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Genetics for the General Internist

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ABSTRACT

The internist's goal is to determine a patient's disease risk and to implement preventative interventions. Genetic evaluation is a powerful risk assessment tool, and new interventions target previously untreatable genetic disorders. The purpose of this review is to educate the general internist about common genetic conditions affecting adult patients, with special emphasis on diagnoses with an effective intervention, including hereditary cancer syndromes and cardiovascular disorders. Basic tenets of genetic counseling, complex genetic disease, and management of adults with genetic diagnoses also are discussed.

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The geneticist shares tools with the general internist: family history, physical examination, and laboratory evaluation. Often, a diagnosis can be confirmed or discounted without genetic testing, but clinical ambiguity or the potential for intensive or invasive monitoring may make specific tests to look for a gene or protein change helpful. Tested DNA is primarily isolated from peripheral blood leukocytes although isolating DNA from cheek swabs is becoming more common. The specific gene of interest is amplified from genomic DNA using the polymerase chain reaction and is sequenced by dideoxy chain-termination (Sanger) sequencing. Modifications of these techniques detect derangements and deletions affecting gene sequence. New technology is making genetic testing faster and cheaper, so whole genome sequencing may soon replace single-gene analysis,[1,2] and this will make ordering and interpreting genetic test results more complex.

Many patients predate the teaching of molecular genetics, so education about DNA, genes, and inheritance must precede informed consent. Patients should learn about legal protections against genetic information dissemination and discrimination in employment and health insurance (**Table 1**),[3] and also be aware that these protections do not extend to life or disability insurance. Genetic test costs vary from $100 to >$10,000, depending on how many and what size genes are being tested and who performs the test. Each insurance policy states whether and to what extent it covers genetic testing—not exploring this before testing exposes the patient to large medical bills. Finally, follow-up is important to monitor each patient's response to testing. Relief, fear, anger, and guilt are all normal reactions to either normal or disease-predicting test results. Complex family dynamics (eg, mistaken paternity, undisclosed adoption) can complicate result interpretation; clinicians must be prepared to deal with the emotional consequences of their discovery. Genetic counselors provide the support required for successful care of the genetics patient. A certified genetic counselor has earned a masters degree with scientific as well as communication and counseling coursework[4] and must pass a genetic counseling board examination before certification.

CANCER GENETICS

Evaluation for breast/ovarian cancer syndrome is the most common cancer genetics referral, but people with a family history of colon or endocrine cancers also may require genetic evaluation. Indications for referral for a hereditary cancer syndrome include: early age of cancer diagnosis, multiple cancers in an individual person or family, and diagnosis of specific cancers that often have a genetic basis

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(**Table 2**).[5,6] The genetic evaluation should include: 1) obtaining a complete family history and assembling a multigeneration pedigree; 2) determining whether the patient's history is consistent with a familial cancer syndrome; 3) deciding which family member is the most informative person to test; 4) determining whether insurance will pay for the cost of testing; 5) counseling on the potential outcomes and implications of testing; and 6) discussing the patient's test result and his/her response to these when testing is completed. This complex process is best performed by a genetic counselor.

Most familial cancer syndromes are inherited in an autosomal dominant manner. Each affected person should have an affected parent (although limited penetrance and *de novo* mutation can cause violation of this rule), and each child of an affected person is at 50% risk of inheriting the mutated version of the causative gene. Models, such as BRCAPRO, predict the probability that a gene mutation will be found in someone with the patient's family history, and this is key in the coverage decision of most insurances. Examination of the pedigree helps to ascertain what other family members should be tested because they are at risk of carrying a gene mutation. If at all possible, a person who has been diagnosed with a potentially inherited cancer should be tested because a negative test result in a person without cancer is not informative. A patient from a cancer-affected family can test negative because he/she did not inherit a mutated gene copy or because this family's cancer is caused by a mutation in an untested gene. While genetic testing is often performed on someone whose mother or sister died of breast cancer, it is impossible to reassure the tested patient with negative test results unless a mutation has been found in an affected family member.

