REVIEW

The Role of Genetic Testing and Effect on Patient Care

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The heralded report of the first draft of the Human Genome Project highlights the role genetics plays in nearly all medical disciplines, including dermatology. Many inherited disorders have dermatological features, and dermatological pathologic conditions frequently can be traced to a genetic cause. Suspicion of a genetic disorder is often suggested first by a practitioner such as a dermatologist, who is likely to be the first to identify characteristic features of the disease. This review highlights the relationship between the clinician and genetics professional in genetic testing using a case example of a familial cancer syndrome, Cowden syndrome, as a model.

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With the completion of the first draft of the human genome[1] comes the promise of further genetic testing options and, possibly, prevention and therapeutic options for genetic conditions. In the last century, cutaneous manifestations of hereditary disorders have been recognized. Many genetic disorders have characteristic skin findings, and, conversely, familial clustering is seen in many dermatological disorders (**Table**). Anecdotal information suggestive of the genetic bases of many dermatological disorders has given way to quantitative information obtained through the rapid development of genetic technologies. It is now possible to determine some of the genes that, when mutated, result in familial disorders. Although these new discoveries clarify some of the mysteries of human disease, the basis of genetic disorders is complex. For the practicing clinician, the application of these new discoveries to patient care is complicated, particularly given the rapidity of the genetics information evolution. As a result, the field of medical genetics has evolved to provide expertise in familial disorders and to assist in the provision of services in other medical specialties, including dermatology. In the context of this new genetics information, we suggest an approach to the identification of genetic disorders based on dermatological findings, using familial cancer syndromes as a paradigm.

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EVALUATION FOR A GENETIC DISORDER

Given the numerous genetic syndromes with cutaneous manifestations, maintaining expertise on every disorder becomes difficult. The key is recognizing the possibility of a disorder and determining whether the complexity of the issue requires further consultation. Identification of clinical features, evaluation of family history, and, occasionally, performance of basic diagnostic procedures are the fundamental tools for establishing the possibility of a genetic syndrome.

A syndrome is a combination of signs and symptoms that forms a distinct clinical picture indicative of a particular disorder.[3] Familial cancer syndromes are genetic disorders in which cancer appears to cluster within the family history. One of the first reports of a familial cancer syndrome was in 1913 from a pathologist, Warthin,[4] who reported his seamstress' family history of cancers of the bowel, uterus, stomach, and other organs. This family illustrates the clustering of cancers seen in hereditary nonpolyposis colon cancer syndrome, also known as Lynch

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Dermatological Features of Selected Familial Disorders*

Dermatological Finding	Genetic Disorders
Eruptions, cysts, nevi, and growths	**Gardner syndrome (familial adenomatous polyposis)**
	Acrodermatitis enteropathica
	Hypercholesterolemia
	Fabry disease
	Pseudoxanthoma elasticum
	Basal cell nevus syndrome
	Cowden syndrome
Pigmentation anomalies	Multiple lentigines syndrome (LEOPARD)
	Adrenocortical unresponsiveness to corticotropin
	Fanconi anemia
	Peutz-Jeghers syndrome
	Incontinentia pigmenti
	Hypomelanosis of Ito
	Neurofibromatosis
	Tuberous sclerosis
	Hemochromatosis
	Waardenburg syndrome
	Albinism
	Chédiak-Higashi syndrome
	Focal dermal hypoplasia (Goltz syndrome)
Photosensitivity	**Xeroderma pigmentosum**
	Bloom syndrome
	Variegate porphyria
	Erythropoietic protoporphyria
	Hartnup disease
Others	de Lange syndrome
	Nail-patella syndrome
	Ectrodactyly–ectodermal dysplasia–clefting
	Ehlers-Danlos syndrome
	Ataxia telangiectasia syndrome
	Refsum disease
	Sjögren-Larsson syndrome
	Sjögren syndrome (sicca syndrome)

*Boldface type indicates cancer syndromes. Adapted from Robinson and Linden.[2]

syndrome. Since Warthin's report, various familial cancer syndromes have been described, with many having dermatological features. Therefore, knowledge of familial cancer syndromes has direct relevance for clinicians in dermatology.

