

Family History: The Three-Generation Pedigree

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The collection of a family history ranges from simply asking patients if family members have the same presenting illness to diagramming complex medical and psychosocial relationships as part of a family genogram. The three-generation pedigree provides a pictorial representation of diseases within a family and is the most efficient way to assess hereditary influences on disease. Two recent events have made family history assessment more important than ever: the completion of the Human Genome Project with resultant identification of the inherited causes of many diseases, and the establishment of national clinical practice guidelines based on systematic reviews of preventive interventions. The family history is useful in stratifying a patient's risk for rare single-gene disorders and more common diseases with multiple genetic and environmental contributions. Major organizations have endorsed using standardized symbols in pedigrees to identify inherited contributions to disease. (Am Fam Physician 2005;72:441-48. Copyright© 2005 American Academy of Family Physicians.)



ILLUSTRATION BY MARK SCHULER

► See editorial on page 386.

ACE This article exemplifies the AAFP 2005 Annual Clinical Focus on the legal, social, clinical, and ethical issues of medical genomics.

A glossary of genomics terms is available online at <http://www.aafp.org/afpglossary.xml>.

A three-generation pedigree has been used for diagnostic consideration or risk assessment of rare single-gene or chromosomal disorders. However, the utility of family history in the assessment of risk for common diseases is becoming increasingly recognized.¹⁻³ Most common diseases result from a combination of environmental factors and variations in multiple genes. Inherited variations within these genes confer individual risks that can differ greatly from the population-based average. Assessment of family history is useful to detect increased risks for diseases that have modifiable risk factors or preventable exposures. Clinical preventive measures for asymptomatic patients recommended by the U.S. Preventive Services Task Force involve a consideration of relevant family history (Table 1⁴⁻¹³). Family history assessment also can help identify relatively rare conditions that may not be considered in a differential diagnosis (Table 2). Alternatively, when a relatively common disease is caused by an inherited mutation in a single gene, family history assessment may lead to early

diagnosis and more aggressive management (Table 3).

Prevention efforts are enhanced by family discussions that shed light on lifestyles or family behaviors that have adverse health consequences. Prevention also is achieved by identifying patients with a higher risk than the population average because of shared inherited factors associated with disease. In some cases, standard screening may be supplanted by targeted genetic testing and a change in clinical intervention for persons at high risk for disease, such as those with a strong family history of cancer.

Office Collection of Family History

Physicians can use several approaches to collect family information and construct a pedigree. The most traditional approach is physician-directed questioning of the patient or family informant. Nurses, physician assistants, and other trained clinical staff also may complete this process. This approach typically takes 15 to 30 minutes. Alternatively, patients can be provided with questionnaires about their family history information before

an office visit. This method still requires a health professional to review the information and create a pedigree.

Unfortunately, a health maintenance visit does not allow for this amount of time to devote to family history collection.¹⁴ In reality, the average office visit lasts 16 minutes, and family history discussion has been observed to last less than three min-

utes.^{15,16} Many physicians compensate for this time limitation by collecting family history information piecemeal over several visits. Checklists may be used in an attempt to speed data collection, but the usefulness of this approach may be limited by patient recall. Checklists also may not distinguish which relatives are affected or their degree of relatedness to the patient. Additionally,