CLINICAL SIGNIFICANCE

- Genetic information increasingly informs medical decision-making.
- Recognition of familial cancer syndromes allows implementation of surveillance and treatment protocols to prevent cancer or to detect it at an early, treatable stage.
- Death from inherited cardiovascular disease can be prevented with accurate diagnosis and timely intervention.
- Advances in medical care allow people with genetic diseases to live longer; they require special monitoring to prevent adult manifestations of their disease.

Families affected by the breast/ovarian cancer syndrome are recognized after family members are diagnosed with premenopausal breast cancer, breast and ovarian cancer, bilateral breast cancer, and/or male breast cancer. Two genes, *BRCA1* and *BRCA2*, are responsible for the majority of breast/ovarian cancer syndrome cases.[7-9] Other causes of a strong family history of breast cancer include rarer autosomal dominant syndromes (eg, Li-Fraumeni or Cowden syndrome) or a complex genetic trait. A woman who tests negative for a hereditary cancer syndrome may still require intensive breast cancer screening based on her family and personal histories.

When breast/ovarian cancer syndrome is suspected, an affected family member should be tested for *BRCA1* and *BRCA2* mutations by complete gene sequencing. If no mutation is found, then BART testing looks for exon rearrangements in the *BRCA1* gene. Gene sequencing can reveal: a mutation known to be deleterious; no deleterious mutation; or a sequence variation of uncertain significance, which is the most difficult result to interpret. Like any language, DNA accepts some variation in spelling and grammar. For instance, it can be difficult to determine whether the word "dawg" is recognized as a 4-legged barking creature or whether it is discarded as nonsense by the cellular machinery. With increased experience, many variations of uncertain significance are reassigned as "deleterious" or "polymorphism without known functional consequence." How to counsel the patient in the meantime is based largely on personal and family history. In a woman of Ashkenazi Jewish heritage, testing for 3 founder mutations is >95% sensitive to detect a disease-causing mutation.[10] A person from a family with an identified *BRCA* gene mutation needs to be tested only for the mutation found in affected family members.

Table 1 Protections for Genetic Health Information

Health Insurance Portability and Accountability Act HIPAA, Enacted 2003	Genetic Information Nondiscrimination Act GINA, Enacted 2008
Genetic information may fall under Protected Health Information (PHI)	Prohibits discrimination in health coverage or employment based on genetic information
Insurers may not exclude someone from group coverage but may request genetic results and charge higher premiums to an individual	Insurers may not request, require, or use genetic information for deciding on coverage, rates, or preexisting conditions
Plan may not require test results in order to reimburse cost of test	Employers may not use genetic information for hiring, firing, or promotion decisions

Table 2 Indications for Evaluation for a Cancer Genetic Syndrome[5,6]

Suspicion of inherited cancer susceptibility syndromes
Multiple affected family members in successive generations
Early age of onset
Multifocal or bilateral tumors
Questions about cancer risk in offspring or extended family members
Occurrence of cancer frequently associated with germ line mutations (eg, pheochromocytoma, medullary thyroid cancer)

A woman with a deleterious *BRCA* gene mutation has an 85% lifetime risk for developing breast cancer and 20%-60% risk for ovarian cancer.[11] Mutation carriers are advised to: undergo intensive screening for breast and ovarian cancer; consider taking a chemopreventive agent for breast cancer; and consider risk-reducing surgery. Women with elevated breast cancer risk based on family or personal history but without an identified *BRCA* mutation, are managed with a combination of these options based on individual risk estimates made using Gail or Claus models.[12-14]

Yearly mammogram and yearly breast magnetic resonance imaging, often spaced 6 months apart and accompanied by bi-yearly clinical breast examinations, are used to screen high-risk women for breast cancer.[15] Twice-yearly ovarian cancer screening includes pelvic examination, measuring tumor marker CA125 level, and imaging the ovaries and uterus by ultrasound. Screening starts at age 25 years (breast) and 35 years (ovarian), or 10 years younger than the earliest cancer diagnosis in the family.[15] Data support the life-saving benefit of intensive breast imaging[16-19] but not ovarian cancer screening, although there is a paucity of data in the high-risk population.[20]

