, Gallo, Martin, and Bodurtha

Most pediatric primary care clinicians collect family history information without a disease in mind. However, in clinical practice, family history information is used predominantly for diagnostic purposes in those who are already presenting with symptoms. Family history information provides guidance for referrals and diagnostic testing, thus potentially decreasing costs. Collection of family history information can also provide opportunities for patient education and motivation for behavior change.

For pediatric patients, family history information can be collected by parents or by several relatives and then compiled, and children can be encouraged to become involved in taking their family history. Family history information can also be collected directly by primary care clinicians or their staff. Questionnaires can be filled out at home, with administration through the mail, Internet, or telephone, or during an office visit. If collected in advance, family history information can help guide an office visit. Questions can be (1) broad and open-ended, (2) electronic medical chart checklists, or (3) disease or guideline focused. It was noted that general questions usually receive negative responses, and use of a systems-review approach, as outlined by Bennett,1 was recommended. Nonetheless, for some potentially stigmatizing conditions such as psychiatric disorders, using open-ended questions and allowing parents to discuss family history in an unstructured manner might be more effective. Web-based tools, as well as checklists and mnemonics (listed in Tables 1 and 2), can be helpful, although many do not focus on pediatric concerns or include risk assessment. Available guidelines on the use of family history information usually relate to specific conditions and are limited, with little uniformity.

Use of family history information in pediatric settings benefits from a family-centered approach, in which conditions are discussed in the context of the family and the emphasis is placed on family responsibility and ownership of the information. Clearly explaining the health benefits of family history collection for the child and addressing family concerns are important in obtaining reliable information. Successful programs that include use of family history in prevention of common complex conditions, such as the Healthy Eating and Activity Together (HEAT) program on obesity2 and the Keep Your Children/Yourself Safe and Secure (KySS) program on mental health,3 were presented at the meeting.
Use of family history information in pediatric primary care does face substantial barriers. Many pediatric primary care clinicians do not have the necessary time or training to fully interpret pedigrees to determine risk level and might not recognize red flags (such as early age of onset or death) or patterns indicating family history of a condition. Particularly for common complex conditions, some clinicians might not prioritize use of family history if the benefits to patient care are not immediate. Lack of reimbursement for family history collection and interpretation is a major concern, and deciphering insurance issues can be challenging. Lack of time, even during the many well-child visits, is also a major hurdle for pediatric clinicians.

In terms of the family history itself, information on patients’ relatives might be unobtainable or inaccurate. The smaller size of families, single-parent families, and changing family structures can mean that pedigrees are less informative. A discrepancy might exist in reporting the family history of conditions in paternal relatives compared with those of maternal relatives.

Family history tools that address clinicians’ lack of time and the need for guidance in risk assessment are needed. Tools for incorporation into medical school and medical practice are sorely needed. The following tables provide a summary of several available resources.

### TABLE 1 Available Family History Web Resources Tools

<table>
<thead>
<tr>
<th>Source</th>
<th>Web Address</th>
<th>Information Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Medical Association: prenatal, pediatric, and adult family history forms</td>
<td><a href="http://www.ama-assn.org/ama/pub/category/2380.html">www.ama-assn.org/ama/pub/category/2380.html</a></td>
<td>Prenatal tool has checklist for whether any family history is present for several single-gene and common complex disorders; pediatric and adult questions are open-ended, with focus on developmental milestones for pediatric form and establishment of family structure and present health status of relatives for adult form.</td>
</tr>
<tr>
<td>US Surgeon General: My Family Health Portrait</td>
<td><a href="http://www.hhs.gov/familyhistory">www.hhs.gov/familyhistory</a></td>
<td>Pedigree-drawing tool that collects information on family history of coronary artery disease, stroke, diabetes, breast cancer, ovarian cancer, and colon cancer; additional conditions can be added by the user; conditions present in each relative are noted on pedigree.</td>
</tr>
<tr>
<td>March of Dimes: genetics and your practice</td>
<td><a href="http://www.marchofdimes.com/gyponline/index.htm">www.marchofdimes.com/gyponline/index.htm</a></td>
<td>Detailed checklist to assess family history and other aspects of pediatric primary care.</td>
</tr>
<tr>
<td>Virginia Department of Health: Bright Futures</td>
<td><a href="http://www.brightfutures.org/mentalhealth/pdf/professionals/ped_intake_form.pdf">www.brightfutures.org/mentalhealth/pdf/professionals/ped_intake_form.pdf</a></td>
<td>Brief section on family medical history of common complex conditions; also contains several questions on social history.</td>
</tr>
<tr>
<td>LabCorp: general family history assessment</td>
<td><a href="http://www.labcorp.com/genetics/fha/genetic_questionnaire.html">www.labcorp.com/genetics/fha/genetic_questionnaire.html</a></td>
<td>Checklist to assess whether any family history is present for several single-gene and common complex disorders.</td>
</tr>
<tr>
<td>Norwich Union: health tree</td>
<td><a href="http://www.norwichunion.com/healthtree/index.htm">www.norwichunion.com/healthtree/index.htm</a></td>
<td>Pedigree-drawing tool that collects information on family history of select common complex conditions and displays results as a family-tree graphic.</td>
</tr>
</tbody>
</table>