TABLE 1
USPSTF Recommendations Based on Family History

<i>Level</i>	<i>Topic</i>	<i>Recommendation</i>	<i>Clinical considerations</i>
A	Aspirin for primary prevention of cardiovascular events ⁴	Discuss aspirin chemoprevention with adults who are at increased risk of coronary heart disease.	Risk assessment should include questions about age, sex, diabetes, elevated total cholesterol levels, low high-density lipoprotein cholesterol levels, elevated blood pressure, family history, and smoking.
A	Screening for colorectal cancer ⁵	Screen men and women 50 years and older for colorectal cancer.	Initiating screening at an earlier age is reasonable in persons at higher risk (e.g., those with a first-degree relative who receives a diagnosis before 60 years of age). Expert guidelines exist for screening very high-risk patients, including those with a history suggestive of familial polyposis or hereditary nonpolyposis colorectal cancer.
B	Behavioral counseling in primary care to promote a healthy diet ⁶	Counsel adult patients with hyperlipidemia and other known risk factors for cardiovascular and diet-related chronic disease.	—
B	Chemoprevention of breast cancer ⁷	Discuss chemoprevention with women at high risk for breast cancer and at low risk for adverse effects of chemoprevention.	Older age, a family history of breast cancer, and a history of atypical hyperplasia on breast biopsy are the strongest risk factors for breast cancer.
B	Screening for abdominal aortic aneurysm ⁸	Perform one-time ultrasound screening in men 65 to 75 years of age who have ever smoked.	Major risk factors include age (65 years or older), male sex, and a history of smoking (at least 100 cigarettes in a person's lifetime). A first-degree family history of abdominal aortic aneurysm that required surgical repair also increases men's risk.

NOTE: The USPSTF identifies situations where family history may significantly change a patient's risk from the population average. In these instances (particularly for level D or I recommendations), clinical consideration and expert opinion is indispensable.

USPSTF = U.S. Preventive Services Task Force; A = strongly recommended based on good evidence; B = recommended based on at least fair evidence; D = not recommended for asymptomatic patients based on at least fair evidence; I = insufficient evidence to recommend for or against providing the service. Information from references 4 through 13.

unknown family medical information, a patient's focus on an acute problem, and fear of discrimination may impede collection of a complete and accurate family history.

Patient Collection of Family History

With guidance, patients may construct their own pedigrees, which should be reviewed by the physician to assure their accuracy. The

American Medical Association has developed a pocket guide that provides instructions and examples for patients on how to generate a pedigree. It is available online at <http://www.ama-assn.org/ama/pub/category/2380.html>.

A print and Web-based tool developed as part of the U.S. Surgeon General's Family History Initiative¹⁷ is available online at <http://www.hhs.gov/familyhistory>. This

<i>Level</i>	<i>Topic</i>	<i>Recommendation</i>	<i>Clinical considerations</i>
B	Screening for breast cancer ⁹	Perform screening mammography, with or without clinical breast examination, every one to two years in women 40 years of age and older.	Women at increased risk for breast cancer (e.g., those with a family history of breast cancer in a mother or sister, a previous breast biopsy revealing atypical hyperplasia, first childbirth after age 30) are more likely to benefit from regular mammography than women at lower risk.
B	Screening for lipid disorders in adults ¹⁰	Screen men 20 to 35 years of age and women 20 to 45 years of age with diabetes, a family history of cardiovascular disease before age 50 in male relatives or age 60 in female relatives, or a family history suggestive of familial hyperlipidemia.	—
D	Screening for pancreatic cancer ¹¹	Do not screen routinely for pancreatic cancer in asymptomatic adults using abdominal palpation, ultrasonography, or serologic markers.	Persons with hereditary pancreatitis may have a higher lifetime risk for developing pancreatic cancer.
I	Screening for prostate cancer ¹²	Evidence is insufficient to recommend for or against routine screening for prostate cancer using prostate-specific antigen testing or digital rectal examination.	Men older than 45 years of age who are at increased risk (e.g., black men, men with a family history of prostate cancer in a first-degree relative) are most likely to benefit from screening.
I	Newborn hearing screening ¹³	Evidence is insufficient to recommend for or against routine screening of newborns for hearing loss during postpartum hospitalization.	The screening yield and proportion of true-positive results will be substantially higher when screening is targeted at high-risk infants (e.g., those admitted to the neonatal intensive care unit for two days or more, infants with syndromes known to include hearing loss or a family history of childhood sensorineural hearing loss, congenital infections, and craniofacial abnormalities).

