Research Priorities for Evaluating Family History in the Prevention of Common Chronic Diseases

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Introduction

Family history is not a new concept in medicine and public health. It is a risk factor for many chronic diseases of public health significance, including coronary heart disease,[1] diabetes,[2] several cancers,[3] osteoporosis,[4] and asthma.[5] To assess the current evidence regarding use of family history for disease prevention, we convened a workshop in May 2002 entitled Family History for Public Health and Preventive Medicine: Developing a Research Agenda. The workshop brought together experts in many fields (e.g., cardiovascular disease, cancer, diabetes, asthma, behavioral sciences, economics, epidemiology, medical genetics, genetic counseling, preventive medicine, and public health) to discuss the use of family medical history for identifying persons at increased risk for certain common chronic diseases (i.e., those that could be prevented or where early detection could result in delayed onsets or improved health outcomes). The meeting agenda and summary are available on the Centers for Disease Control and Prevention website (www.cdc.gov/genomics/). This article summarizes the ideas discussed at the workshop regarding a research agenda to assess the validity and utility of using family history to prevent common chronic diseases. In addition, we describe specifications for a family history tool that could be evaluated in different public health and clinical settings.

Family History for Public Health and Preventive Medicine

Although family history is a risk factor for most chronic diseases of public health significance, it may be underutilized in the practice of preventive medicine and public health to assess disease risk and to influence early detection and prevention strategies. Geneticists have long recognized that the gateway to discovering inherited disorders and disease susceptibility is through pedigree analysis, which includes a thorough recording of family medical history that is then interpreted through pattern recognition.[6] In the clinical genetics setting, the pedigree is usually constructed through a face-to-face interview with the patient and includes at least three generations of family members. The interview includes assessment of medical conditions in each relative, including specific genetic disorders, birth defects, mental retardation, age at diagnosis, current age or age of death, questions about certain behaviors (e.g., alcohol and tobacco use), and questions about consanguinity and ethnicity. Depending on family size, these interviews can be lengthy, taking ≥30 minutes.

In the public health and preventive medicine setting, collection and interpretation of family history information might have its greatest impact when focused on common chronic diseases such as cancer and cardiovascular disease. Family history of common diseases reflects inherited genetic susceptibilities as well as shared environment and cultural and behavioral factors. Research, such as that described by Keku et al.[7] in this issue, is attempting to identify the specific components of family history, including genetic polymorphisms and environmental factors that may contribute to disease. Until these factors are clearly defined, family history may be useful for identifying apparently healthy people who may be at increased risk for disease in the future.

A public health–oriented, family history tool designed for use in diverse populations must be simple, easily applied, and inexpensive. In developing such a tool, a balance must be maintained between keeping it simple and gathering enough information to make prediction possible. Collecting the appropriate information may enable classification of people into different risk groups. For example, Scheuner et al.[8] developed a scheme that classifies family history risk into three groups (high, moderate, and average) for particular diseases on the basis of the number of affected relatives and age at disease onset. This risk stratification could be used to guide and inform prevention activities (Figure 1). Persons who are average risk (i.e., the risk level of the general population) could be encouraged to adhere to standard public health recommendations for maintaining good health. Persons with an increased risk (i.e., those classified as being at high and moderate

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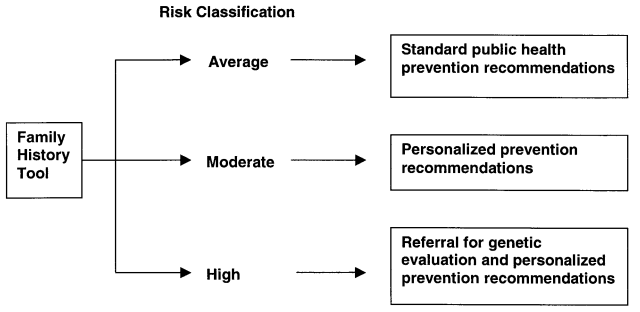

Figure 1. Proposed scheme for using family history to guide and inform prevention activities.

risk) could be given personalized prevention recommendations, specific to their familial risk, that might include assessment and modification of risk factors, lifestyle changes, alternative early detection strategies, and chemopreventive therapies (e.g., aspirin for cardiovascular disease[9] or oral contraceptives for ovarian cancer[10]). Persons characterized as being at high risk might need a genetic consultation to assess a possible inherited disorder that would include genetic counseling, education, and possible genetic testing; such persons may also benefit from receiving recommendations regarding screening and prevention appropriate for their risk. Risk assessment and classification will be unique for each disease included in the family history tool and will need to be periodically re-evaluated because family history changes over time.