### TABLE 2 Available Family History Mnemonics and Checklists

<table>
<thead>
<tr>
<th>FGENES (Genetics and Primary Care Initiative acronym)</th>
<th>Family history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group of congenital anomalies</td>
<td>Extreme or exceptional presentation of common conditions</td>
</tr>
<tr>
<td>Neurodevelopmental delay or degeneration</td>
<td>Extreme or exceptional pathology</td>
</tr>
<tr>
<td>Surprising laboratory values</td>
<td>Miscarriages, high blood pressure, lung problems (asthma), heart problem, learning problems, and mental health</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Kemper’s pediatric mental health checklist</th>
<th>Nongenetic conditions: behavioral or other environmental risk factors such as smoking or alcoholism in family?</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCREEN questions</td>
<td>Reproduction: pregnancy, infertility, or birth defects in family?</td>
</tr>
<tr>
<td>Some Concerns about diseases or conditions that seem to run in the family?</td>
<td>Early disease, death, or disability: early onset of chronic disease or early deaths in family?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SIDE questions</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>Nongenetic conditions: behavioral or other environmental risk factors such as smoking or alcoholism in family?</td>
</tr>
<tr>
<td>Similar problems?</td>
<td>Any</td>
</tr>
<tr>
<td>Inherited conditions?</td>
<td>Inherited conditions?</td>
</tr>
<tr>
<td>Deaths (unexplained)?</td>
<td>Deaths (unexplained)?</td>
</tr>
<tr>
<td>Extraordinary laboratory tests or reactions?</td>
<td>Extraordinary laboratory tests or reactions?</td>
</tr>
</tbody>
</table>
residency education would be helpful also. One key issue of family history collection is the need for updating information; thus, tools that are dynamic would be most useful. Tools that use a modular design, asking questions about each family member individually, and have specific closed-ended items, with systematic inquiries about conditions, have been found to work best.5

Both the public and pediatric clinicians need to be educated about the importance of family history. Clinicians should understand the basics of collecting family history information and how to ask follow-up questions. Underreporting is a key issue, and clinicians need to know when to pursue information further; for example, patient reports that indicate no family history of any cancer are likely incomplete and should be explored further. In addition to physicians, nurse practitioners and other pediatric primary care clinicians should be targeted. Moreover, guidance on specific conditions for which family history collection is most useful is also needed. Public interest in family history is key to increasing accuracy of reporting and could spur clinicians to incorporate it into their practices. If the public perceives that the benefits of family history information outweigh the risks involved in revealing this information, more people will be inclined to share this information with clinicians and relatives.

In the future, electronic medical charts that integrate and cross-reference information on different family members could greatly assist family history collection. Privacy and confidentiality concerns would have to be addressed; one solution suggested would be to have a checkbox in each patient’s record to indicate whether information can be shared with other relatives and placed in their records. Also, electronic medical chart prompts that suggest conditions to consider with a given family history would be valuable. When possible, coordination with medical genetics departments to interpret family histories would be beneficial, especially considering the level of complexity involved in interpreting family history risk. For example, self-administered family histories could be collected electronically, with those results that indicate a potential genetic condition being automatically sent to the medical genetics department and the pediatric primary care clinician.

A complementary approach would be the compilation of a list of “red-flag” conditions, established by convening family support groups for rare conditions for which early diagnosis through family history can result in successful interventions before serious complications. Preferably, diagnostic tests would exist to test the child immediately to determine if he or she is affected. A universal family history alert form could be created and distributed through the family support organizations to all family members. This form would assist families in alerting pediatric clinicians to the family history of the disorder for each new child and would explain the disorder, how it can be diagnosed, and what follow-up would be required.

For a more detailed discussion of the use of family history information in primary care, see the article by Trotter and Martin (p S60).

ACCE FRAMEWORK

Presentation by Yoon

ACCE refers to analytic and clinical validity, clinical utility, and ethical, legal and social issues and provides a structure for evaluation of the use of family history information in general, as well as its application to specific conditions.6,7 This public health approach highlights the application of family history information to prevention rather than to the more established diagnostic use. Two main concepts of ACCE are validity (whether disease information about close relatives could be useful for predicting a person’s own risk of disease) and utility (whether individuals who have been identified as being at above-average risk benefit from targeted interventions beyond what is recommended for the public at large). ACCE has previously been used as a research framework for the CDC Family History Public Health Initiative, which focuses on the use of family history for assessing risk of common complex diseases and influencing early detection and prevention strategies.6,7 Targeted, personalized prevention messages that focus on higher-risk families are meant to augment, not supplant, the population-based approach.

Analytic Validity

Analytic validity addresses the accuracy and reliability of family history reports. This not only includes information on the condition itself, but also on age of onset and type of relative. Other considerations include which settings and formats yield more valid information. Analytic validity is measured through sensitivity (identification of relatives with a disease) and specificity (identification of relatives without a disease). Generally, studies have found higher specificities than sensitivities, which indicates underreporting.8

Several factors can influence the completeness and accuracy of a family history, including the type and severity of the disorder, whether the disorder has a clear case definition, whether the disorder is in the public eye, incomplete or imprecise past diagnoses, and the time since diagnosis or death of the affected relative. Analytic validity is usually highest with first-degree relatives,9 and the amount of interaction with relatives might also affect reporting. Other concerns include lack of knowledge of conditions leading to sentinel events (e.g., high blood pressure before heart attack) and reporting the cause of death rather than the underlying disease.
Clinical Validity
Clinical validity deals with the accuracy of disease risk predictions that are derived from family history information. The type of relative, age of onset, family size, and number of affected (and unaffected) relatives can all influence this prediction. Clinical validity is also evaluated by using sensitivity (in this case identifying individuals who will develop the disease) and specificity (identifying individuals who will not develop the disease). Another important measure is positive predictive value, which is the probability that an individual will develop a disease given a positive family history. This calculation includes prevalence of the condition so that values will be higher for more-common conditions.