TABLE 2
Symptoms and Family History Suggestive of Single-Gene Disease

<i>Primary symptom</i>	<i>Family history</i>	<i>Disease</i>	<i>Gene</i>
Fatigue or arthralgias	Diabetes or cirrhosis	Hereditary hemochromatosis	<i>HFE</i>
Nonfebrile seizure	Seizures, developmental delay, mental retardation, tumors	Tuberous sclerosis	<i>TS1, TS2</i>
Recurrent UTI or hematuria	Hypertension, nephrolithiasis, cerebral aneurysm, or renal failure	Autosomal-dominant PKD	<i>ADPKD1, ADPKD2</i>
Shortness of breath	Epistaxis, telangiectasias	Hereditary hemorrhagic telangiectasia	<i>ENG, ACVRL1</i>
Shortness of breath	Heart failure (cor pulmonale)	Idiopathic pulmonary hypertension	<i>BMPR2</i>
Syncope	Syncope, sudden death	Long QT syndrome	Multiple

UTI = urinary tract infection; PKD = polycystic kidney disease.

tool, which is available in English and Spanish, guides the collection of family history, which is then transferred to a printable, standardized, three-generation pedigree. Specific questions target six adult diseases: heart disease; diabetes; stroke; and breast, ovarian, and colon cancers. These diseases are highlighted because they are common and require a change in clinical evaluation or intervention based on family history. Families are encouraged to seek specific information directly from family members, their physician, and medical records.

Assessment

Regardless of whether family history was collected in the physician's office or the patient's home, assessment should occur at

the initial patient evaluation and be updated periodically to identify newly diagnosed medical or developmental conditions within the family. Physicians should begin with recording the current age and age at onset of symptoms or diagnosis of the patient and first-, second-, and third-degree relatives on each side of the family. The age and cause of death for deceased family members also should be recorded. The accuracy of information generally decreases as the degree of relatedness decreases. Therefore, physicians should note when information is from a medical source instead of a family report.

The most useful family history includes medical, developmental, and pregnancy outcome information on first-, second-, and third-degree relatives.¹⁸ The degree of relatedness indicates the percentage of shared genes (*Table 4*). For example, the half-sibling and the uncle of a patient inherit the same proportion of genes (25 percent) identical to the patient's. Standard symbols and diagrams allow rapid attribution of diseases to particular branches of the family (*Figure 1*¹⁹). Having two relatives from the same side of the family affected with cancer (one with endometrial cancer and the other with colon cancer) increases suspicion for hereditary nonpolyposis colon cancer (an inherited form of colon cancer) more than if one relative was from the paternal side of the family and the other from the maternal side.

Medical information often is not known because of generational, cultural, or health

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TABLE 3
Common Diagnoses Suggestive of Single-Gene Disease

Diagnosis	Family history	Disease etiology	Gene
DVT	DVT, pulmonary embolism	Hereditary thrombophilia Most common: activated protein C resistance-factor V Leiden	Multiple; <i>F5</i>
Emphysema	Emphysema	α -1 antitrypsin deficiency	<i>SERPINA</i>
Glaucoma (primary open-angle)	Glaucoma	Hereditary glaucoma	<i>MYOC</i>
Pancreatitis	Pancreatitis	Hereditary pancreatitis	<i>PRSS1</i>

DVT = deep venous thrombosis.

literacy issues. For example, older relatives mistakenly may believe that discussion of a cancer diagnosis is futile, because in the past there was not effective treatment. A couple planning to have children may not know the relevance of inquiring about previous miscarriages in the family, and family members may not volunteer this emotionally sensitive information. Conditions that are thought to occur sporadically actually could be inherited. For example, a family history of multiple relatives with Down syndrome suggests an inherited translocation, not sporadic non-disjunction. A woman may not realize that her paternal grandmother's and aunt's breast cancer diagnoses confer the same risk to her as if they were maternal relatives. Therefore, encouraging ascertainment of health information for three generations of relatives is warranted.