Identification of multiple cases of cancer either in the patient or the patient's family history is typically the first clue when suspecting a familial cancer syndrome. Family history assessment and individual clinical evaluation are the most useful tools for the identification of genetic disorders. If time permits, obtaining a standard family tree, or pedigree, aids in recognizing heritable characteristics. A pedigree includes the health history of (1) first-degree relatives of the patient (parents, siblings, and children); (2) second-degree relatives (nieces and nephews, aunts and uncles, and grandparents); and (3) third-degree relatives (first cousins). Useful facts can be derived from directed questions regarding cancer diagnoses and any other unusual features, such as cutaneous lesions. Directed questions are important when time constraints limit the amount of family history taken. Additional important information includes the country of origin of ancestors and particular religious or cultural affiliations, because certain inherited syndromes are more frequent in particular ethnic or cultural groups. Many syndromes have significant variation in the type and degree of effects, and care should be taken that subtle characteristics are not missed.

Certain hallmark features are frequently seen in pedigrees with familial cancer syndromes: (1) several relatives with the same or related cancers, (2) a younger age of onset than is usually seen, (3) an excess of multiple primary cancers, and (4) a recognizable pattern of inheritance.[5] Most familial cancer syndromes are inherited in an autosomal dominant pattern, but some syndromes follow other inheritance patterns (ie, X-linked or autosomal recessive). Dominant inheritance is characterized by the transmission of disease through each generation, although skipping of generations may appear because of milder or nonexistent effects in certain individuals.

Once the suspicion of a genetic syndrome has been raised because of clinical features, family history, or both, diagnostic procedures may assist in the diagnosis. This testing may include procedures such as colonoscopy for the presence of colonic polyps, or biopsy of skin lesions to obtain pathologic samples. The procedures performed depend on a given syndrome and situation.

Genetic testing, including prenatal testing, is available for several disorders. There are complex issues that arise, specifically with genetic testing for familial cancer syndromes, including (1) the amount of genetic variation that exists within an individual cancer syndrome, (2) the technical difficulty involved in testing and interpreting results, and (3) the psychosocial, emotional, and familial effects resulting from testing.[6] Many clinicians in busy practices do not have adequate time to deal with these difficult issues in an in-depth manner. Genetics professionals, however, are uniquely prepared to address these issues on a consultative basis.

There are several models of provision of genetic services. Geneticists, physicians with fellowship training in medical genetics, perform physical examinations and diagnosis of genetic disorders. Some disorders are exclusively diagnosed by physical examination, while others may be diagnosed by genetic or other testing methods. Frequently, diagnoses are made on the basis of a combination of the physical features of the disorder and the testing results, eg, genetic, biochemical, histological, or other testing.

Genetic counselors in the United States are typically advanced-degree trained health professionals with expertise in medical genetics. A survey of the National Society of Genetic Counselors[7] found that 94% of genetic counselors have master's degrees in human or medical genetics and training typically is provided by specially accredited genetic counseling programs. Family history evaluation and genetic testing are performed by geneticists and genetic counselors.

Genetic testing is available for many of the familial cancer syndromes, and the genes associated with these disorders tend to be of 2 different types: oncogenes and tumor suppressor genes. Genes that cause cancer when

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inappropriately activated are known as *oncogenes*. More frequently found in familial cancer syndromes, *tumor suppressor genes* are genes that, when altered, no longer properly control cell growth. Testing for genes implicated in familial cancer syndromes can be performed in several ways.

Some of the testing methods for familial cancer syndromes include cytogenetic analysis, protein analysis, functional analysis, and, most frequently, molecular analysis. Cytogenetic analysis is for visualization of the chromosome structure. Frequently, these studies are done to determine whether there are extra or missing chromosomes or large structural rearrangements. Protein assays identify gene mutations that cause absent or abnormally sized proteins. Functional assays distinguish between gene mutations that have no effect (polymorphisms) and mutations that affect function of the gene. Molecular testing technologies, on a basic level, evaluate gene alterations either at the whole gene level or at the individual DNA sequence level.

Besides the inherent complexity of the testing process, many other issues arise from genetic testing. For example, only a small number of all cancer cases are due to genetic disorders; therefore, calculation of the probability of a syndrome is crucial before testing. Testing should be initiated in an affected individual in the family first to have the highest probability of detecting a genetic alteration. Presence of an alteration does not ensure diagnosis of a familial cancer syndrome, because some mutations do not have an adverse effect on gene function. Identifying a deleterious (disease-causing) mutation in an affected individual generally confirms the diagnosis of an inherited cancer syndrome. Unaffected members of the family may then pursue genetic testing. However, cancer development is not always inevitable in unaffected members who are found to have the familial mutation, because in many syndromes not all carriers of deleterious mutations develop cancer during their lifetime. Also, in those individuals without the familial mutation, cancer may develop in the absence of a genetic predisposition, as it does in the general population. Not finding a mutation in an affected member of the family does not rule out a disease, because the sensitivity of genetic tests may not be high and there may be mutations in other genes. Ethical, legal, and social issues also arise in risk assessment and testing.

