Can Family History be used as a "Genetic Test" for Prevention and Public Health?

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Genetics of Common Disorders

"The observant practitioner in any specialty, however, could not help but notice the familial nature of the diseases that constituted the bulk of his or her practice, nor could he or she fail to note the variation in expression of those diseases among the patient population, even among patients from the same family."

Family History as a Risk Factor for Disease

"Family history for a specific disease reflects the consequences of genetic susceptibilities, shared environment and common behaviors."

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Family history is a risk factor for common diseases

- Population-based studies RR estimates –

  CHD 2-5 type II diabetes 2-6
  asthma 2-4 breast cancer 2-6
  colorectal cancer 2-5

- FHx explains a significant fraction of prevalent CHD – 14% Utah families had 72% early CHD and 48% all CHD

- 5-20% of people report a FHx of colorectal cancer

Characteristics	Single–Gene	Complex
Gene(s)	Segregates	segregates
Disorder	Segregates	aggregates
Number of gene products	primarily one	multiple
Role of environment	often overridden by effect(s) of gene mutation	important
Age at onset	often younger	often older
Risks for relatives of probands	more predictable, often larger	less predictable, often smaller
Cumulative health-care burden Prevalence Variability in symptom expression	Lower Relatively rare Generally less variable	Higher Common Generally more variable

Evaluating Genetic Tests

The ACCE Model

Definitions

- Genetic test: the analysis of human DNA, RNA, chromosomes, proteins, or metabolites **that detects genotypes, mutations, or chromosomal changes.** Under GINA, a genetic test does not include the analysis of proteins or metabolites directly related to the manifestation of a disease that could reasonably be detected by a healthcare professional with appropriate training and expertise in the field of medicine involved.

Components of ACCE

The ACCE wheel shows the relation among each of the four components of evaluation and the elements of each component. At the hub are the clinical disorder being evaluated and the setting in which testing is done (e.g., classic cystic fibrosis in the setting of prenatal screening). The evaluation process begins only after the clinical disorder and setting have been clearly established.

Analytic Validity

- The **analytic validity** of a **genetic test** defines its ability to accurately and reliably measure the genotype of interest.
- The **analytic validity** of **family history** addresses how accurately the tool identifies disease among a person's relatives.
- Specific elements of analytic validity include sensitivity and specificity.

How valid is Family History information?

Individuals report their family history with accuracy rates of between 65% and 89% when self-reported family history is compared with medical records and other more objective sources.

Bowen DJ, Ludman E, Press N, Vu T, Burke W. Achieving utility with family history : Colorectal cancer risk. Am J Prev Med 2003;24:177-182.

How valid is Family History information?

The sensitivity of the proband's report of diabetes was 0.87, 0.72, and 0.83 for parents, siblings, and spouses, respectively, and specificity was 0.98 for each relative type. In the San Luis Valley Diabetes Study, there was complete agreement between proband and family reports, suggesting that family history information collected from the proband is reliable and accurate.

Harrison TA, Hindorff LA, Kim H, Wines RCM, Bowen DJ, McGrath BB, Edwards KL. Family history of diabetes as a potential public health tool. Am J Prev Med

Accuracy of Family History

- Utah study of CHD showed 77% sensitivity and 85% specificity.
- Diseases that occur earlier and are more severe tend to be reported more accurately than those that occur later and are less severe.

Research Questions for Analytic Validity of Family History

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

- The **clinical validity** of a **genetic test** defines its ability to detect or predict the associated disorder (phenotype).
- **Clinical validity** addresses how well **family history** of disease can be used to stratify disease risk and predict future disease in a person.
- The specific elements include sensitivity, specificity, negative and positive predictive value.

Prevalence and relative risk estimates to family history for selected disease

Disease	U.S. prevalence of the disease	Risk due to family history
Cardiovascular disease	58 million	OR= 2.0 (one 1st-degree relative)[38] OR= 5.4 (two or more 1st-degree relatives with onset <55yr)[39]
Breast cancer	3 million women	RR= 2.1 (one 1st-degree relative)[40] RR= 3.9 (three or more 1st-degree relatives)[41]
Colorectal cancer	Yearly incidence= 130,000	OR= 1.7 (one 1st-degree relative)[26] OR= 4.9 (two 1st-degree relatives)[27]
Prostate cancer	Yearly incidence= 200,000	RR= 3.2 (one 1st-degree relative)[42] RR= 11.0 (three 1st-degree relatives)[43]
Melanoma	200,000	OR= 2.7 (one or more 1st-degree relatives)[44] OR= 4.3 (one 1st-degree relative)[45]
Type II diabetes	13 million	RR= 2.4 (mother)[46] RR= 4.0 (maternal and paternal relatives)[47]
Osteoporosis	8 million women 2 million men	OR= 2.0 for osteoporotic fracture (female 1st-degree relative)[48] RR= 2.4 for wrist fracture (father)[49]
Asthma	17 million	OR= 3.0 (mother)[50] RR= 7.0 (mother and father)[51]