Consanguinity, the shared relationship of a common ancestor, is frequent in many cultures and should be considered in the evaluation of a patient with unusual symptoms or those suggestive of a rare disease. Persons from cultures within which intermarriage remains common share a greater proportion of genes. In Iraq, for example, 29.2 percent of marriages are between first cousins, and 57 percent of marriages demonstrate some amount of consanguinity.²⁰ An autosomal-recessive disease is more likely to occur in a consanguineous family because of the increased probability of a person having two copies of the same mutation in a gene.²¹ Recurrence of common complex diseases also may be increased in the children of consanguineous parents because of a greater proportion of shared genes.

Physicians should identify patients' ances-

tries and, if known, the countries of origin of their grandparents. A single gene may have genetic variations whose frequencies differ depending on ancestral origin. A low mean corpuscular volume and normal iron studies in a patient without chronic disease signals a diagnosis of thalassemia trait. If a patient and partner with these findings are certain that their ancestors were from Africa, they have a very low likelihood of having a clinically affected child. But if the patient or partner has an ancestor from southeast Asia, there is an increased chance of thalassemia H or even fatal hydrops in their child. Many diseases are more prevalent in certain ancestral groups. For example, persons of Ashkenazi Jewish or Muslim Arabic origin share odds of one in four for carrying a defective gene for familial Mediterranean fever.²² In these patients, awareness of their disease risk is important because early diagnosis avoids prolonged evaluation for other disorders and makes effective treatment possible.

The recall of spontaneous abortions, stillbirths, illnesses, and deaths of family members may evoke strong emotional responses in patients. Feelings of guilt and blame are

TABLE 4
Shared Genes in Blood Relatives

First-degree relative (50% shared genes)	Second-degree relative (25% shared genes)	Third-degree relative (12.5% shared genes)
Children	Aunts and uncles	Cousins
Parents	Grandparents	Great-grandparents
Siblings	Half siblings Nieces and nephews	

not unusual in families in which several relatives are affected by the same condition. Visualizing the family history in pictorial form may clarify risks to a patient that had not been appreciated previously. Establishing a relationship with a geneticist or genetic counselor may be helpful, although genetics professionals are not widely available. Extra clinic time and the assistance of mental health professionals may be required.

Relatives sometimes may be identified

who have significant risk for a disease and in whom early intervention may improve outcomes. The patient should be encouraged to notify these family members of their risk and refer them to a physician. In these cases, the physician's obligation to warn other family members directly is not clear.²³ There have been successful claims of negligence against physicians for failure to warn patients that their family members were at increased risk for colon and breast cancers.²⁴

Pedigree Symbols

○ = Female

□ = Male

◇ = Sex unknown

○ An arrow is used to identify the patient. If the patient is affected by a particular disease or condition, he or she is the proband. If the patient is seeking knowledge about a disease or condition in his or her family, he or she is the consultand.

◻ A diagonal line is used to indicate that the person has died. Cause of death and age at the time of death are indicated below the symbol.

D. 43 years
Aortic dissection

Ⓟ Ⓟ Ⓟ A "P" inside the symbol of an unborn child indicates a current pregnancy.

△ Miscarriage. Indicate the number of weeks the pregnancy lasted underneath the symbol, as well as any identified physical anomalies or abnormal prenatal test results.

(12 weeks)

○—□ No children (by choice)

○—□ Infertility. Indicate cause, if known.
(azoospermia)

○—/—□ A diagonal line through a marriage or partnership line indicates a divorce or separation.

③ ④ ◇ A number inside a symbol may be used if no information is known about these relatives. For example, the 4 inside the box and the 3 inside the circle indicate that there are 4 brothers and 3 sisters in this family. Alternatively, a number inside a diamond indicates that there are that many children of unrecalled sex in the family.