Research is needed at the population level to determine the prevalence and estimate the population-attributable risk of family history of certain disorders, especially common complex conditions. Interactions with other risk factors such as behavior need to be explored. Current risk-stratification schemes should be validated at the population level, because most of them are largely based on case-control studies or disease registries. The amount of family history information that is collected can also be important. Defining family history as a dichotomous variable may be simplest but does not allow for discrimination between different levels of risk. On the other hand, collection of complete pedigrees may not be feasible either, so a balance must be made between keeping collection simple and gathering enough information to make prediction possible.

Clinical Utility
Clinical utility is concerned with whether awareness of family history risk and targeted interventions affect disease outcome. The added value of family history might include awareness of familial risk acting as a motivating factor for behavioral change and screening uptake, family-centered approaches to risk reduction being more effective and longer-lasting, and cost-effectiveness of earlier and more-frequent screening based on familial risk. However, research is needed to assess whether use of family history information has the expected results, and any health risks associated with family history assessment and intervention must be addressed. For example, individuals might adopt a fatalistic attitude about family history rather than use the information to be proactive about their health. Use of family history information requires changing both patient and clinician behavior, and evidence of clinical utility will be important for implementation.

Ethical, Legal, and Social Issues: Presentations by Ross and Yoon
Use of family history information in pediatric primary care and public health involves a wide range of ethical, legal, and social issues. From a research standpoint, these issues include factors that affect data collection, storage, and interpretation that might negatively impact individuals, families, and society, as well as legal issues regarding informed consent, ownership of data, and obligation to disclose. In both research and clinical settings, verification of information can be hindered by HIPAA (Health Insurance Portability and Accountability Act of 1996) regulations and clinician time constraints. Cultural factors might affect reporting of family history, as might interest in knowing this information. Also, there is a question of whether individuals have an obligation to share their health information with their relatives, which becomes more complex with blended families in which stepparents may be involved in a child's care. One concern is that sharing family history information, both within the family and with health care clinicians, might lead to increased stigmatization and insurance or employment discrimination, especially because family medical history can reveal predictive genetic information. Sensitive information includes not only conditions themselves, such as psychiatric disorders, carrier status, and addictions, but also issues related to family structure, such as adoption, donor gametes, and consanguinity. Furthermore, the clinician's duty to share such information is unclear, especially in situations in which the clinician is caring for multiple members of the same family.

Conditions under which family history information is used must be carefully considered. If no preventive services or treatments are available, labeling an asymptomatic person as being at high risk may be unethical. For example, <3% of the population has the highest-risk genotypes for type 1 diabetes, but 96% of children with these genotypes will not develop the disease, and no effective prevention of type 1 diabetes currently exists. In contrast, if a prevention or cure were to become available, failing to determine risk status might be unethical. Availability of presymptomatic diagnosis, early treatment, or increased surveillance does not necessarily mean that assessment of risk is beneficial. For example, studies on early screening and surgery for neuroblastoma created morbidity in patients whose lesions might have been benign, and recommendations for children with heart defects to avoid competitive sports may be unnecessarily restrictive and promote a sedentary lifestyle that places these children at risk for obesity and its attendant health consequences.

Taking a broader view, some might question whether family history information should be prioritized, given the current state of knowledge and potentially greater relevance of other factors such as environment (eg, living conditions, violence, poverty, illiteracy, family exposures to foods high in fats and sugar, and drug, tobacco, and alcohol use). For those changes that are universally beneficial, continuing the standard public health approach is appropriate and necessary. Nevertheless, on
the basis of increasing rates for obesity and diabetes, for example, it is clear that the population-wide approach that focuses on lifestyle has its limits. Family history can be used to augment the population-wide approach by identifying and focusing more-intensive interventions for high-risk families. However, family history information may fail to identify those who are at increased risk but may not be able to provide adequate information for risk assessment. This might include members of vulnerable populations, such as children in single-parent families, children whose parents have less education, and the uninsured. Nevertheless, for a majority of the population, family health history may motivate behavior change and screening uptake.

MODEL TOOLS

Presentations by Yoon and Kloza

Family Healthware

Family Healthware is a self-administered, Web-based family history–collection and risk-assessment tool developed by the National Office of Public Health Genomics and the Division of Cancer Prevention and Control at the CDC. Family Healthware focuses on adult health care and collects information on 6 common complex conditions: coronary artery disease, stroke, diabetes, breast cancer, ovarian cancer, and colorectal cancer. Family Healthware takes an integrated approach to disease prevention, focusing on risk factors shared by >1 condition (eg, diet and exercise) to promote a public health approach to the use of family history information for disease prevention. After collecting health and behavioral information on an individual, Family Healthware then collects information on that person’s first- and second-degree relatives, starting with the family structure. For each relative mentioned, Family Healthware systematically asks whether this relative had any of the 6 conditions and, if so, in which age range the condition was diagnosed. The individual’s level of family history risk (weak, moderate, or strong) for each of the 6 conditions is determined by using risk-stratification algorithms, and these risk assessments are tied to risk-appropriate and evidence-based prevention strategies. These strategies include recommended screening tests and lifestyle changes and take into account the health and behavioral information provided on the individual. Each individual receives a summary page for each condition with his or her level of risk and an explanation of why he or she is at that level of risk. All assessments end with the recommendation to discuss the results with a health care clinician, and Family Healthware includes a resource guide for clinicians. This guide includes information on key risk factors for the conditions, red flags, and whether known genomic conditions feature these diseases, as well as what steps the clinician might want to take with patients in the different risk strata. Family Healthware is not yet available for public use, because it is undergoing evaluation.

