Summary of Workgroup Meeting on Use of Family History Information in Pediatric Primary Care and Public Health

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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 workshop 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. Also, the younger age of many parents means that many heritable health problems might not manifest in parents or even grandparents until the child is older.

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 professional education may help in understanding the role of family history in pediatric primary care.

### TABLE 1: Available Family History Web Resources Tools

<table>
<thead>
<tr>
<th>Source</th>
<th>Web Address</th>
<th>Information Available</th>
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<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.bm2">www.marchofdimes.com/gyponline/index.bm2</a></td>
<td>Detailed checklist to assess family history and other aspects of pediatric primary care</td>
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<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>
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<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>
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</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>
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<tbody>
<tr>
<td>Kemper’s pediatric mental health checklist</td>
<td>Group of congenital anomalies</td>
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<tr>
<td>SCREEN questions</td>
<td>Extreme or exceptional presentation of common conditions</td>
</tr>
<tr>
<td>SIDEm (Nongenetic family history checklist)</td>
<td>Neurodevelopmental delay or degeneration</td>
</tr>
<tr>
<td>SIDE questions</td>
<td>Extreme or exceptional pathology</td>
</tr>
<tr>
<td></td>
<td>Surprising laboratory values</td>
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<tr>
<td></td>
<td>Miscarriages, high blood pressure, lung problems (asthma), heart problem, learning problems, and mental health</td>
</tr>
<tr>
<td></td>
<td>Some Concerns about diseases or conditions that seem to run in the family?</td>
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<tr>
<td></td>
<td>Reproduction: pregnancy, infertility, or birth defects in family?</td>
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<tr>
<td></td>
<td>Early disease, death, or disability: early onset of chronic disease or early deaths in family?</td>
</tr>
<tr>
<td></td>
<td>Ethnicity</td>
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<tr>
<td></td>
<td>Nongenetic conditions: behavioral or other environmental risk factors such as smoking or alcoholism in family?</td>
</tr>
<tr>
<td></td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>Similar problems?</td>
</tr>
<tr>
<td></td>
<td>Inherited conditions?</td>
</tr>
<tr>
<td></td>
<td>Deaths (unexplained)?</td>
</tr>
<tr>
<td></td>
<td>Extraordinary laboratory tests or reactions?</td>
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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 Program, 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 (eg, 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-intense 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.\(^6\)\(^7\) 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.\(^23\) 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-repetitive 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. Assessment of family history 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 (\( \geq 170 \) 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-
mal 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, pre-symptomatic 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. O’Loughlin et al 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 history and unknown hypercholesterolemia status in relatives.

From a public health perspective, the goal is to maximize case detection to have a major impact at the population level. 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. Marks et al 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
could be unethical. However, 1 research consideration might be collecting the family history information and possibly even storing biological samples in biobanks for the future. Family histories of more common cancers, such as skin cancers, may also be important in pediatric settings. Gritz et al found that only 22% of dermatologists took a family history, whereas 76% recommended sunscreen use. In addition to the population-based recommendation of sunscreen use for all children, family history of skin cancer might be an indication for more intensive monitoring.

Likewise, for psychiatric disorders, identification of syndromes, which might be aided by use of family history, can affect management. For example, autism can occur as part of a syndrome, and schizophrenia and bipolar disorder are 2 aspects of velocardiofacial syndrome. Discussion of family history of psychiatric disorders involves special attention to setting the stage for having open discussions with patients and their families.

INFORMATICS: PRESENTATION BY SAVEL

Universal acceptance and use of tools to assess family history in the pediatric setting will require consideration of biomedical and health informatics issues. One important goal of informatics is the integration of information from different systems, individuals, and entities, which relies in part on the development and use of data standards. To be useful, standards must be nationally or internationally accepted and always maintained and updated. Thus, an understanding of these data standards will be important if family history tools are to be developed for the pediatric setting.

There are many types of standards (eg, messaging and terminology) that must be addressed to achieve successful integration. One example of a standard is a controlled vocabulary (ie, a terminology or coding system). A controlled vocabulary establishes unique identifiers for the content, which allows different representations of the same concept (eg, “heart disease,” “cardiovascular disease,” or “coronary artery disease”) to be linked to the same code. The controlled vocabulary plays a key role in facilitating this semantic interoperability.

Another type of standard focuses on the transmission, or messaging, of data. An example of a standards-development organization that focuses on the messaging of health care data is Health Level 7 (HL7; see www.hl7.org). This type of standard helps facilitate syntactic interoperability, which is the structuring of information to allow disparate systems to process the information in the same way.

Using a language analogy, semantic interoperability focuses on the words, whereas syntactic 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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