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CLINICAL PEARL

Capturing the Power of the Family History

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Family history plays an invaluable role in patient health, providing important clues and insight that allow physicians to predict and detect disease before obvious symptoms appear. The key to using family history effectively is having the knowledge to filter the relevant from the irrelevant and pick up on the subtle clues that provide clarity (in a perhaps muddled pool of family lore and misinformation).

Families share not only genetic makeup but environment and lifestyle habits, all of which contribute to health. For example, a family that spends a lot of time outdoors exposed to the sun will have members who are at an increased risk for skin cancer, regardless of their "genes." These shared factors are what give family history an impact on an individual patient's health. While many health conditions and diseases are not strictly hereditary and cannot easily be observed to be passed on in families, the history of such conditions in families can help to determine whether, in your patient's case, the information has significance for future screening and management.

Some health conditions are strictly hereditary, passed down in a dominant, recessive, or X-linked manner. Others involve more complex interaction of genes, while still others are caused by a combination of genetic inheritance and environment. Recessive conditions may be masked, with some members being unknown carriers for a condition that is only revealed when two carriers produce an affected offspring. Hence parental consanguinity can unmask a recessive condition in a family. Clues to detection of carrier status lie in the family's ancestry. For example, certain populations, including individuals of Mediterranean, Middle Eastern, and Far Eastern ancestry have a higher carrier frequency for Beta-thalassemia, and, when a member of the family is born with this condition, all other members may be tested for carrier status to determine their likelihood of having a child with Beta-thalassemia. Table 1 highlights some conditions that are more common among specific ethnic groups.

Table 1: Incidences of conditions more common in specific ethnic groups

Ethnicity	Disorder	Carrier frequency
European American	Cystic fibrosis	1/29
Ashkenazi Jewish	Tay-Sachs Canavan Familial dysautonomia Cystic fibrosis	1/30 1/40 1/30 1/29

	Gaucher disease	1/15
Asian	Alpha-thalassemia Beta-thalassemia Cystic fibrosis	1/20 1/50 1/90
African American	Sickle cell anemia Beta-thalassemia Cystic fibrosis	1/10 1/75 1/65
Hispanic	Cystic fibrosis Beta-thalassemia	1/46 1/30-1/50
Mediterranean	Beta-thalassemia Sickle cell anemia	1/25 1/40
French Canadian	Tay-Sachs Cystic fibrosis	1/15 1/29

Identifying dominant conditions is generally straightforward; an individual with the dominant genetic alteration or mutation expresses the trait, and one can see the condition being passed on from generation to generation. Such is the case with Huntington's disease. The presence of some of these conditions, such as hereditary breast and ovarian cancer, can be masked by variable expressivity or incomplete penetrance, appearing to skip generations. Men are as likely to carry a BRCA mutation as women, but have much less risk of cancer, thus are often "silent" carriers.

The same genetic alteration can cause different presentations of the same condition within individually affected family members. Due to this variable expressivity, individuals within the same family who have neurofibromatosis type 1 may manifest symptoms ranging from cafe au lait spots and Lisch nodules only to plexiform neurofibromas and optic gliomas. Similarly, individuals with the same hereditary condition can have premutations of the disease symptoms that forewarn of a possible full mutation and its associated disease in generations to come. For example, the X-linked condition, fragile X syndrome involves repeats of the nucleotides that make up our DNA. A certain number of repeats within a specific range on the chromosome causes mental retardation, specific behaviors, and various dysmorphic features. If a male child has a premutation (not enough genetic repeats to cause fragile X syndrome, but more than the average number), he may develop fragile X-associated tremor/ataxia syndrome as an adult; a female child with the premutation may develop fragile X-associated premature ovarian failure, with menopause occurring under the age of 40. If these characteristics are seen within a family, they can increase suspicion for fragile X, and the testing of individuals in the family may identify carriers that could lead to full-spectrum fragile X mental retardation in subsequent generations.

Another genetic phenomenon that can mask the presence of a hereditary condition is incomplete penetrance. Here, the underlying genetic mutation is present but the condition does not necessarily manifest itself physically in that individual. Hemochromatosis is an example of a condition that is incompletely penetrant. It has

been determined by large population testing that many Caucasian individuals harbor the genetic mutations that cause hemochromatosis, but never develop symptoms of the disease. This is a caution against broad-based population genetic screening, as many variations in our DNA are not good predictors of ultimate disease.

A chronic common disease such as type 2 diabetes clearly involves hereditary or familial predisposition, but may only manifest in the presence of certain lifestyle or environmental factors, such as obesity and being sedentary. Similarly, these common diseases have more than one possible etiology. For example, approximately 10 percent of cancers are strictly hereditary, caused by a single genetic mutation that confers high risk of cancer. Another 20 percent of breast cancers are caused by familial predisposition, with multiple weak genetic factors as well as environmental influences playing a role in risk. The remaining 70 percent of cancers are currently considered sporadic, meaning that unaffected members of the family have minimal or no increased risk of developing the cancer.

