n the past 15 years, clinically based genetic testing has evolved from an uncommon analysis ordered for the rare hereditary cancer family to a widely available tool ordered on a routine basis to assist in surgical decision making, chemoprevention, and surveillance of the patient with cancer, as well as management of the entire family. The evolution of this field has created a need for accurate cancer genetic counseling and risk assessment. Extensive coverage of this topic by the media and widespread advertising by commercial testing laboratories have further fueled the demand for counseling and testing.

Cancer genetic counseling is a communication process between a health care professional and an individual concerning cancer occurrence and risk in his or her family. The process, which may include the entire family through a blend of genetic, medical, and psychosocial assessment and intervention, has been described as a bridge between the fields of traditional oncology and genetic counseling.

The goals of this process include providing the client with an assessment of individual cancer risk, while offering the emotional support needed to understand and cope with this information. It also involves deciphering whether the cancers in a family are likely to be caused by a mutation in a cancer gene and, if so, which one. There are >30 hereditary cancer syndromes, many of which can be caused by mutations in different genes. Therefore, testing for these syndromes can be complicated. Advertisements by genetic testing companies bill genetic testing as a simple process that can be carried out by health care professionals with no training in this area; however, there are many genes involved in cancer, the interpretation of the test results is often complicated, the risk of result misinterpretation is great and associated with potential liability, and the emotional and psychological ramifications for the patient and family can be powerful. A few hours of training by a company generating a profit from the sale of these tests does not adequately prepare providers to offer their own genetic counseling and testing services. Furthermore, the delegation of genetic testing responsibilities to office staff is alarming and likely presents a huge liability for these ordering physicians, their practices, and their institutions. Providers should proceed with caution before taking on the role of primary genetic counselor for their patients.
Counseling about hereditary cancers differs from “traditional” genetic counseling in several ways. Clients seeking cancer genetic counseling are rarely concerned with reproductive decisions that are often the primary focus in traditional genetic counseling, but are instead seeking information about their own and other relatives’ chances of developing cancer. In addition, the risks given are not absolute but change over time as the family and personal history changes and the patient ages. The risk reduction options available are often radical (e.g., chemoprevention or prophylactic surgery), and are not appropriate for every patient at every age. The surveillance and management plan must be tailored to the patient’s age, childbearing status, menopausal status, risk category, ease of screening, and personal preferences, and will likely change over time with the patient. The ultimate goal of cancer genetic counseling is to help the patient reach the decision best suited to her personal situation, needs, and circumstances.

There are now a significant number of referral centers across the country specializing in cancer genetic counseling and the numbers are growing. However, some experts insist that the only way to keep up with the overwhelming demand for counseling will be to educate more physicians and nurses in cancer genetics. The feasibility of adding another specialized and time-consuming task to the clinical burden of these professionals is questionable, particularly with average patient encounters of 19.5 and 21.6 minutes for general practitioners and gynecologists, respectively. A more practical goal may be to better educate primary care providers in the area of generalized risk assessment so that they can screen their patient populations for individuals at

<table>
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<th>TABLE 1.1</th>
<th>How to Find a Genetic Counselor for your Patient</th>
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gtc clinic@u.washington.edu  
A listing of US and international genetics clinics providing evaluation and genetic counseling |
| **Informed medical decisions** | www.informeddna.com—(800) 975–4819  
Nationwide network of independent genetic counselors that use telephone and internet technology to bring genetic counseling to patients and providers. Covered by many insurance companies. |
| **National society of genetic counselors** | www.nsgc.org—click “Find a Counselor” button—(312) 321–6834  
For a listing of genetic counselors in your area who specialize in cancer. |
| **NCI cancer genetics services directory** | www.cancer.gov/cancertopics/genetics/directory—(800) 4-CANCER  
A free service designed to locate providers of cancer risk counseling and testing services. |
high risk for hereditary cancer and refer them on to comprehensive counseling and testing programs. Access to genetic counseling is no longer an issue because there are now internet-, phone-, and satellite-based telemedicine services available (Table 1.1), and several major health insurance companies now cover these services.6–8