Surgeon General’s Family History Initiative: My Family Health Portrait

My Family Health Portrait, the tool developed as part of the Surgeon General’s Family History Initiative, collects family history information on an individual’s relatives and draws a pedigree indicating the different conditions present in each relative. My Family Health Portrait asks about the same disorders as Family Healthware and allows for additional conditions to be included. However, My Family Health Portrait does not provide any risk assessment or personalized prevention recommendations.

First Page

Unlike Family Healthware and My Family Health Portrait, First Page focuses on prenatal health care and mainly deals with single-gene disorders. The first-level screen for First Page is a paper-based, self-administered family history questionnaire. Each question is designed to be a screening test for the potential presence of a disorder for which a diagnostic test is available to determine if the fetus is affected with the condition. First Page is intended to be administered in the clinician’s office, with affirmative answers to questions cueing the clinician to ask a series of secondary questions to determine which relatives are affected, whether genetic testing has been done, and other information needed to clarify and categorize the patient’s risk further. Algorithms provide guidance with regard to determining the patient’s level of risk, and recommended next steps are included as well. The resource guide for clinicians includes information on laboratory tests, brief descriptions of the disorder, and other information designed to educate primary care clinicians without providing an excess of information.

Evaluations of First Page found that its use did not affect the number of telephone calls to genetic centers, the type of calls, or whether calls resulted in a referral (E. Kloza, MS, CGC, verbal communication, 2006). However, it did affect the type of referral, with family history accounting for 27% of telephone calls, compared with 13% previously, and maternal indications increasing from 10% to 20% (E. Kloza, MS, CGC, verbal communication, 2006). Surveys of clinicians using First Page indicated that clinicians felt that First Page made them feel confident discussing genetics issues, simplified risk assessment, and helped address genetic risks earlier in pregnancy.

SINGLE-GENE DISORDERS

An important aspect of the meeting was discussion of conditions that might be included in pediatric family history tools. The ACCE framework provided a method...
for evaluating different conditions.\(^6\)\(^7\) Criteria such as whether the condition constituted a substantial public health burden, whether the condition had a well-defined case definition, awareness of the disease among relatives, accuracy of reporting by family members, available interventions or prevention, and family history being an established risk factor were also considered.\(^6\)\(^8\) Because both single-gene disorders and common complex conditions can be relevant in pediatric settings, sections on both were included. The single-gene disorders session had presentations on cystic fibrosis (CF), polycystic kidney disease (PKD), and fragile X syndrome (FXS).

**Cystic Fibrosis: Presentation by Parad**

CF is increasingly included in state newborn screening panels, and population-based CF-carrier testing is becoming more widespread as well. Detection of carriers and affected children through this screening may change the traditional view of family history but does not preclude its importance. The 1997 National Institutes of Health Consensus Conference led to National Institutes of Health, American College of Medical Genetics, and American College of Obstetrics and Gynecology joint guidelines\(^15\) for CF-carrier testing, which targeted adults with a CF family history, reproductive partners of people with CF, and couples in whom both members are white and planning a pregnancy or seeking prenatal care as main indications for testing. Also, DNA diagnostic testing benefits from the focus provided by family history: CF Foundation data from 1992 showed that approximately one quarter of the alleles in CF-affected individuals are attributable to mutations that occurred at a \(<1\%\) frequency and, thus, might be missed by the 25-mutation carrier-screening panel recommended by the American College of Medical Genetics.

Approximately 10% to 15% of newly presenting patients have a CF family history, with rates increasing with population-based and newborn screening. Data from the Massachusetts newborn screening program, in which family history was examined in greater depth by using information from a subpopulation that underwent genetic counseling, showed that 16.7% of CF newborn screen–positive children had a CF family history, defined as having an affected relative, a carrier relative detected through population screening, or a relative with a positive newborn screen, with only 2% having an affected family member (R. Parad, MD, MPH, verbal communication, 2006). In the 3-year period studied (2002–2005), CF newborn screen–positive children with a CF family history increased from 10% to 22%, mostly because of positive maternal carrier testing (R. Parad, MD, MPH, written communication, 2007). Although 98% of the counseled families said that they shared information on positive carrier status with other family members, many pediatricians had not been told by the obstetrician or the mother of the mother’s carrier status, either positive or negative, or, if positive, which mutation was detected (R. Parad, MD, MPH, verbal communication, 2006). This finding illustrates the need for an improved continuum of care in which maternal medical and family history information is transmitted to the pediatric clinician. (For more on this topic, see the article by Dolan and Moore [p S66].)

**Autosomal-Dominant PKD: Presentation by Chapman**

Autosomal-dominant PKD occurs with a prevalence of 1 in 400 to 1 in 1000 in the non-Hispanic white population\(^16\) and is the fourth most common cause of renal failure, comprising \(~5\%\) of the population with renal failure.\(^17\) Although PKD is a dominant trait, \(~10\%\) to 15% of affected individuals do not have an affected parent despite the high degree of penetrance of PKD (A. Chapman, MD, verbal communication, 2006). Criteria for PKD diagnosis varies depending on whether family history is present, with fewer cysts at a younger age required in the presence of a PKD family history.\(^18\) Some risk factors could be addressed presymptomatically, including birth control pill use and multiple pregnancies in women at high risk of developing PKD. Other aspects of the phenotype could require screening, such as hypertension, which occurs in 60% of patients with PKD by 30 years of age, and asymptomatic intracranial aneurysm, which occurs in 5% to 8% of individuals with PKD and is increased to 10% to 12% with a family history of this complication in a first-degree relative.\(^19\)\(^22\)