During a genetics consultation, genetics professionals also consider the psychological and social effects of genetic risk assessment, not only on the patient but also on the patient's family. Issues that arise include effects on body image, familial relationships, finances, and insurability. In theory, genetic information could be used by health insurers, life insurers, disability insurers, and employers for discrimination against those with increased risk of disease because of genetic disorders. At least 38 states have laws against the use of genetic information for health insurance discrimination; however, there is not universal protection against all forms of discrimination. Therefore, the practitioner offering genetic testing has the responsibility to inform the patient regarding the risks, benefits, and limitations of genetic testing to provide true informed consent. A case example illustrates these points and the interaction between the dermatologist and the genetics professional.

DISEASE DESCRIPTION

The following case example describes a patient with Cowden syndrome. Cowden syndrome is an autosomal dominant disorder with a 50% probability of inheritance for offspring of affected individuals. Hallmark features of the disease include multiple hamartomas and increased risk of cancer of the breast, thyroid, and, possibly, other tissues such as the endometrium. Malignant melanoma also has been reported in individuals with Cowden syndrome. Trichilemmomas, hamartomas of the infundibulum of the hair follicle, and mucocutaneous papillomatous papules occur in more than 90% of affected individuals and are characteristic features of the disease.[8,9] The expression of the disease can be variable, with some individuals having subtle features and others exhibiting more severe symptoms. The incidence of the disease was estimated in a Dutch study to be 1 in 250 000, but this may be an underestimation because of underdiagnosis of the disorder.[10] Mutations in the *PTEN* gene, located at chromosome 10q22-23, cause Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome (also known as Bannayan-Zonana, Bannayan-Riley-Smith, or Ruvalcaba-Myhre-Smith syndrome).[11-13] Also inherited as an autosomal dominant disorder, Bannayan-Riley-Ruvalcaba syndrome causes different effects, including developmental delay, macrocephaly, lipomatosis, vascular malformations, and speckling of the penis, although caused by mutations in the same gene. In 1995, diagnostic criteria for Cowden disease were developed by the International Cowden Consortium and adopted by the National Comprehensive Cancer Network Genetics/High Risk Cancer Surveillance Panel. More recently, endometrial carcinoma has been suggested to be added to the criteria list. Of the cases that follow the original consortium criteria, data suggest that about 80% have *PTEN* mutations.[14] Surveillance for individuals with Cowden syndrome follows surveillance for the likely tumors.

CASE EXAMPLE

Ms D was referred for genetic counseling by her dermatologist, primarily based on her diagnosis of multiple facial trichilemmomas. She indicated that her dermatologist was concerned that she might have Cowden syndrome, which she understood was a genetic condition. This possible diagnosis had been raised 5 years previously by her dermatologist, but she was not emotionally ready to consider it until now. Ms D stated that she had not researched the disease because she was "too afraid of what she would find."

Ms D is 58 years old and white. She was diagnosed as having 4 facial trichilemmomas at age 50. She was treated with surgery and chemotherapy for endometrial cancer at age 47. She was diagnosed with squamous cell carcinoma of the eyelid at age 42 and with basal cell carcinoma of the face 3 times, at ages 35, 40, and 43. She has hypothyroid disorder and has been successfully controlled with medication since she was 25. She has been followed up