Chemoprevention with 5 years of tamoxifen or raloxifene (postmenopausal only) reduces the invasive breast cancer risk in high-risk women by 50%.[21-23] Unfortunately, tamoxifen increases uterine cancer risk, and both slightly increase the risk of blood clots.[22] Recently, the aromatase inhibitor exemestane has been reported to decrease breast cancer risk by 65% in high-risk women and to minimally impact quality of life.[24]

Risk-reducing surgical options include bilateral modified radical mastectomy, which can be followed by reconstructive surgery and reduces breast cancer risk by 90%.[25-27] Total abdominal hysterectomy with bilateral oophorectomy reduces ovarian cancer risk by 90%[28,29] and breast cancer risk by 50% if performed premenopausally.[30-32] Surgery is recommended around age 40 years or when child-bearing is complete. After surgery, most clinicians provide symptom education and recommend self-awareness and self-examinations, while some physicians continue with less intensive breast screening after mastectomy or less intensive ovarian cancer screening after oophorectomy.

Hereditary nonpolyposis colon cancer syndrome (HNPCC or Lynch syndrome) is the most common familial colon cancer syndrome and accounts for ~3% of colorectal cancer.[33,34] Lynch syndrome increases colon cancer risk in affected people (80% lifetime risk), and uterine cancer risk in affected women (20%-60%).[35,36] Other gastrointestinal, urinary tract, brain, and skin cancers also occur more commonly in affected individuals.[35,36] People with colon cancer (especially those diagnosed before age 55 years), colon and uterine or renal cancer, or a family history of colon and uterine cancer should receive genetic evaluation.[37] Experts recommend that all colorectal cancer samples be tested for signs of Lynch syndrome, and this is justified through cost-benefit analyses.[38-40] Tissue screening is performed by assessing micro-satellite instability or immunohistochemical staining for absence of 4 major mismatch repair proteins: MLH1, MSH2, MSH6, and PMS2. The presence of micro-satellite instability or the absence of mismatch repair protein staining can result from either inherited (germline) mutation or from somatic changes that are isolated to the tumor. Thus, positive tumor testing must be confirmed by sequencing the potentially affected gene(s) from an individual's nontumor (genomic) DNA. If a mutation is found, other at-risk family members can be tested for that specific mutation.

HNPCC screening regimens are intensive and include yearly or bi-yearly colonoscopy starting at age 25 years, or 10 years younger than the earliest colon cancer in the family.[39,41] No randomized controlled trials of this protocol have been reported, but descriptive trials report that frequent surveillance allows colorectal cancer detection at an earlier stage and decreases colorectal cancer mortality.[41] Generally, women are screened for uterine and ovarian cancer with yearly transvaginal ultrasound and endometrial biopsy starting at around age 35 years,[39] and prophylactic hysterectomy with bilateral salpingo-oophorectomy is often performed around age 40 years may improve survival.[42] Patients are not screened routinely for other cancers; however, upper endoscopy may be considered in families or populations where gastric cancer is prevalent.[41]

Many patients report a family history of cancer; referral depends on who was diagnosed (many members of one side of the family vs scattered family members), age at which they were diagnosed, and what kind was diagnosed (eg, prostate cancer is less often familial than is ovarian cancer). Families with multiple cancer-affected members and family members with bilateral cancer, 2 separate cancers, or early diagnoses suggest a cancer syndrome. Referral to a cancer genetic counselor is an effective way to initiate appropriate testing. Evaluation for a cancer syndrome can take weeks, so appropriate cancer screening should be initiated and concerning symptoms investigated while awaiting results. If a specific syndrome is diagnosed, then appropriate screening protocols can be instituted. These regimens are intensive and recommendations change frequently; consequently a high-risk clinic or specialty provider might be helpful.