**WHO IS A CANDIDATE FOR CANCER GENETIC COUNSELING?**

Only 5% to 10% of most cancers are due to single mutations within autosomal dominant inherited cancer susceptibility genes.9 The key for clinicians is to determine which patients are at greatest risk to carry a hereditary mutation. There are seven critical risk factors in hereditary cancer (Table 1.2). The first is early age of cancer onset. This risk factor, *even in the absence of a family history*, has been shown to be associated with an increased frequency of germline mutations in many types of cancers.10 The second risk factor is the presence of the same cancer in multiple affected relatives on the same side of the pedigree. These cancers do not need to be of similar histologic type in order to be caused by a single mutation. The third risk factor is the clustering of cancers known to be caused by a single gene mutation in one family (e.g., breast/ovarian/pancreatic cancer or colon/ovarian/uterine cancers). The fourth risk factor is

<table>
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<tr>
<th>TABLE 1.2 Risk Factors that Warrant Genetic Counseling for Hereditary Cancer Syndromes</th>
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<tr>
<td>1. Early age of onset (e.g., &lt;50 years for breast, colon, and uterine cancer)</td>
</tr>
<tr>
<td>2. Multiple family members on the same side of the pedigree with the same cancer</td>
</tr>
<tr>
<td>3. Clustering of cancers in the family known to be caused by a single gene mutation (e.g., breast/ovarian/pancreatic; colon/uterine/ovarian; colon cancer/polyps/desmoid tumors/osteomas)</td>
</tr>
<tr>
<td>4. Multiple primary cancers in one individual (e.g., breast/ovarian cancer; colon/uterine; synchronous/metachronous colon cancers; &gt;15 gastrointestinal polyps; &gt;5 hamartomatous or juvenile polyps)</td>
</tr>
<tr>
<td>5. Ethnicity (e.g., Jewish ancestry for breast/ovarian cancer syndrome)</td>
</tr>
<tr>
<td>6. Unusual presentation of cancer/tumor (e.g., breast cancer in a male; medullary thyroid cancer; retinoblastoma; even one sebaceous carcinoma or adenoma)</td>
</tr>
<tr>
<td>7. Pathology* (e.g., triple-negative (ER/PR/Her2) breast cancer &lt;60; medullary breast cancers are over-represented in women with hereditary breast and ovarian cancer; a colon tumor with an abnormal microsatellite instability (MSI) or immunohistochemistry (IHC) result increases the risk for a hereditary colon cancer syndrome)</td>
</tr>
</tbody>
</table>

*An evolving area of risk assessment
the occurrence of multiple primary cancers in one individual. This includes multiple primary breast or colon cancers as well as a single individual with separate cancers known to be caused by a single gene mutation (e.g., breast and ovarian cancer in a single individual). Ethnicity also plays a role in determining who is at greatest risk to carry a hereditary cancer mutation. Individuals of Jewish ancestry are at increased risk to carry three specific BRCA1/2 mutations. The presence of a cancer that presents unusually, in this case breast cancer in a male, represents a sixth risk factor and is important even when it is the only risk factor present. Finally, the last risk factor is pathology. This risk factor is listed in Table 1.1 in italics because it is a new and evolving entity. It appears that certain types of cancer are overrepresented in hereditary cancer families. For example, medullary breast cancer appears to be overrepresented in BRCA1 families. Triple-negative breast cancers (ER−, PR−, Her2−) are also overrepresented in BRCA1 families, and the National Comprehensive Cancer Network (NCCN) has recently updated their BRCA testing guidelines to include individuals diagnosed with a triple-negative breast cancer <age 60. However, breast cancer patients without these pathologic findings are not necessarily at lower risk to carry a mutation. In contrast, patients with a borderline or mucinous ovarian carcinoma appear to be at lower risk to carry a BRCA1 or BRCA2 mutation and may instead carry a mutation in a different gene. It is already well established that medullary thyroid carcinoma (MTC), sebaceous adenoma or carcinoma, adrenocortical carcinoma before the age of 25, and multiple adenomatous, hamartomatous, or juvenile colon polyps are indicative of other rare hereditary cancer syndromes. These risk factors should be viewed in the context of the entire family history, and must be weighed in proportion to the number of individuals who have not developed cancer. Risk assessment is often limited in families that are small or have few female relatives; in such families, a single risk factor may carry more weight.