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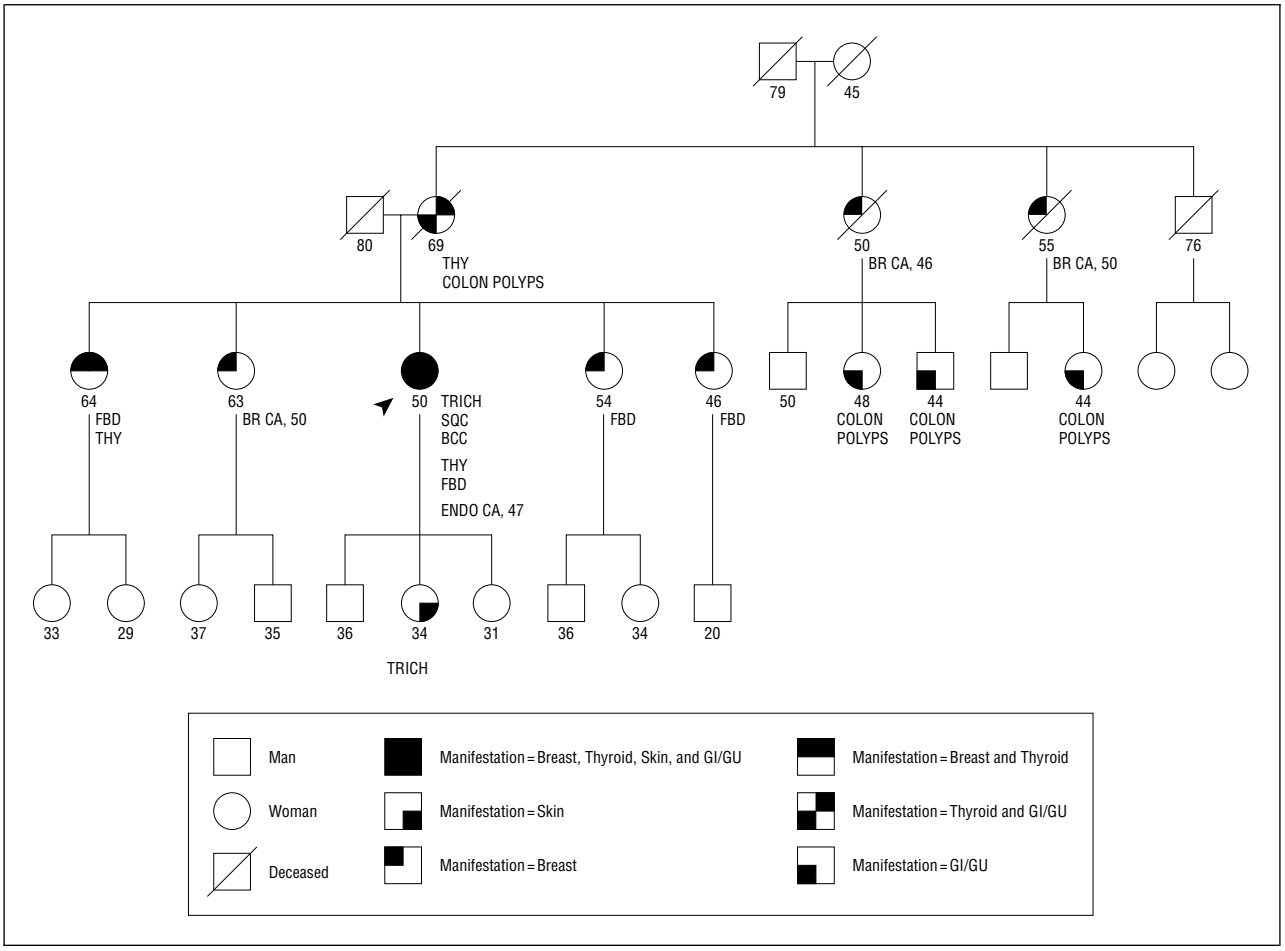

Figure 1. Case example pedigree. THY indicates thyroid disease; BR CA, breast cancer; FBD, fibrocystic breast disease; TRICH, trichilemmomas; SQC, squamous cell carcinoma; BCC, basal cell carcinoma; ENDO CA, endometrial cancer; GI/GU, gastrointestinal and genitourinary; and arrowhead, proband.

by a breast surgeon for fibrocystic breast disease since she was 34. She has 3 children, ages 36, 34, and 31.

The family history was reviewed, indicating that Ms D has 4 sisters and no brothers. Two sisters (ages 54 and 46) have been diagnosed as having fibrocystic breast disease. One sister (age 64) has fibrocystic breast disease and thyroid disease. Another sister (age 63) had breast cancer at age 50. Ms D's mother had colon polyps of unknown histopathologic origin at age 67 and had a history of thyroid disease. Two of her maternal aunts were diagnosed as having breast cancer at ages 46 and 50. Additional family history included multiple maternal cousins with colon polyps of unknown histopathologic origin (**Figure 1**).

Based on her personal and family history, a diagnosis of Cowden syndrome was discussed. The diagnostic criteria, natural history, and genetics of the disease were described to the patient. Based on the description of the disease, Ms D recognized the features of Cowden syndrome in herself and in some of her family members.

She and the genetic counselor explored the emotional and psychosocial ramifications of having a genetic disorder. Ms D was most concerned about her children and whether they could have the disease as well. Appropriate medical examinations to look for signs of the disease were discussed, as well as the availability of genetic testing for *PTEN* mutations. Ms D declined genetic testing, explaining that it was "too much" for her to consider at the time.