COMMON GENETIC CONSULTATIONS

Adult genetics practice involves more than cancer. Tall, thin young adults are often referred for Marfan syndrome evaluation. Marfan syndrome is an autosomal dominant disorder caused by a mutation in the gene encoding fibrillin-1. Malfunction of this connective tissue protein causes a characteristic physical appearance and a high risk of aortic root dissection and retinal detachment.[43] Monitoring aortic root size allows preventative repair or replacement of damaged tissue when the rate of dilation or root size crosses a danger threshold.[43,44] Beta blockade may slow the rate of aortic dilation,[45] and clinical trials are studying whether angiotensin-receptor blockers can do likewise.[46,47]

Cardiac conduction abnormalities are another treatable genetic disorder. Long QT (LQT), short QT, Brugada, and catecholaminergic polymorphic ventricular tachycardia syndromes are caused by mutations changing ion channel proteins.[48] LQT is the most common of these syndromes and is diagnosed by the length of the QTc interval (>470-480 ms). In someone with a history of syncope or childhood "epilepsy" or a family history of long-QT syndrome, congenital deafness, or sudden cardiac death, a QTc as low as 400 ms should trigger suspicion.[49] Treatment has progressed beyond avoiding triggers like exercise, becoming startled, or feeling strong emotions; now patients avoid QT-prolonging medications and may take beta-blockers. People with a high risk of sudden death by arrhythmia receive an implanted cardiac defibrillator.[48] People with one abnormal LQT gene copy are predisposed to cardiac conduction abnormalities, thus the disease is transmitted as an autosomal dominant disorder. When 2 copies of a mutant LQT gene are present, the phenotype is more severe and congenital deafness can result (Jervell and Lange-Nielsen syndrome). More than 20 genes have been associated with ion channel dysfunction, and genetic testing is not 100% sensitive. Like other genetic tests, channelopathy test results should be interpreted in the context of family history and the phenotype of others with the same mutation.[48]

Venous thromboembolism (VTE) occurs under a variety of circumstances, but its diagnosis should always trigger questions about that patient's personal and family history of blood clotting. A genetic predisposition to blood clotting is found in a quarter of all people with VTE and ~60% of familial cases.[50] Known genetic causes of hypercoagulability include the Factor V Leiden (R506Q) mutation and a prothrombin gene mutation at nucleotide 20210. If a person has more than one risk factor (>1 mutation or lack of antithrombin III activity, deficiency of protein C or protein S), clotting risk increases synergistically.[51] People with even a single mutation must take special care during events associated with acquired hypercoagulability (eg, surgery, pregnancy, immobility, hormone use). Genetic evaluation for VTE starts with testing for Factor V Leiden and the prothrombin 20210A gene mutation.[50] Finding a thrombophilia-associated mutation influences the length of time a person remains on anticoagulation after a first VTE event, supports the need for indefinite prophylaxis after a second event, and may indicate aggressive prophylaxis during times of acquired hypercoagulability.[51]

Patients often ask whether they will get a disease that has affected a parent. Alzheimer disease (AD) is common; risk increases with age, and no effective prevention is known. Having a parent with AD doubles a person's risk of developing the disease (lifetime risk ~25%). In 25% of AD cases, the affected person has 2 or more affected family members and the disease is called familial.[52] Less than 2% of AD cases are familial and early onset (<60 years old), and only in these families are disease-predicting mutations found in the presenilin-1, presinilin-2, or amyloid precursor protein genes.[52] In most AD-affected families, no test can predict AD development. *ApoE e4* allele status can help confirm a diagnosis but doesn't predict disease—people

Table 3 Recommended Monitoring for Adults with Down Syndrome[54] and NF1[55,56]

Medical Problem	Onset	Screening
Down syndrome		
Cardiac disease (mitral valve)	Congenital or acquired	Yearly auscultation, may need echo
Hypothyroidism	Childhood +	Yearly TSH
Diabetes	Teens +	Yearly blood sugar monitoring
Mental health disorders	Teens +	Screen for depression, OCD, abuse,
Obesity and low muscle tone	Childhood +	Obstructive sleep apnea
Atlantoaxial instability	Childhood +	Symptoms of spinal cord compression
Periodontal decay	Teens +	Twice-yearly dental visits
Alzheimer's disease	40-50 years	Anticipatory guidance, estate planning
NF1		
Hypertension	Teens +	Yearly blood pressure screening
Pheochromocytoma	10+ years	Yearly blood pressure and symptom screening
Breast cancer	<50 years	Mammogram starting at age 40 years
Malignant nerve sheath tumor	5-75 years	Symptom-based monitoring
Osteopenia/osteoporosis	Teens +	Symptom awareness, DEXA from 40?