Suggested guidelines for risk stratification based on family history

- **High risk**
  - **Premature disease in a 1st-degree relative**
  - **Premature disease in a 2nd-degree relative (coronary artery disease only)**
  - **Two affected 1st-degree relatives**
  - **One 1st-degree relative with late or unknown disease onset and an affected 2nd-degree relative with premature disease from the same lineage**
  - **Two 2nd-degree maternal or paternal relatives with at least one having permature onset of disease**
  - **Three or more affected maternal or paternal relatives**
  - **Presence of a "moderate risk" family history on both sides of the pedigree**

- **Moderate risk**
  - **One 1st-degree relative with late or unknown onset of disease**
  - **Two 2nd-degree relatives from the same lineage with late or unknown disease onset**

- **Average risk**
  - **No affected relatives**
  - **Only one affected 2nd-degree relative from one or both sides of the pedigree**
  - **No known family history**
  - **Adopted person with unknown family history**

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Risk estimates for colorectal cancer for three risk groups as defined by family history

Risk group	Average	Moderate	High
Risk factor	No 1st-degree relative with colorectal cancer[26]	Any 1st-degree relative with colorectal cancer after age 50[26]	Two 1st-degree relatives with colorectal cancer[27,28]
Prevalence of the risk factor	9/10	1/10	1/50-1/8,000
Absolute risk	0.04	0.06	0.20[a]-~1
Relative risk	reference	1.7	4.9-~30
Attributable fraction[b]	-	0.07	0.07-0.004

[a]Estimated based on a relative risk of 4.9 and compared with people with no family history.
[b]Calculated using Levin's formula[37] for population attributable risk.

Research Questions on Clinical Validity of Family History

- 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

- The **clinical utility** of a **genetic test** defines the elements that need to be considered when evaluating the risks and benefits associated with its introduction into routine practice. The natural history of the specific disorder needs to be understood so that such considerations as optimal age for testing might be taken into account. Another factor to be considered is the availability and effectiveness of interventions aimed at avoiding adverse clinical consequences (if no interventions are available, for example, testing may not be warranted).

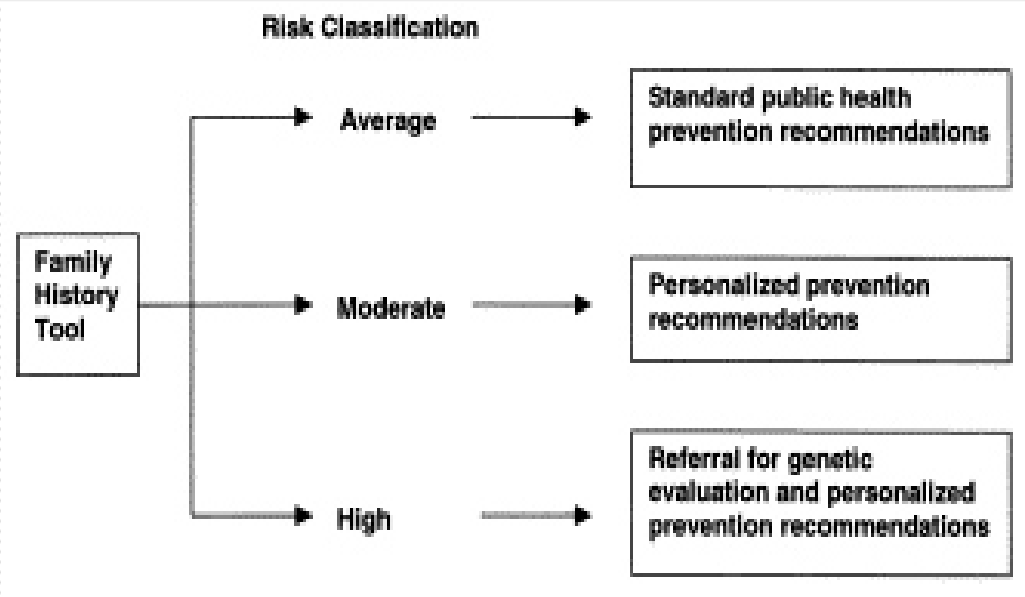
- **Clinical utility** is an assessment of the impact and usefulness of the **family history** tool for individuals, families, and society.

- Can family history information be used as a motivator to change behavior – i.e. adherence to screening guidelines, or lifestyle modification?

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**

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



Research Questions on Clinical Utility of Family History

- 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?

Research Questions for Ethical, Legal, and Social issues in Family History

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?

NIH State-of-the-Science Conference: Family History and Improving Health August 24-26, 2009 Bethesda, Maryland

- What are the key elements of a family history in a primary care setting for the purposes of risk assessment for common diseases?
- What is the accuracy of the family history, and under what conditions does the accuracy vary?
- What is the direct evidence that getting a family history will improve health outcomes for the patient and/or family?
- What is the direct evidence that getting a family history will result in adverse outcomes for the patient and/or family?
- What are the factors that encourage or discourage obtaining and using a family history?
- What are future research directions for assessing the value of family history for common diseases in the primary care setting?

Summary: Can Family History be used as a "Genetic Test" for Prevention and Public Health?

- Yes and No.
- It is not a "genetic test" as defined by GINA.
- It is a "genetic test" in that it predicts risk for disease based on inheritance.
- Its analytic validity, clinical validity, clinical utility and ELSI can be assessed like other genetic tests
- It contains richer information than genetic tests alone because it also reflects environmental and behavioral factors.
- Hopefully, more answers to specific questions on the use of family history will be available after the NIH conference in August.