⌈ □ ⋮ ⌋ A symbol inside brackets and attached with a dotted line indicates that this person was adopted.

■ ● Shaded or patterned symbols can be used to represent family members affected by the same conditions. If multiple diseases or disorders occur within the family, various shading or patterns can be used to distinguish between diseases. The condition and representative shading and pattern should be indicated in a key.

NOTE: Additional information can be found in reference 19.

Figure 1. Standard pedigree symbols used in the collection of a family history.

The exact duty of the physician in these instances often is untested, particularly given the restrictions of the Health Insurance Portability and Accountability Act, and is subject to individual state court interpretation. Therefore, disclosure to other family members must be considered carefully with respect to privacy and weighed against a duty to warn.

When Family History Suggests a Genetic Condition

In some patients, the family history may be significant enough (e.g., multiple affected relatives with early onset of a disease) to consider genetic testing for an identified or suspected mutation in a single gene. If the tested gene is a component of a complex disease, a found mutation offers susceptibility or predictive, but not confirmatory, information. The degree of risk attributable to variations or mutations in a single gene can range from a modest contribution in complex disease to near 100 percent certainty. For example, a variation in the *APC* gene found in the Ashkenazi Jewish population confers a modest risk of colorectal cancer.²⁵ Other mutations in the same gene cause familial adenomatous polyposis with a near 100 percent lifetime risk of colorectal cancer.

Susceptibility or predictive testing for familial cancers may significantly decrease morbidity or mortality by changing the management of the disease. Alternative screening with lower specificity but higher sensitivity may be sought (e.g., magnetic resonance imaging for early breast cancer detection), and chemoprophylaxis may be offered (e.g., tamoxifen [Nolvadex] for breast cancer prevention). Aggressive screening and surgical prophylaxis may be initiated (e.g., colonoscopy for detection and removal of precancerous lesions in patients with hereditary nonpolyposis colon cancer). Early surgical intervention may be recommended as preventive measures (e.g., in family members of a patient with a mutation of the *MEN2A* gene who inherit a mutation in the *RET* gene and are virtually certain to develop medullary thyroid carcinoma) or offered (e.g., mastectomy or oophorectomy may

Genomics Glossary

Complex disease: The presence of disease is not matched by a specific variation in a single gene. Multiple genetic and environmental factors act collectively to cause complex disease; however, variations in one or several genes may dramatically alter the likelihood of a disease and its severity.

Consanguinity: A genetic relationship between persons descended from a common ancestor. Consanguinity increases the likelihood of inheriting identical versions of a given gene.

Consultand: Person who seeks genetic counseling for knowledge about a disease or condition in the family.

Predictive genetic testing: Determination of genetic variation in an asymptomatic person to ascertain whether the probability for a given disease or condition is greater than the population-based average.

Proband: The person in a family affected with a disease or condition that raises suspicion that other family members may have an increased propensity for the same disease or condition.

be chosen by patients with an unidentified *BRCA1/2* mutation). Predictive testing for noncancerous conditions also may be initiated. In an adult who has asthma that cannot be improved with bronchodilators, the risk of α -1 antitrypsin deficiency increases if there is a family history of emphysema or bronchiectasis. If airflow obstruction is found to be incompletely reversible on pulmonary function testing, the patient is a candidate for genetic testing.²⁶

Family history also may guide diagnosis even when DNA-based genetic testing is not available for an inherited condition. In a child presenting with a syncopal episode, a family history of syncope prompts consideration of long QT syndrome.²⁷ In an adult presenting with fatigue or arthralgias, a family history of diabetes and cirrhosis should signal measurement of transferrin saturation and consideration of hereditary hemochromatosis.²⁸

New guidelines incorporating genomic principles into family history assessment are increasing the utility of this powerful clinical tool. Taking a traditional "targeted" family history may be necessary in an emergency or when time is limited, but it should not be a substitute for maintaining a three-generation pedigree for every patient.

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