The goal of taking a family history is to be able to capture the histories that indicate a possible risk to patients or their offspring and to then be able to make appropriate recommendations and referrals based on this information. While the role of a geneticist or genetic counselor is to make sense of a family history, it is important for physicians to recognize which patients should receive this type of referral. Though most physicians agree on the importance of family history to clinical care, they admit that the lack of detail in the family histories does not allow them to properly identify those patients who would benefit from referral to a geneticist or genetic counselor [1].

Barriers to Family History Taking

Several barriers to sufficient family history taking have been identified. Most often cited is time constraint. Many physicians report a lack of time to take a detailed family history for each patient [1, 2]. One solution might be inclusion of family history questions in a patient's previsit paperwork, which could then be followed by specific questions during the patient's visit. The SCREEN tool (table 2), created as a starting point for family history questioning, may be useful in previsit paperwork [3]. This can then be expanded upon when the patient is seen. Once a family history has been obtained, the information should be updated during each successive visit because family history is dynamic. While a grandmother with post-menopausal breast cancer wouldn't be of great concern, if the patient's mother then developed ovarian cancer, suspicion of a possible predisposition to hereditary disease would increase

Table 2: SCREEN for family history

SC	Some concerns	Do you have some concerns about conditions that run in your family?
R	Reproduction	Have there been problems with infertility, birth defects, miscarriages, or other pregnancy problems in your family?
E	Early disease, death, or disability	Has anyone in the family become ill or died at an early age?
E	Ethnicity	What is the ethnic background of your family?
N	Nongenetic	Are there other risk factors that run in your family?

Another reported barrier to good family history taking is the patient's lack of information [1, 4]. Some families are genealogists, while others tend to be rather secretive about health information, and still others have beliefs and barriers that limit their exposure to health care and proper diagnosis. A good tool for such patients is the death certificate. Death certificates are often used in the genetics realm to identify the actual cause of death or the primary cancer diagnosis or to rule out questionable conditions that are part of the family lore. These documents can be easily obtained online. Patients can be encouraged to obtain medical records and pathology reports for family members affected with health conditions because it provides a wealth of information for that individual's own health.

Lastly, physicians cite as barriers their own lack of comfort with being able to identify patients who are at risk based on the family history. For these reasons, use of published family history tools and recommendations can supply valuable insight.

Making Sense of the Family History

Inquiries into family history should go back three degrees from the patient—in other words, it is not only the immediate family that is important but information on aunts, uncles, grandparents, and cousins also. Healthy family members are as noteworthy as those with medical problems. Relatives' causes of and ages at death and ages at diagnoses are important. A family history of one paternal aunt who had myocardial infarction at age 45 and 10 healthy siblings who lived to old age is of less concern than a paternal aunt with a myocardial infarction at age 45 who had one brother—the patient's father, who died at a young age in an accident. Equal weight should be given to both sides of the family, even if the condition in question is one that is only observed in one sex, such as ovarian or prostate cancer. While these cancers only occur in individuals of a specific sex, predisposition can be passed on from either side of the family.

Some hereditary or familial conditions raise red flags. These include conditions that present at an unusually young age, conditions that appear in multiple family members on the same side of the family, multiple rare conditions that present on one side of the family, more than one unusual condition or primary cancer diagnosis in a single individual, or a clear pattern of inheritance. For example, a family history of a mother with breast cancer at 65 is of less concern than a family history of a sister with bilateral breast cancer at 40, due to the unusually early age of diagnosis and the bilateral presentation.

Rare physical characteristics also have clinical value. Unusually short or tall stature can suggest a skeletal dysplasia that can have other health consequences. Dysmorphic features or mental retardation may be part of specific genetic syndromes. A good question to ask is whether there is anyone in the family who is blood related and looks very different from the rest of the family. Hypotonia, multiple birth anomalies, and ambiguous genitalia are examples of other physical characteristics that may be present in family members and impact health care for patients or their offspring. A family history that reveals these conditions may warrant referral for genetic counseling.

For patients considering reproduction, a history of birth defects, infertility, and miscarriage are critical. Family or personal history of such birth defects as cleft lip, ventricular septal defect, and spina bifida will have a bearing on risk for a patient's offspring. History of infertility or multiple miscarriages can be clues to an underlying genetic cause, such as being a carrier of a balanced chromosomal translocation. Though that individual has a normal genetic complement, the unusual arrangement of the chromosomes can lead to genetic aberration in offspring.

Some patterns and occurrences warrant suspicion of a hereditary condition. If the family history raises concern, the next step is evaluation or appropriate referral. Geneticists and genetic counselors are trained to take thorough family histories and determine whether there is any risk to the patient or his or her offspring based on the information collected. A strong family history of specific illness, such as early heart disease, may warrant enhanced screening in itself, and, if properly identified, can lead to early detection and treatment [5].

Online tools have been created to help the clinician and patient in gathering more thorough family histories, some of which can be updated by the patient and his or her family on a regular basis [2, 6]. The Office of the Surgeon General has named Thanksgiving "Family History Day," encouraging people to collect, share, and update their medical family history when they gather for the holiday every year. After all, family is the core of family history, and, in the world of genetics, what provides information for your patient does so for the entire family.

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