In addition to assessing individual risk for chronic diseases, family history information could be used to assess risk on a population basis. For example, family history questions for common conditions (e.g., cancer, heart disease, and diabetes) could be incorporated into population-based studies (e.g., the Behavioral Risk Factor Surveillance Survey,[11] the National Health Interview Survey,[12] and the National Health and Nutrition Examination Survey[13]). Data routinely collected in these surveys on certain conditions and behaviors (e.g., obesity, blood pressure, exercise, diet, smoking, and alcohol use) could then be stratified by family history risk. Currently, these risk factors are examined by race, gender, age, income, and educational level; family history would add another dimension that may help identify population-based targets for health promotion messages or interventions.

Analytic Framework for Evaluating Family History

We used an evaluation framework to structure the workshop presentations and to help identify gaps in knowledge about the validity and utility of family history information for disease prevention. The framework was based on recommendations made by the Secretary's Advisory Committee on Genetic Testing for assessing the benefits and risks of genetic tests.[14] This framework, originally developed for the evaluation of predictive genetic tests, was used because it could easily be applied to the use of family history for determining risk of future disease. Table 1 defines the four elements of the evaluation framework: (1) analytic validity; (2) clinical validity; (3) clinical utility; and (4) the ethical, legal, and social implications of testing or screening. A more detailed discussion about the use of the framework for evaluating family history can be found in Yoon et al.[15]

Diseases To Be Included in a Family History Tool

To be practical, a family history tool that will be used in public health settings by a substantial number of people from various populations can cover only a limited number of diseases. Part of the research agenda will be determining which diseases should be included. Workshop participants suggested several criteria that could

Table 1. Elements and key components of evaluation framework for family history as screening tool

Elements	Definition	Components
Analytic validity	An indicator of how well a test or tool measures the property or characteristic (disease status among relatives) that it is intended to measure	Analytical sensitivity Analytical specificity
Clinical validity	A measurement of the accuracy with which a test or tool identifies or predicts a clinical condition	Clinical sensitivity Clinical specificity Positive predictive value Negative predictive value
Clinical utility	Degree to which benefits are provided by positive and negative test results (presence and absence of family history for disease)	Availability of effective interventions Health risks and benefits Economic assessment
Ethical, legal, and social implications	Issues affecting data collection and interpretation that might negatively impact individuals, families, and society	Stigmatization Discrimination Psychological harm Risks to privacy and confidentiality

Table 2. Criteria for selecting diseases to include in family history tool

- Substantial public health burden
- Well-defined case definition
- Awareness of disease among relatives
- Accurately reported by family members
- Family history is established risk factor
- Effective interventions for primary and secondary prevention

be used to select these diseases (Table 2). The criteria reflect public health objectives and priorities as well as the ability to obtain valid information. The diseases included in the tool should be associated with substantial public health burden, which is usually assessed in terms of prevalence, morbidity, mortality, associated disability, and healthcare costs.[16] The diseases should have well-defined case definitions and should be those of which relatives are likely to be aware. These factors will affect how accurately a person can report the disease status of their relatives and the ability of the tool to predict disease risk. Family history should be an established risk factor for the disease, and effective interventions should be available for primary and secondary disease prevention.

The workshop focused on coronary heart disease, type 2 diabetes, asthma, and colorectal cancer as examples of potential candidates for inclusion in a family history tool. The articles in this theme issue are based on presentations made at the workshop. Kardia et al.[1] have summarized the literature and found that family history is a significant predictor of risk for coronary heart disease (CHD) even after adjusting for traditional risk factors (e.g., hypertension, smoking, and abnormal lipoprotein levels). Validation studies demonstrate that CHD can be accurately reported by family members,[17] and practice guidelines for preventing or managing early CHD have been established.[18] Using the criteria suggested by the workshop participants, CHD is a good candidate for inclusion in a family history–screening tool.