A less common, but extremely important, finding is the presence of unusual physical findings or birth defects that are known to be associated with rare hereditary cancer syndromes. Examples include benign skin findings, autism, large head circumference and thyroid disorders in Cowden syndrome, ontogenic keratocysts in Gorlin syndrome, and desmoid tumors or dental abnormalities in familial adenomatous polyposis (FAP). These and other findings should prompt further investigation of the patient’s family history and consideration of a referral to genetic counseling.

In this chapter, the breast/ovarian cancer counseling session with a female patient will serve as a paradigm by which all other sessions may follow broadly. However, as testing evolves from targeted testing of 1 or 2 genes to multigene panels, genetic counseling and test interpretation will become more complex.

**COMPONENTS OF THE CANCER GENETIC COUNSELING SESSION**

**Precounseling Information**

Before coming in for genetic counseling, the counselee should be given some basic information about the process. This information, which can be imparted by telephone
or in the form of written material, should outline what the counselee can expect at each session, and what information he/she should collect before the first visit. The counselee can then begin to collect medical and family history information and pathology reports that will be essential for the genetic counseling session.

**Family History**

An accurate family history is undoubtedly one of the most essential components of the cancer genetic counseling session. Optimally, a family history should include at least three generations; however, patients do not always have this information. For each individual affected with cancer, it is important to document the exact diagnosis, age at diagnosis, treatment strategies, and environmental exposures (i.e., occupational exposures, cigarettes, other agents). The current age of the individual, laterality, and occurrence of any other cancers must also be documented. Cancer diagnoses should be confirmed with pathology reports whenever possible. A study by Love et al. revealed that individuals accurately reported the primary site of cancer only 83% of the time in their first-degree relatives with cancer, and 67% and 60% of the time in second- and third-degree relatives, respectively. It is common for patients to report a uterine cancer as an ovarian cancer, or a colon polyp as an invasive colorectal cancer. These differences, although seemingly subtle to the patient, can make a tremendous difference in risk assessment. Individuals should be asked if there are any consanguineous (inbred) relationships in the family, if any relatives were born with birth defects or mental retardation, and whether other genetic diseases run in the family (e.g., Fanconi Anemia or Cowden syndrome), as these pieces of information could prove important in reaching a diagnosis.

The most common misconception in family history taking is that somehow a maternal family history of breast, ovarian, or uterine cancer is more significant than a paternal history. Conversely, many still believe that a paternal history of prostate cancer is more significant than a maternal history. Few cancer genes discovered thus far are located on the sex chromosomes, and therefore both maternal and paternal history are significant and must be explored thoroughly. It has also become necessary to elicit the spouse’s personal and family history of cancer. This has bearing on the cancer status of common children, but may also determine if children are at increased risk for a serious recessive genetic disease such as Fanconi anemia. Children who inherit two copies of a *BRCA2* mutation (one from each parent) are now known to have this serious disorder characterized by defective DNA repair and high rates of birth defects, aplastic anemia, leukemia, and solid tumors. Patients should be encouraged to report changes in their family history over time (e.g., new cancer diagnoses, genetic testing results in relatives), as this may change their risk assessment and counseling.