TSH = thyroid-stimulating hormone; OCD = obsessive compulsive disorder; NF1 = neurofibromatosis 1; DEXA = dual-energy X-ray absorptiometry.

Table 4 Frequently Updated Resources for Genetic Information

http://www.generviews.org	Reviews of >2000 genetic disorders with diagnostic, management, and surveillance recommendations; contact information for genetics professionals; testing resources
http://www.ncbi.nlm.nih.gov/omim	Gene-specific disease information
http://www.cancer.gov	Information about cancer and genetic cancer syndromes with patient education material
http://www.cancer.gov/cancertopics/pdq/genetics	Information about genetic cancer syndromes

with no *ApoE e4* alleles get AD, and people with 2 *ApoE e4* alleles live into old age without AD.[53] Coronary artery disease has a similarly complex genetic basis. In coronary artery disease, more is known about the role of modifiable risk factors like hypertension, cholesterol levels, and tobacco use; however, only tests for familial hyperlipidemia are highly predictive.[53]

In a patient with a family history of sudden death, the causes should be elucidated and discussed. Arrhythmia suggests QT abnormalities or cardiomyopathy. Aortic aneurysm occurs with Marfan syndrome and other connective tissue disorders. Early myocardial infarction raises suspicion of familial hyperlipidemia or homocysteine disorders. Stroke risk increases with cardiovascular malformation from von Hippel-Lindau disease or cavernous hemangioma syndrome. Pulmonary embolism occurs with thrombophilia or cancer. Each potential diagnosis requires a specific evaluation, and clinical geneticists are trained to coordinate the evaluation and to return the patient to their primary care practitioner with management recommendations.

THE ADULT PATIENT WITH A CHILDHOOD-ONSET GENETIC DISEASE

As medical care improves, people with genetic disease evident in childhood are requiring an internist's care. Internists must recognize and treat disease manifestations that persist into or manifest in adulthood. Down syndrome has adult manifestations including hypothyroidism, diabetes, obesity, obstructive apnea, mental illness, tooth decay, and continuing cardiac dysfunction (**Table 3**).[55] Adults with Down syndrome routinely live into their 60s, and most will show symptoms consistent with Alzheimer disease by their mid 40s.[52] There is no difference in treatment for AD in the setting of Down syndrome, but the onset of AD can be devastating for someone who may be marginally independent at best. The parents of a Down syndrome patient are essential caregivers but may experience frailty and memory problems just as their Down syndrome children are undergoing functional decompensation. The general internist must anticipate this and encourage Down syndrome patients (or their caregivers) to plan for their physical and financial care before a crisis develops.

Café au lait spots and neurofibromas trigger childhood neurofibromatosis 1 evaluation, but the disease also affects adult health (**Table 3**). Malignant peripheral nerve sheath tumors occur in ~10% of patients, and hypertension from vascular disease or pheochromocytoma is common.[56] Women with neurofibromatosis 1 have a 30%-60% risk of breast cancer, often occurring before age 50 years. The fracture risk is increased in both genders due to decreased bone strength.[57] The internist must screen for neurofibromatosis-associated disease, especially the subtle changes that indicate a growing malignant tumor.

CONCLUSION

Caring for the genetic issues of adult patients starts by taking a basic genetic history and recognizing what problems need further evaluation. Few general internists have time to take a 4-generation pedigree, but asking about sudden/early death, blood clotting, and cancer will uncover many treatable genetic disorders. Confirming or excluding a specific genetic diagnosis often requires reviewing records of family members or specific testing. The patient with a specific syndrome should be managed in order to minimize risk of disease-related morbidity and to maximize continued functional capability. Most genetic disorders are rare; management recommendations are seldom evidence based and change as research advances and specialty practice evolves. The Web sites in **Table 4** provide accurate genetic information, as can an adult geneticist.

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