Type 2 diabetes is another potential candidate with several well-established risk factors, including age, race, ethnicity, obesity, and lack of exercise. Because of the alarming increase in the latter two risk factors in the U.S. population, diabetes is reaching epidemic proportions.[19,20] Harrison et al.[2] found that family history risk estimates for type 2 diabetes varied from a 1.4- to 6.1-fold increase in risk, depending on the study design and case definition. Some of the discrepancies in familial risk estimates might result from misclassification because some studies included both type 1 and type 2 diabetes among cases. Because many diabetes cases are undiagnosed,[21] persons may be unaware of diabetes in their family, resulting in an underestimate of disease occurrence. However, despite this lack of specificity, identification of a familial risk for diabetes is likely to be of benefit because persons who are at risk can prevent the condition through both lifestyle and medical therapy.[22–24] Because most type 2 diabetes results from insulin resistance,[25,26] ascertaining family history information for other conditions associated with insulin resistance (e.g., cardiovascular disease, hypertension, and lipid abnormalities) may improve familial risk stratification for diabetes.[27–29]

Asthma is another candidate disease for which difficulties with the case definition may affect the validity of family history information. Several studies suggest that family history is a useful tool to identify increased risk of asthma; however, the degree of risk is uncertain.[5] The case definitions for asthma in the studies varied and included parental reporting of wheezing, current wheeze or cough, physician-diagnosed asthma, and recent use of asthma medications. Although asthma is a public health priority with rising prevalence and associated morbidity, the usefulness of family history for primary prevention and for identifying risk for severe diseases is not clear. More data are needed to assess the clinical validity and utility of risk stratification based on family history for asthma prevention.

Several cancers might be good candidates for inclusion in a family history tool. Results from a validation study of the accuracy of a proband's report of cancer among their relatives demonstrate a high degree of accuracy for breast, ovarian, colorectal and prostate cancers.[3] However, other cancers of the female pelvic organs (e.g., cervical and endometrial) had lower accuracy.[3] Studies have also indicated that rare cancers (e.g., osteosarcomas) and cancers in organs not easily distinguished from neighboring organs are usually not reported with a high degree of accuracy.[30] In addition, rare cancers may not meet the criteria for diseases of public health importance. Melanoma would seem like a good candidate based on rising prevalence rates, a strong familial component, and preventability, but when reported, melanoma is often confused with basal and squamous cell carcinomas.[31] However, distinguishing between types of skin cancer may not be necessary in a family history tool. If a person has a family history of skin cancer, regardless of type, the recommended interventions may be the same depending on the level of familial risk.

Several other diseases have been discussed as candidates for inclusion in a family history tool (e.g., osteoporosis, arthritis, schizophrenia, depression, Alzheimer's disease, psoriasis, inflammatory bowel disease, and alcoholism). For these disorders, a sufficient number of eligibility criteria, as specified by the workshop participants, were not met due to a lack of evidence regarding the validity and utility of using family history for early detection or for improving prevention efforts. However, all of these conditions with a strong familial

component and of public health concern warrant further consideration and evaluation.

The workshop participants also discussed whether the collection of risk-factor data should be included in a family history tool. These factors might include tobacco and alcohol use, body mass index, exercise, and diet. Risk factor information could be used in combination with family history to classify people into risk groups. In a study of pancreatic cancer, the relative risk associated with having a first-degree family member with pancreatic cancer diagnosed before age 60 was 2.49 (95% confidence interval [CI], 1.32–4.69). However, when family history was combined with ever having smoked, the relative risk increased to 8.23 (95% CI, 2.18–31.07).[32] Although questions about risk factors to a family history tool might elicit useful information, it would add to the length and complexity of the instrument since obtaining valid information regarding diet, alcohol, and tobacco use would be difficult in only a few brief questions.

Options for Ascertaining Family History

Examples of several family-history collection instruments were presented at the workshop, and the participants discussed the attributes that should be considered for a public health–oriented tool. Although the multigeneration pedigree is considered ideal because it captures large amounts of information, it requires training and skill to create, is time consuming, and is of questionable usefulness as a population-based screening tool. Ideally, a public health–based family history tool should be easy to administer and adaptable for use in many different settings.