A detailed family history should also include genetic diseases, birth defects, mental retardation, multiple miscarriages, and infant deaths. A history of certain recessive genetic diseases (e.g., ataxia telangiectasia, Fanconi anemia) can indicate that healthy family members who carry just one copy of the genetic mutation may be at increased risk to develop cancer. Other genetic disorders, such as hereditary hemorrhagic
Principles and Practice of Oncology: Handbook of Clinical Cancer Genetics

telangiectasia, can be associated with a hereditary cancer syndrome caused by a mutation in the same gene; in this case juvenile polyposis.  

**Dysmorphology Screening**

 Congenital anomalies, benign tumors, and unusual dermatologic features occur in a large number of hereditary cancer predisposition syndromes. Examples include osteomas of the jaw in FAP, palmar pits in Gorlin syndrome, and papillomas of the lips and mucous membranes in Cowden syndrome. Obtaining an accurate past medical history of benign lesions and birth defects, and screening for such dysmorphology can greatly impact diagnosis, counseling, and testing. For example, *BRCA1/2* testing is inappropriate in a patient with breast cancer who has a family history of thyroid cancer and the orocutaneous manifestations of Cowden syndrome.

**Risk Assessment**

 Risk assessment is one of the most complicated components of the genetic counseling session. It is crucial to remember that risk assessment changes over time as the person ages and as the health status of their family members change. Risk assessment can be broken down into three separate components:

(1) What is the chance that the counselee will develop the cancer observed in his/her family (or a genetically related cancer such as ovarian cancer due to a family history of breast cancer)?
(2) What is the chance that the cancers in this family are caused by a single gene mutation?
(3) What is the chance that we can identify the gene mutation in this family with our current knowledge and laboratory techniques?

 Cancer clustering in a family may be due to genetic and/or environmental factors, or may be coincidental because some cancers are very common in the general population. While inherited factors may be the primary cause of cancers in some families, in others, cancer may develop because an inherited factor increases the individual’s susceptibility to environmental carcinogens. It is also possible that members of the same family may be exposed to similar environmental exposures, due to shared geography or patterns in behavior and diet, that may increase the risk of cancer. Therefore, it is important to distinguish the difference between a familial pattern of cancer (due to environmental factors or chance) and a hereditary pattern of cancer (due to a shared genetic mutation). Emerging research is also evaluating the role and clinical utility of more common low-penetrance susceptibility genes and single-nucleotide polymorphisms (SNPs) that may account for a proportion of familial cancers.

 Several models are available to calculate the chance that a woman will develop breast cancer including the Gail and Claus models. Computer-based models are also available to help determine the chance that a *BRCA* mutation will be found in a family. At first glance, many of these models appear simple and easy to use and it may be tempting to rely on these models, exclusively, to assess cancer risk. However,
each model has its strengths and weaknesses, and the counselor needs to understand the limitations well and know which are validated, which are considered problematic, when a model will not work on a particular patient, or when another genetic syndrome should be considered. For example, none of the existing models are able to factor in other risks that may be essential in hereditary risk calculation (e.g., a sister who was diagnosed with breast cancer after radiation treatment for Hodgkin’s disease).

**DNA Testing**

DNA testing is now available for a variety of hereditary cancer syndromes. However, despite misrepresentation by the media, testing is feasible for only a small percentage of individuals with cancer. DNA testing offers the important advantage of presenting clients with *actual risks* instead of the empiric risks derived from risk calculation models. DNA testing can be very expensive (full sequencing of the *BRCA1/2* genes currently costs >$3,300). All patients being offered *BRCA* testing should also be offered *BRCA* rearrangement testing (BART) which looks for large structural rearrangements within these genes.\(^\text{14}\) It is the clinician’s responsibility to discuss and order this test separately (an additional $700). Importantly, testing should begin in an affected family member, whenever possible. Most insurance companies now cover cancer genetic testing in families where the test is medically indicated.

The results of DNA testing are generally provided in person in a result disclosure session. It is recommended that patients bring a close friend or relative with them to this session who can provide them with emotional support and who can help them listen to and process the information provided.