PKD has a long phase of asymptomatic disease, with disease progression occurring while individuals have normal laboratory test results and even normal blood pressure levels and physical examination results. A study on attitudes about presymptomatic testing for PKD included 141 individuals with PKD and 137 who were at risk for the disorder.\(^21\) In this study, 97% of those at risk stated that they would undergo self-testing to find out if they had the disease, 88% of those with PKD and 89% of those at risk would screen their offspring, 65% with PKD and 50% at risk would screen prenatally, and 4% with PKD and 8% at risk would terminate a pregnancy if the offspring were known to have PKD.\(^23\) Concern about insurance discrimination is an important issue with PKD. Surveys of 350 individuals with PKD before end-stage renal disease found that 88% have medical insurance, 25% disclosed their health status to their employer, 35% disclosed their condition to their medical insurer, 57% chose their jobs on the basis of insurance availability, 37% would not change jobs because of the possibility of losing their current medical insurance, and 30% had previously been denied insurance coverage.\(^24\) Genetic testing for PKD is quite costly and is indicated for family members who would like to donate a kidney to an affected family member, for family planning, and for diagnosis when the phenotype is unclear (A. Chapman,
FXS: Presentation by Sherman

FXS is a highly penetrant X-linked genetic disorder that is present in all ethnic and racial groups. The prevalence is ~1 in 4000 males and 1 in 8000 females of Northern European ancestry. In ~98% of the cases, the disease results from 1 type of mutation, expansion of a trinucleotide-repeat sequence located in the 5'-untranslated region of the Fragile X Mental Retardation 1 (FMR1) gene. The expansion occurs primarily when the gene is transmitted from mother to child but is also unstable when transmitted from father to daughter. Those with >200 repeats have the full mutation and show symptoms of FXS, a type of mental retardation (MR), with significant cognitive impairment in all affected males and ~50% of affected females. Individuals with 55 to 200 repeats carry the premutation. This form of the mutation occurs in ~1 in 250 females and 1 in 881 males. Interestingly, 2 disorders are associated with the premutation and not with the full mutation: premature ovarian failure (POF) in women and fragile X–related tremor/ataxia syndrome (FXTAS) predominantly in males. Approximately 1% of women in the general population have POF, compared with 15% of those with the premutation. Male premutation carriers have a 30% lifetime risk of developing FXTAS, which translates to a prevalence of 1 in 2700.

Both the full and premutation phenotypes could be considered in assessing whether a patient has a family history of fragile X–associated disorders. Although some patients might be aware of a family history of FXS, questions would center around more-general presentations such as MR and autism, POF, or tremor/ataxia. The question of how often the more-general phenotypes would represent FXS must be addressed. Of patients with MR, 2% to 3% of males will have FXS, with a lower percentage (2%) for those with mild MR and a higher percentage (3%–5%) of those with moderate MR. S. Sherman, PhD, verbal communication, 2006). Approximately 7% of individuals with autism have the full mutation. For females, only ~1% of those with MR would have FXS, although this is higher than the carrier frequency. Follow-up questions could be asked to discern patterns that are consistent with X-linked transmission: more male than female relatives are affected and there is no male-to-male transmission. Also, relatives with FXS should have had their problems develop early in life and would not be expected to have significant dysmorphology.

Surveys to assess the frequency of premutations among those with symptoms of premutation-associated disorders are just beginning. Approximately 2% of men with ataxia and 0% of those with essential tremor have been found with the premutation. Approximately 3% of women with POF who lack a family history of POF and 11% with a family history have the premutation. For ataxia and POF, these conditions represent a significant increase over the carrier frequency in the general population. Questions about POF would address at what age close female relatives went through menopause, noting any who did so before 40 years of age, and whether any female relatives had infertility problems and, if so, whether they did not respond to assisted reproductive technology, consistent with the premutation trait. For FXTAS, issues to address would include whether any older male relatives have been diagnosed with tremor in their hands and have trouble walking without assistance and, if so, whether the age of onset was after 50 years of age, as would be expected with FXTAS. The specific diagnosis would probably not be helpful, because FXTAS is often diagnosed incorrectly as another disease such as Parkinson or Alzheimer disease. Assessment of family history would be similar whether the patient is male or female, although for male patients, the focus would be on maternal relatives and siblings because of the X-linked nature of the mutation.

Consideration of the criteria for selecting a disease for a family history tool, as outlined by Yoon et al., can be helpful in evaluating whether fragile X–associated disorders should be included. FXS and the premutation-related phenotypes do represent a substantial public health burden. For those with FXS, costs involved include special education and services, medication, and cognitive and behavioral interventions. The cost in seeking diagnosis is an issue for POF and FXTAS, as well as additional costs for ultimately unsuccessful fertility treatments for those with POF. FXS does have a well-defined case definition, with a simple DNA test available for diagnosis. Premutations can also be detected by using a DNA test, although both POF and FXTAS show reduced penetrance, with only 15% of women who carry the premutation having problems significant enough to seek diagnosis and only 30% of premutation carrier males having tremor/ataxia. Awareness of FXS among relatives is increasing as a result of education efforts but remains variable. As with all single-gene conditions, family history is clearly an established risk factor. For those individuals who inherit the full mutation or premutation, effective interventions exist, but none can prevent symptoms. For FXS, early diagnosis and interventions can lead to improved outcomes. For women at risk for POF, early reproduction would be recommended, as would smoking cessation, because smoking can accelerate progression of the condition. No interventions for FXTAS exist currently. Barriers to use of FXS family history include the labor-intensive evaluation of MR and the complicated inheritance and risk assessment of FXS and the premutation-related traits. An important ethical consideration is that FXS family history can re-
veal increased risk for adult-onset conditions (POF and FXTAS) presymptomatically in pediatric patients.

**COMMON COMPLEX CONDITIONS**

Discussion of common complex conditions focused mainly on birth defects and coronary artery disease.