A core set of questions should be developed and evaluated using different formats and among different population groups. The tool could be a self-administered paper questionnaire or computer based. Self-administered, computer-based questionnaires could include an algorithm in the software that would interpret the data and provide both a brief synopsis of disease risk and recommendations for clinical follow-up. Questionnaires could be completed in association with visits to healthcare providers, in specific settings (e.g., clinics, schools, and drugstores), or at home. Patients and their providers could discuss the implications of the family history information and keep it updated during annual visits. Questionnaires completed at home have the advantage of allowing people to confer with relatives or review family records, potentially improving the reporting accuracy. Electronic tools have an added advantage in that they can be easily stored, retrieved, and updated. In addition, Internet-based tools could be linked with useful websites that provide further information about disease prevention and health promotion.

Evaluation of Family History Tools

Research to Assess Analytic Validity

Once a prototype family history tool has been developed, the analytic validity of the instrument should be assessed in different settings. Analytic validity, as described by sensitivity and specificity measurements, is usually estimated by comparing the information obtained by the screening tool with a "gold standard" that is assumed to yield more valid information (e.g., interviews with relatives or review of medical records, death certificates, disease registry records, and pathology reports). When well designed, validation studies are resource intensive, which may explain why most of the published studies use only one gold standard for comparison.

Several studies have been conducted to validate reporting of CHD events by family members.[1] In one study, a family history questionnaire administered to high school students was compared with reports from the students' relatives. The questionnaire was found to be 79% sensitive and 91% specific.[33] Reporting of CHD has been validated in several studies, with most concluding that reporting is reasonably accurate.[1,34] A limited but growing body of literature is available from both population-based and clinical settings regarding the assessment of sensitivity for reporting cancer family history.[3,35] Less is known about the validity of reporting diabetes, asthma, mental illness, and other diseases of public health importance.

The workshop participants outlined the issues that could form the basis of a research agenda for evaluating the validity and utility of family history tools. These issues are formulated as questions in Table 3. The questions were adapted from a model process developed by the Foundation for Blood Research for evaluating genetic tests.[36] Some of these questions may be answered by data from existing studies, whereas others may require the funding and implementation of new studies. Because the purpose of a public health–oriented family history tool is to predict future disease, data collected from healthy persons must be validated. Most of the data in the literature are derived from registry-based or case–control studies. Case patients may recall disease among relatives more accurately than controls,[37] although some models indicate that the impact of differential misclassification is likely minimal.[38] Disease status is not the only characteristic of the proband that may affect the validity of reporting. Age, gender, race/ethnicity, and socioeconomic status were also considered by the workshop participants to be factors that should be evaluated.

At the workshop, data from an analysis of family history reporting that was collected in the Healthstyles[39] 2001 survey were presented. Participants in this nationwide, population-based survey were asked if their biological mother, father, or siblings ever had asthma or heart disease. Of the 3719 respondents, 15% could

Table 3. Specific questions for assessing the validity and utility of family history information for disease prevention[a]

Element	Specific questions
Analytic validity	What is the sensitivity and specificity for reporting each disease included in the tool and how does the sensitivity and specificity vary by: 1) Type of relative (e.g., parents, siblings, children, grandparents, aunts and uncles) 2) Proband characteristics (e.g., age, gender, race/ethnicity, socioeconomic status, and disease status) 3) Disease characteristics (e.g., prevalence, morbidity, mortality, diagnostic criteria, and social acceptability) 4) Disease terminology (e.g., heart disease vs coronary artery disease) 5) Phrasing of the question (e.g., "Have you ever had. . ." vs "Has a doctor ever told you that you had. . .") How accurate is age of onset information? What settings yield more valid information? What formats yield more valid information? What gold standards exist to validate the reported data?
Clinical validity	Does the clinical validity improve if age of diagnosis is known? Does information about distant relatives (second- and third-degree) improve clinical validity? What is the relative risk associated with each disease for each strata of the family history risk-classification scheme (i.e., high, moderate, and average)? What is the prevalence of the disease in each population to be screened? What is the probability that a person will develop disease given a positive or negative family history? How valid is the risk classification system for predicting disease? What classification system for family history risk results in the highest predictive value? Has the tool been adequately validated in populations to which it may be offered? How often should family history information be updated? What are the factors (e.g., genetic, environmental, and behavioral) that modify the relationship between familial risk and disease occurrence?
Clinical utility	What is the natural history of the disease (may determine when family history should first be ascertained)? Are there effective interventions for primary and/or secondary prevention? Is there general access to the interventions? What strategies could be adopted to improve compliance with recommended interventions? Are educational materials available to explain familial risk and the recommended interventions? What is the short-term and long-term impact of a positive or negative family history on screening and disease prevention? Are there any health risks associated with the family history assessment and subsequent interventions? What are the financial costs associated with the family history assessment? What are the economic benefits associated with interventions resulting from the assessment? What methods exist for evaluating and monitoring the family history assessment process and its benefits and risks?
Ethical, legal, and social implications	Are there legal issues regarding informed consent, ownership of the data, obligation to disclose, or reporting requirements? What is known about stigmatization, discrimination, privacy/confidentiality, and personal/family and social issues associated with family history assessment and risk labeling? What safeguards have been described to protect privacy and are these safeguards in place and effective?