One of the most crucial aspects of DNA testing is accurate result interpretation. One study found that test results for the hereditary colon cancer syndrome FAP were misinterpreted more than 30% of the time by those ordering the testing.\(^\text{32}\) More recent data have shown that many medical providers have difficulty interpreting even basic pedigrees and genetic test results.\(^\text{33–35}\) In a survey of over 2,000 physicians, only 13% of internists, 21% of Ob/Gyns, and 40% of oncologists correctly answered four basic knowledge questions about genetic aspects of breast cancer and *BRCA* testing. This deficiency in knowledge did not necessarily deter them from discussing or ordering testing.\(^\text{5}\) Misinterpretation of results is now the greatest risk of genetic testing and is very common.\(^\text{36}\) Interpretation is becoming increasingly complicated as more tests become available. For example, one study demonstrated that approximately 12% of high-risk families who test negative by standard *BRCA1* and *BRCA2* testing are found to carry a deletion or duplication in one of these genes, or a mutation in another gene.\(^\text{37}\) This is particularly concerning in an era in which testing companies are canvassing physicians’ offices and are encouraging them to perform their own counseling and testing. The potential impact of test results on the patient and his/her family is great, and therefore, accurate interpretation of the results is paramount. Professional groups have recognized this and have adopted standards encouraging clinicians to refer patients to genetics experts to ensure proper ordering and interpretation of genetic tests. The US Preventive Services Task Force recommends that women whose
family history is suggestive of a BRCA mutation be referred for genetic counseling before being offered genetic testing. The American College of Surgeons Commission on Cancer standards include “cancer risk assessment, genetic counseling, and testing services provided to patients either on site or by referral, by a qualified genetics professional.”

Results can fall into a few broad categories. It is important to note that a “negative” test result can actually be interpreted in three different ways, detailed in (2), (3), and (4) below:

1. **Deleterious mutation “positive”**: When a deleterious mutation in a cancer gene is discovered, the cancer risks for the patient and her family are relatively straightforward. The risks associated with most genes are not precise and should be presented to patients as a risk range. When a true mutation is found, it is critical to test both parents—whenever possible—to determine from which side of the family the mutation is originating, even when the answer appears obvious.

2. **True negative**: An individual does not carry the deleterious mutation found in her family which ideally has been proven to segregate with the cancer family history. In this case, the patient’s cancer risks are usually reduced to the population risks.

3. **Negative**: A mutation was not detected and the cancers in the family are not likely to be hereditary based on the personal and family history assessment. For example, a patient is diagnosed with breast cancer at age 38 and comes from a large family with no other cancer diagnoses and relatives who died at old ages of other causes.

4. **Uninformative**: A mutation cannot be found in affected family members of a family in which the cancer pattern appears to be hereditary; there is likely an undetectable mutation within the gene, or the family carries a mutation in a different gene. If, for example, the patient developed breast cancer at age 38 has a father with breast cancer and paternal aunt who developed breast and ovarian cancers before age 50, a negative test result would be almost meaningless. It would simply mean that the family has a mutation that could not be identified with our current testing methods or a mutation in another cancer gene. The entire family would be followed as high risk.

5. **Variant of uncertain significance**: A genetic change is identified whose significance is unknown. It is possible that this change is deleterious or completely benign. It may be helpful to test other affected family members to see if the mutation segregates with disease in the family. If it does not segregate, the variant is less likely to be significant. If it does, the variant is more likely to be significant. Other tools, including a splice site predictor, in conjunction with data on species conservation and amino acid difference scores can also be helpful in determining the likelihood that a variant is significant. It is rarely helpful (and can be detrimental) to test unaffected family members for such variants.

In order to pinpoint the mutation in a family, an affected individual most likely to carry the mutation should be tested first, whenever possible. This is most often a
person affected with the cancer in question at the earliest age. Test subjects should be selected with care, as it is possible for a person to develop sporadic cancer in a hereditary cancer family. For example, in an early-onset breast cancer family it would not be ideal to first test a woman diagnosed with breast cancer at age 65, as she may represent a sporadic case.