Two months later, Ms D returned for genetic counseling and indicated that she wanted to pursue genetic testing. She had taken time to reflect on the information provided at the previous counseling visit and had discussed it with her husband, children, and other at-risk family members. Ms D was outspoken about her hopes that she had not passed it on to her children. The genetic counselor explained the inheritance of Cowden syndrome and the possibility of a 50% risk of inheritance for each of her children. Ms D indicated that it would be difficult for her to find out that any of her children had inherited the disease, but she was ready to accept the possibility.

The genetic counselor and Ms D researched whether the cost of testing would be covered by her insurance. It was not a covered benefit, and Ms D was not in a financial situation to pay for the testing herself. The genetic counselor indicated that, in the absence of genetic testing, there were other options for her children. Specifically, they should each have a dermatological evaluation, with a focus on the cutaneous manifestations of Cowden disease. Cancer surveillance would be most important for those children with the hallmark skin findings, but all of her children should be followed up for breast and thyroid cancer.

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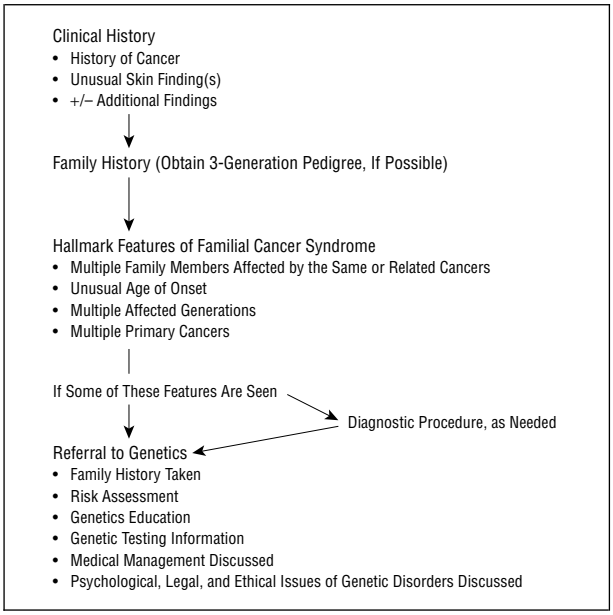

Figure 2. Evaluation of a suspected familial cancer syndrome.

A month later, Ms D returned with one of her daughters who had multiple facial trichilemmomas. It was assumed that the daughter had Cowden syndrome as well. The genetic counselor reviewed the disease and genetics and focused special attention on the emotional ramifications of having a genetic condition. Genetic testing for mutations in the *PTEN* gene was discussed, and the daughter's insurance company agreed to pay for the testing. Six weeks after her blood draw, she returned with her husband to find that she did indeed have a deleterious *PTEN* mutation. Although this result only confirmed the dermatologist's and genetic counselor's suspicion, it was now possible to offer genetic testing to the other members of the family.

Ms D's other 2 children presented to the genetic counselor for testing. Both decided to pay for testing themselves and to not involve their insurance company because they were concerned about genetic discrimination. Although Ms D's son was found to not carry the familial mutation, Ms D's other daughter did carry the mutation and was advised to undergo increased surveillance for breast and thyroid cancer. On a mammogram, a small focus of ductal carcinoma in situ was identified.

CONCLUSIONS

The case report illustrates the relationship between the dermatologist and the genetics professional. Suspicion of a genetic disorder, on the part of the clinician, was based on identification of unusual features, including the skin lesion's pathologic abnormalities and the clustering of cancer within the patient's medical history and her family history. The genetics professional was prepared to more fully explore the family history; provide assessment of the probability of a disorder based on family history; educate the patient about the natural history and genetics of the syndrome; discuss the advantages, disadvantages, and limitations of genetic testing; and provide support regarding psychosocial issues, family dynamics, and insurance concerns. Management recommendations were provided by the genetics professional, but surveillance was carried out by other appropriate practitioners, including the dermatologist. A simple management algorithm (**Figure 2**) of the identification of a possible disorder by a practitioner, then referral to a genetics service, and finally return of patient care to appropriate practitioners can be applied to nearly all familial disorders scenarios.

The mapping of the human genome promises greater understanding of the basis of genetic disease, but the clinical application of this information may take years to fully develop. Genetic testing is a complex process that requires understanding of not only the disorder but also the social, legal, ethical, and financial implications for the patient at risk. The developing field of medical genetics is poised to work with other clinicians to provide comprehensive care.

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