**Birth Defects: Presentation by Romitti**

The article by Romitti (p S71) contains a detailed discussion of the issues covered on use of family history of birth defects evaluated with the ACCE framework and additional criteria presented by Yoon et al.6,7

Structural birth defects (ie, physical abnormalities that can adversely affect health or development) need to be identified early, especially when the patient is asymptomatic, and collection of family history reports can aid in this process. Families with a history of certain birth defects might also benefit from cascade testing, and detection of an affected child could provide an opportunity to stress to the family the importance of making other relatives aware of their risk. Development of a standardized approach to transmit this information, such as a letter to be distributed to family members, might improve the quality of data and patient care. One concern about collection of family history reports of birth defects in a public health setting is that, even with high specificity, the number of false-positives could be far higher than the number of true-positives, because birth defects are rare conditions. Still, public health research on birth defects would benefit from examination of the occurrence of birth defects among family members of patients.

Issues to address include how family history could improve birth defects surveillance, possibly by improving the diagnosis of birth defects that might not be readily apparent; how to improve ascertainment of birth defects family history information from medical and vital records; what might aid assessment of reliability of family history information in case and control patients; and how to differentiate between recurrence risk and recall bias. In turn, these improvements in research would benefit patient care by improving recurrence estimates for affected families.

**Dyslipidemia, Atherosclerosis, and Coronary Artery Disease: Presentation by Stevens**

As the most common cause of death in the United States and the leading cause of hospitalizations and health care costs, coronary artery disease represents a substantial public health burden.27 Hypercholesterolemia is a leading risk factor for cardiovascular disease, and diet can affect cholesterol levels. Although the effects in children are presymptomatic, with clinical sequelae not occurring until adulthood, 36% of US youth have a cholesterol level that is higher than normal (>170 mg/dL).28 Early prevention in childhood is important, because the disease process begins in childhood and adolescence, with elevated low-density lipoprotein (LDL) levels associated with atherosclerotic lesions.29-31

In terms of timing, the preparticipation physical evaluation for high school athletics offers an opportunity for pediatric care clinicians to focus on family history of heart disease, including atherosclerosis, sudden cardiac death, and congenital heart defects, as well as risk-factor assessment and reduction directly with the adolescent. Questions can also be included on potentially relevant outcomes such as stillbirths, sudden infant death syndrome, seizure disorders, and congenital deafness, as well as other risk factors including lipid levels, hypertension, obesity, diabetes, smoking, physical activity, and nutrition. Such screening should not, however, be limited to those in competitive athletics who are undergoing a school-mandated preparticipation physical evaluation; all adolescents should undergo this type of evaluation.

Disease progression is more common and occurs faster in those with genetic disorders that lead to more significantly elevated LDL levels, increased triglyceride levels, or decreased high-density lipoprotein levels; thus, early identification of individuals with these disorders could be beneficial. These disorders include familial hypercholesterolemia (incidence of 1 in 500 for heterozygotes), familial combined hyperlipidemia (incidence of 1 in 100 to 1 in 200), polygenic hypercholesterolemia (incidence of 1 in 20 to 1 in 100), and familial dysbetalipoproteinemia (incidence of 1 in 100 but is clinically manifest only in 1 in 5000 because of the need for triggers such as obesity and diabetes).32,33 Those at risk would include individuals who have a parent with hypercholesterolemia or a first-degree relative with early atherosclerosis. Lipoprotein analysis is recommended for those with a family history of hypercholesterolemia and a total cholesterol assay for those with a parental hypercholesterolemia level of >240 mg/dL.34 Identification of family history in 1 relative may trigger screening of others in the family.

Cardiovascular risk assessment and treatment in the primary care setting can provide care to more of those at risk and decrease costs by careful selection of those with more significant dyslipidemias, hypertension, or other risk factors for referral to a specialist. The pediatric primary care clinician should also practice global primary prevention by encouraging a healthy diet, promoting increased physical activity, and discouraging smoking. Interventions include daily active play or exercise and a diet that has an appropriate number of calories to promote normal growth, is low in saturated fat and cholesterol, and is increased in monounsaturated fat and dietary fiber. This can be challenging for both the patient and clinician, especially because lifestyle changes do not work for all patients. Besides lifestyle modifications, treatment can include drugs such as statins, which diminish progression of atherosclerosis in children as determined by endothelial function35 and decreased inti-
al medial thickness of arteries, a measure of atherosclerosis. Other medications used in children include bile-acid sequestrants, niacin, cholesterol-absorption inhibitors, and fibrates. Indications for drug therapy include lipid level and pattern, comorbidities, risk factors, and family history. Individuals with borderline LDL levels might be more likely to be treated if they have a family history of premature (<55 years of age) cardiovascular disease or other risk factors. Treatment regimens are generally not based on diagnosis of a specific genetic disorder but on the lipid levels themselves and assessment of other disorders (such as diabetes mellitus) or risk factors (such as metabolic syndrome, obesity, and hypertension). Less knowledge exists about the role of emerging risk factors and markers such as hyperhomocysteinemia and C-reactive protein (a marker for inflammation) in children. Although there is clear evidence that accumulation of risk factors and atherosclerosis begin in childhood and adolescence and that lifestyle and pharmacologic treatment can positively affect lipid levels and even cause regression of lesions and improved endothelial function, it is not yet proven that institution of aggressive treatment in this age group alters the disease in adulthood.

For a discussion of the use of family history of cardiovascular disease in the public health setting, see the article by Valdez et al (p S78).