If a mutation is detected in an affected relative, other family members can be tested for the same mutation with a great degree of accuracy. Family members who do not carry the mutation found in their family are deemed "true negative." Those who are found to carry the mutation in their family will have more definitive information about their risks to develop cancer. This information can be crucial in assisting patients in decision making regarding surveillance and risk reduction.

If a mutation is not identified in the affected relative it usually means that either the cancers in the family (a) are not hereditary or (b) are caused by an undetectable mutation or a mutation in a different gene. A careful review of the family history and the risk factors will help to decipher whether interpretation (a) or (b) is more likely. Additional genetic testing may need to be ordered at this point. In cases in which the cancers appear hereditary and no mutation is found, DNA banking should be offered to the proband for a time in the future when improved testing may become available. A letter indicating exactly who in the family has access to the DNA should accompany the banked sample.

The penetrance of mutations in cancer susceptibility genes is also difficult to interpret. Initial estimates derived from high-risk families provided very high cancer risks for \( BRCA1 \) and \( BRCA2 \) mutation carriers. More recent studies done on populations that were not selected for family history have revealed lower penetrances. Since exact penetrance rates cannot be determined for individual families at this time, and because precise genotype/phenotype correlations remain unclear, it is prudent to provide patients with a range of cancer risk, and to explain that their risk probably falls somewhere within this spectrum.

Female carriers of \( BRCA1 \) and \( BRCA2 \) mutations have a 50% to 85% lifetime risk to develop breast cancer and between a 15% and 60% lifetime risk to develop ovarian cancer. It is important to note that the classification “ovarian cancer” also includes cancer of the fallopian tubes and primary peritoneal carcinoma. \( BRCA2 \) carriers also have an increased lifetime risk of male breast cancer, pancreatic cancer, and possibly melanoma. Carriers of Lynch syndrome mutations (also known as hereditary nonpolyposis colorectal cancer [HNPCC]) have a 65% to 85% lifetime risk to develop colon cancer, and female carriers have at least a 40% to 60% lifetime risk of uterine cancer, and as great as a 10% to 12% risk of ovarian cancer. Individuals with Lynch syndrome have an increased risk for a variety of other types of cancers, including head and neck, other gastrointestinal, urinary tract, and hematologic malignancies.

**Options for Surveillance and Risk Reduction**

The cancer risk counseling session is a forum to provide counselees with information, support, options, and hope. Mutation carriers can be offered: earlier and more
aggressive surveillance, chemoprevention, and/or prophylactic surgery. Detailed management options for BRCA carriers are discussed in this chapter; however, management options for some of the other major cancer syndromes are listed in the site-specific chapters.

Surveillance recommendations are evolving with newer techniques and additional data.

At this time, it is recommended that individuals at increased risk for breast cancer, particularly those who carry a BRCA mutation have annual mammograms beginning at age 25, with a clinical breast examination by a breast specialist, a yearly breast MRI with a clinical breast examination by a breast specialist, and a yearly clinical breast examination by a gynecologist. It is suggested that the mammogram and MRI be spaced out around the calendar year so that some intervention is planned every 6 months. Recent data suggest that MRI may be safer and more effective in BRCA carriers <40 years and may someday replace mammograms in this population.50

BRCA carriers may take tamoxifen or Evista in hopes of reducing their risks of developing breast cancer. Both of these medications are selective estrogen receptor modulators (SERMs) that have been proven effective in women at risk due to a positive family history of breast cancer.51,52 There are limited data on the effectiveness of prophylactic SERMs in BRCA carriers53–55; however, there are some data to suggest that BRCA carriers taking tamoxifen as treatment for a breast cancer reduce their risk of a contralateral breast cancer.56 In addition, the majority of BRCA2 carriers who develop breast cancer develop an estrogen-positive form of the disease,57 and it is hoped that this population will respond especially well to chemoprevention. Further studies in this area are necessary before drawing conclusions about the efficacy of SERMs in this population. Prophylactic bilateral mastectomy appears to reduce the risk of breast cancer by >90% in women at high risk for the disease.58 Before genetic testing was available, it was not uncommon for entire generations of cancer families to have at-risk tissues removed without knowing if they were personally at increased risk for their familial cancer. Fifty percent of unaffected individuals in hereditary cancer families will not carry the inherited predisposition gene, and can be spared prophylactic surgery or invasive high-risk surveillance regimens. Therefore, it is clearly not appropriate to offer prophylactic surgery until a patient is referred for genetic counseling and, if possible, testing.59