[a]Adapted from a model process developed by the Foundation for Blood Research[36] for evaluating genetic tests.

not provide a complete family history. Incomplete reporting was significantly associated with older age, black and Hispanic race/ethnicity, low income, and lack of health insurance.[40] Understanding the factors that contribute to the completeness and accuracy of reported family history will aid in the design of appropriate methods for collecting valid information for disease prevention efforts.

Research to Assess Clinical Validity

The ultimate goal of a family history tool is to identify risk for disease among apparently healthy persons so that recommendations can be made for ways to prevent future disease. If a tool is not useful for prediction or intervention, even a highly analytically valid tool will be of limited value. Despite a renewed interest in using family history as a screening tool,[41–43] many questions need to be answered to assess the validity and utility of the approach (Table 3).

Assessment of clinical validity should begin with estimates of the relative and attributable risks associated with family history for each disease and for each strata of the family history classification scheme. Some of this data may already exist from case–control or

large cohort studies. However, for most health conditions, additional research is necessary to determine the core components of the family history that influence disease risk.

Several studies suggest that collecting data on first-degree relatives only (i.e., parents, siblings, and offspring) may be sufficient in determining disease risk[1,3]; the usefulness of collecting information regarding more distant relatives (e.g., grandparents, aunts, and uncles) remains unclear. The age of the index case is a variable that must be considered when deciding whether to include medical history from more distant relatives. Because the conditions of concern have a late onset, limiting family history information to only first-degree relatives might underestimate the familial risk; the disease might only be present in older aunts, uncles, and grandparents. Furthermore, for conditions limited to one gender (e.g., prostate, most breast cancer, and ovarian cancer), information regarding second-degree relatives is often crucial for defining a familial risk.

Another important consideration is age at disease onset. Most of the family history risk classification systems and family risk scores use *age at onset* for estimating risk.[8] Earlier-than-expected age at onset for common chronic disease is associated with increased family history risk compared with diseases occurring late in life,[44] although family history of most common chronic conditions at any age at onset can increase the risk. The definition of *early age at onset*, however, varies by disease and gender. For example, premature coronary artery disease onset has been defined as ≤55 years in males and ≤65 years in females.[8] Early onset for type 2 diabetes, stroke, and most common cancers is defined as ≤50 years regardless of gender. The algorithms that are developed to classify or score family history risk must account for different early onset definitions for different diseases. In addition, because risk assessment based on family history changes over time, recommendations should be made as to how often the information should be updated.

Family size is another factor that can affect risk assessment and prediction. Some of the methods used to estimate family risk scores account for the family size by comparing the observed and expected number of relatives with a particular disease.[45,46] When families are small, disease-specific information from which to predict future disease is limited. A study of methods for calculating family risk scores demonstrated that if the number of family members is minimal and affected relatives are few, categorical definitions or simple counts are likely to be adequate for estimating risk.[46]

The predictive value of family history depends on sensitivity and specificity, as well as the prevalence of the disease in the population. If the prevalence of a disease is low, even a highly valid tool will yield a low predictive value. Testing of the family history tool should be undertaken in different population groups because the disease prevalence may vary. Studying the risk factors that modify the relationship between family history risk and disease occurrence (e.g., genetic, environmental, and behavioral) is also necessary. These should be considered when making recommendations to people on the basis of their family history risk because they may positively or negatively impact the effectiveness of the interventions. Incorporating family history questions into population-based risk factor surveys may help identify some of these factors.