Investigating the Clinical Utility of Family History Information—The Utah Family High Risk Program: Presentation by Johnson

The Utah Family High Risk Program involved intensive interventions with families identified as having a high-risk family history of coronary artery disease or other conditions, with the goal of addressing whether family history could motivate behavior change. The public health interventions were performed in coordination with the Health Family Tree Study, which provided population-based family history risk assessments as part of high school health education classes in Utah from 1983 to 2001. This family history risk assessment indicated that 14% of the families accounted for almost half of the burden of heart attacks in Utah, and a subset of these families were selected for targeted interventions. For each family, health information was collected on the students, parents, siblings, grandparents, aunts, and uncles and included information on personal history of heart attack, coronary bypass surgery, rheumatic or other heart disease, stroke, breast and colon cancer, hip fracture, asthma, Alzheimer disease, high blood pressure, high cholesterol, and diabetes. Lifestyle information was also collected for each family member, including smoking habits, weight, exercise habits, and alcohol use. Family history risk assessments used data specific for the Utah population.

The tailored interventions by public health nurses used an in-home, family-centered approach with standard protocols, education materials, charts to keep track of family history updates, and demonstrations of any applicable screening techniques, as well as referrals to health care clinicians if appropriate. Families received an annual follow-up contact and periodic surveys to evaluate any lifestyle changes made. Families assessed as having a low-risk family history and who did not receive interventions were used as a comparison group. Results suggested that those families that received interventions showed increases in medical examinations, blood pressure checks, weight loss, exercise, blood tests for cholesterol, monthly breast self-examinations, blood tests for sugar, and reduction of dietary fats compared with those that did not receive interventions (J. Johnson, CHES, verbal communication, 2006). However, no substantial improvement was seen in stress management, mammograms, reducing cholesterol in the diet, and increasing fruit and vegetable consumption; also, salt intake increased (J. Johnson, CHES, verbal communication, 2006). The evaluation did have some important limitations. The unit of analysis was the family, not individual family members. The first survey, which was used as a baseline, was conducted after the initial intervention had taken place. Families were not analyzed by disease risk; all families were asked about the same behavior changes regardless of the relevance that making these changes had on their level of risk. Also, some changes might have been a result of life events, not the interventions; for example, as family members aged, they would have had different health care recommendations. The surveys themselves might have reinforced the intervention messages and might have been the reason families reported making changes.

The evaluations indicated that interventions have to be sustained over long periods of time for high-risk families to benefit from them, and results from later years of the study suggested that providing risk assessment alone might not be enough to motivate behavior change (J. Johnson, CHES, verbal communication, 2006). Another issue the study highlighted was lack of clinician awareness about which steps to take after family history risk assessment, especially in younger, presymptomatic patients.

Cost-Effectiveness of the Use of Coronary Artery Disease Family History to Direct Hypercholesterolemia Screening: Presentation by Grosse

To examine the cost-effectiveness of use of family history information, the example of use of coronary artery disease family history to direct hypercholesterolemia screening was presented. Costs included those for screening, follow-up, diagnosis, and treatment, with the cost of delivering the intervention compared with the cost of care for the resulting disease. The most important
aspect of cost-effectiveness is identifying the magnitude and value of improved health outcomes.

A 1998 American Academy of Pediatrics (AAP) recommendation stated that children 2 years of age or older should be screened for hypercholesterolemia if they had a family history of premature heart disease or a parental history of hypercholesterolemia. A subsequent public health study on use of family history to direct hyperlipidemia screening concluded that this method was not cost-effective.19 O’Loughlin et al39 criticized the AAP recommendation because of the limited sensitivity of detection of children with hypercholesterolemia (41%–51%), because the majority of children with this condition do not have a family history that is indicative of hypercholesterolemia. Furthermore, only 7.7% of children with a family history have hypercholesterolemia; thus, screening on the basis of family history would have a 92% false-positive rate and would offer little improvement over random screening, which would detect hypercholesterolemia at a rate of 4.8% overall. Accuracy of family history is also an issue, with studies indicating inaccuracy of parent self-reports of coronary artery disease history40 and unknown hypercholesterolemia status in relatives.41

From a public health perspective, the goal is to maximize case detection to have a major impact at the population level.62 From that perspective, family history might seem to be a low priority. For example, family tracing could reduce by 50% the premature mortality associated with familial hypercholesterolemia but would prevent <1% of all premature mortality that results from coronary artery disease in the population. In contrast, population-based cholesterol screening that targets the upper 5% of the population for intensive intervention would have a small relative effect on mortality associated with familial hypercholesterolemia but would prevent 8% of all premature mortality caused by coronary artery disease.

On the other hand, use of family history could potentially minimize the cost of case detection and thus be cost-effective from a clinical perspective despite identifying a relatively small number of cases. An economic evaluation concluded that the use of family history to direct screening would be more cost-effective than universal or opportunistic screening for familial hypercholesterolemia.43 Marks et al43 used simulation modeling to compare hypothetical screening strategies for identifying individuals with familial hypercholesterolemia. One strategy consisted of cascade testing of family members of individuals diagnosed with familial hypercholesterolemia, in which individuals diagnosed with familial hypercholesterolemia were asked to contact their first-degree relatives to encourage them to undergo genetic or cholesterol testing. This family-tracing strategy was compared with universal cholesterol screening with the assumption that half of the family members would be affected because familial hypercholesterolemia is a dominant disorder. The cost per case of familial hypercholesterolemia detected was projected to be approximately $200 using the family-tracing strategy compared with $14 000 for cholesterol screening of all 16-year-olds. The cost-effectiveness ratio in terms of cost per life-year saved was approximately $9000 for family tracing, $10 000 for universal screening of 16-year-olds, and $30 000 for other types of screening. The primary limitation of the Marks et al study was the fact that the primary benefit of cholesterol screening (namely, identifying those with hypercholesterolemia, >90% of whom do not have familial hypercholesterolemia) was not taken into account. Consequently, the cost-effectiveness ratios for the alternative strategies are misleading. Additional limitations include the fact that scenarios were hypothetical and issues of uptake and compliance were not addressed. The total number of cases that would be identified under any of the strategies was not calculated, and thus the incremental cost-effectiveness of 1 strategy relative to the other could not be determined. Each strategy was compared with no intervention rather than to all other relevant interventions.

Additional cost-effectiveness analysis of the use of family history for assessing risk of familial hypercholesterolemia in a pediatric population is needed. To evaluate the AAP screening protocol, practices that follow the protocol would need to be identified and the analytic validity, clinical validity, and clinical utility of screening would need to be assessed, as would uptake of the screening.

**Use of Family History Information for More Challenging Conditions—Pediatric Cancers and Psychiatric Disorders:**

**Presentation by Bennett**

Although families are often most interested in knowing about conditions such as autism, attention-deficit disorders, learning disabilities, allergies, asthma, alcoholism, psychiatric disorders, and cancer, the pediatric primary care clinician’s ability and knowledge in dealing with family histories of these conditions may be limited. However, aspects of many conditions can lend themselves to use of family history information. For example, in the context of newborn screening, family history of hearing loss can be beneficial in providing anticipatory guidance and focusing genetic testing, especially in cases of syndromic hearing loss.

Knowledge of family history of cancer syndromes, such as the polyposis syndromes (familial adenomatous polyposis/adenomatosis polyposis coli, juvenile polyposis), can guide screening in childhood and possibly surgical intervention during adolescence or earlier. One key challenge in dealing with pediatric cancers is the lack of knowledge about penetrance and expressivity of these diseases. Pediatric identification of some cancer syndromes might not be appropriate, and genetic testing...
Using a language analogy, semantic interoperability focuses on the syntax or structure of the sentence. In leveraging the use of the Extensible Markup Language (XML), HL7 and other standards-development organizations are able to facilitate the development of standards for the structuring of transmitted data that are independent of platform (ie, hardware and software).

HL7 strives to achieve a model that is both structured and flexible to facilitate the integration of diverse types of information, including laboratory, pharmaceutical, radiology, family history, and other clinical data. For example, using HL7 messages, family history information can be transmitted between 2 health care entities so that both are able to achieve a clear understanding of a particular patient’s family history issues. One of the many development efforts of HL7 has been focused on a product known as the Clinical Document Architecture (CDA). The focus of the CDA is to facilitate the transmission of electronic clinical documents, such as progress notes and discharge summaries, from 1 health care entity to another.

Another standards-development organization, the American Society for Testing Materials, has developed a product known as the Continuity of Care Record (CCR). Although the CCR was initially designed to provide a patient data summary (including information such as medical, surgery, and allergy histories) to be transmitted between disparate health care entities, its newest version, CCR 1a, provides significantly more functionality. The American Society for Testing Materials and HL7 have a memorandum of understanding in place and are working to integrate the 2 standards. In addition, in November 2005, HL7 began working on a guide to express the CCR using its CDA.

Consideration of these standards (CCR and CDA) will be important when designing family history tools in the future.

FUTURE CONSIDERATIONS: PRESENTATION BY BACHMAN

Incorporation of the Internet into health care services will facilitate collection of family history information, pedigree construction, and patient and clinician education. In the future, the virtual visit might become a possibility, with online family history risk assessment and links to reference materials (such as relevant guidelines and health information), as well as interactive software. The family history could be dynamic, with linkage to medical reports, laboratory studies, and imaging studies of other family members to provide constant updating, assuming informed consent is provided by all relatives. Electronic medical charts might integrate a patient’s DNA-based information, such as single-nucleotide polymorphism or haplotype data, which could be linked to pharmacogenomic information or sophisticated treatments such as stem cell or gene therapy. From a research standpoint, this might allow studies to be developed on large groups of people with similar conditions who could be characterized molecularly, possibly even integrating biobank information.
CONCLUSIONS

Use of family history information in pediatric primary care and public health requires consideration of several key issues. Whether the focus should be on the individual child or on the family as a whole should be addressed. Which conditions are included must be considered carefully. Although assessing the importance of family history for mendelian disorders may be more straightforward, these conditions affect <4% of the population. Furthermore, the family history may not be informative for these disorders, because even for affected families information reported often includes only common conditions. Also, pediatric primary care clinicians might consider single-gene conditions to be the domain of genetic specialists. The other category to be considered is common complex conditions, signs and symptoms of which might arise in the pediatric period, although not necessarily. Because of their high prevalence, these conditions would have a broad public health scope: even a small relative risk that results from family history could translate to a high attributable risk and a substantial public health impact. Also, this information would more likely be used in the practice of the pediatric primary care clinician, not referred to a specialist. However, common complex conditions present challenges as well. For use of family history to be feasible from a public health standpoint, the health impact must be considered and might be difficult to demonstrate for these conditions. Pediatric primary care clinicians often are not accustomed to dealing with conditions that will not manifest themselves until adulthood. Clinical utility of childhood treatment for many common complex conditions still needs to be demonstrated.

Ethical, legal, and social-issue concerns must be addressed also. Use of family history information must not increase disparities or stigmatization, and tools to obtain and address family history information might need to be different for those with alternative family structures. At the same time, disparity populations might not be aware that their family history information, particularly for common complex diseases, is important and could help them, and thus they might receive substantial benefits from its use. Incomplete family history information would still be better than no family history information. Discussions on the importance of family history could prompt patients to learn more about the health history of relatives with whom they do not have contact and might even act as a unifying force in extended families.

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