Research to Assess Clinical Utility

The clinical utility assessment of family history will involve behavioral research, health services research, cost–benefit analysis, and evaluation research. Table 3 lists questions that need to be answered for each of these areas. The articles from the family history workshop in this theme issue describe in more detail some of the disease-specific research that is needed. Of note is the article by Bowen et al.[47] in this issue that includes a case study in which a complex range of issues are raised by the use of family history to predict a 40-year-old woman's risk of colorectal cancer. These issues include healthcare access and insurance, the use of family history by primary care providers, risk perception, awareness of disease status among relatives, and adherence to prevention guidelines.

Risk perception and its impact on disease prevention were discussed at length during the workshop. Specifically, findings from research that focused on awareness of family history of breast cancer and its affect on behavior change were presented.[48] Despite the abundant media attention that breast cancer has received, studies have found that many women with a family history of breast cancer may not realize that their risk is elevated.[48] A recent study among men with a family history of prostate cancer demonstrated that 38% did not know that they were at increased risk because of family history.[49]

Risk perception is a very complex cognitive process influenced by many factors and life experiences that are unique to individuals. One of the greatest challenges of preventive medicine is conveying the notion of risk so that people can make informed decisions about their health behaviors. Family history assessment involves not only identifying persons who are at increased risk for disease, but also educating them about what that risk means. A meta-analysis of 19 breast cancer studies found that perceptions of elevated risk were positively associated with breast cancer screening.[50] Women were also more likely to be screened if they had a family history of breast cancer. A recent study of colorectal cancer found that a strong family history of cancer was associated with better adherence to sigmoidoscopy recommendations.[51]

Although the literature has demonstrated that a positive association exists between family history and screening behavior, data are limited regarding the impact of family history on lifestyle changes (e.g., diet, exercise, and smoking cessation). One recent study demonstrated that the occurrence of a heart attack or stroke in an immediate family member did not lead to a change in modifiable risk factors in young adults.[52] However, these individuals were not informed of their familial risk, and there was no assessment of their beliefs, attitudes, and perceptions of risk for heart disease or stroke. An intervention that provided counseling and education, risk assessment, and recommendations for prevention might have been successful in changing behaviors in this group. Research is needed to demonstrate the effectiveness of this type of intervention in changing behaviors and preventing disease in individuals with familial risk. This might include clinical trials as well as decision analyses. For example, in this theme issue, Tyagi and Morris[53] used a decision analytic framework to explore the value of family history of colorectal cancer for promoting awareness of increased risk and participation in screening. In another article in this issue, Hunt et al.[54] have shown that using family history of cardiovascular disease to target education efforts is efficient and relatively inexpensive because most cardiovascular disease events, especially those that occur at an early age, are concentrated in a limited number of families.

Research to Assess Ethical, Legal, and Social Issues

Public health professionals should also be aware of the ethical, legal, and social implications of collecting family history information, particularly in the current climate of uncertainty about the privacy of medical information. A number of legal issues can affect the collection of family history information under some circumstances, including informed consent, ownership of the data, obligation to disclose, and reporting requirements. At least two lawsuits have been filed against physicians who did not notify a person of their increased risk for a disease based on a family history.[55] Legal issues related to the use of family history information will vary considerably by setting (i.e., clinical practice vs public health campaign). In addition, the potential negative outcomes of assessing family history must be considered carefully. For example, limited information has been obtained about stigmatization; discrimination; privacy/confidentiality; and personal, family, and social issues associated with family history assessment and risk labeling. Although most public health professionals are aware of the potential for fatalism, anxiety, impairment of self-image, depression, or blame associated with collecting family history information, no data are available to suggest that these unintended behaviors or feelings do in fact occur, or, if they do, how commonly they occur. This is another aspect of obtaining family histories that will require further research.

Conclusion

In summary, a family history tool for public health and preventive medicine should be (1) simple, easily applied, and inexpensive; (2) capable of identifying persons at high and moderate risk for disease; and (3) useful for targeting interventions and positively influencing healthy behaviors, without undue cost or harm. If the research priorities presented herein are satisfactorily addressed, physicians hopefully will routinely ascertain family history information for identifying disease risk and then recommend personalized prevention strategies for their patients. In addition, the establishment of a public health campaign could influence the general public through associated public health messages (e.g., "Know your family history: It might save your life"). The campaign should not detract from current public health messages for achieving a healthy lifestyle. Rather, using family history to find people at moderate or high risk for common chronic diseases may augment current efforts to motivate people to exercise, eat a healthy diet, stop smoking or never start, and participate in screening and prevention programs.

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