Women who carry BRCA1/2 mutations are also at increased risk to develop second contralateral and ipsilateral primaries of the breast.60 These data bring into question the option of breast-conserving surgery in women at high risk to develop a second primary within the same breast. For this reason, BRCA1/2 carrier status can have a profound impact on surgical decision making61 and many patients have genetic counseling and testing immediately after diagnosis and before surgery or radiation therapy. Those patients who test positive and opt for prophylactic mastectomy can often be spared radiation and the resulting side effects that can complicate reconstruction. Approximately 30% to 60% of previously irradiated patients who later opt for mastectomy with reconstruction report significant complications or unfavorable cosmetic results.61,62
Women who carry BRCA1/2 mutations are also at increased risk to develop ovarian, fallopian tube, and primary peritoneal cancer, even if no one in their family has developed these cancers. Surveillance for ovarian cancer is complex, with the recommended interventions being annual transvaginal ultrasounds and CA-125 levels beginning between the ages of 25 and 35 years. The effectiveness of such surveillance in detecting ovarian cancers at early, more treatable stages has not been proven in any population. Some data have indicated that oral contraceptives reduce the risk of ovarian cancer in women carrying BRCA mutations. Recent data indicate that the impact of this intervention on increasing breast cancer risk, if any, is low. Given the difficulties in screening and treatment of ovarian cancer, risk/benefit analysis likely favors the use of oral contraceptives in young carriers of BRCA1/2 mutations who are not yet ready to have their ovaries removed. Prophylactic bilateral salpingo-oophorectomy (BSO) is currently the most effective means to reduce the risk of ovarian cancer and is recommended to BRCA1/2 carriers by the age of 35 to 40 or when childbearing is complete. Specific operative and pathologic protocols have been developed for this prophylactic surgery. In BRCA1/2 carriers whose pathology comes back normal, this surgery is highly effective in reducing the subsequent risk of ovarian cancer. A decision analysis comparing various surveillance and risk-reducing options available to BRCA carriers has shown an increase in life expectancy if BSO is pursued by age 40. A relatively small percentage of women who have this procedure may develop primary peritoneal carcinoma. There has been some debate about whether BRCA1/2 carriers should also opt for total abdominal hysterectomy (TAH) due to the fact that small stumps of the fallopian tubes remain after BSO alone. The question of whether or not BRCA carriers are at increased risk for uterine serous papillary carcinoma (USPC) has also been raised. If a relationship does exist between BRCA mutations and uterine cancer, the risk appears to be low and not elevated over that of the general population. Removing the uterus may make it possible for a BRCA carrier to take unopposed estrogen or tamoxifen in the future without risk of uterine cancer, but this surgery is associated with a longer recovery time and has more side effects than does BSO alone. Each patient should be counseled about the pros and cons of each procedure.

A secondary, but important, reason for female BRCA carriers to consider prophylactic oophorectomy is that it also significantly reduces the risk of a subsequent breast cancer, particularly if they have this surgery before menopause. The reduction in breast cancer risk remains even if a healthy premenopausal carrier elects to take low-dose hormone replacement therapy (HRT) after this surgery. Early data suggest that tamoxifen in addition to premenopausal oophorectomy in BRCA carriers may have little additional benefit in terms of breast cancer risk reduction. Research is needed in balancing quality-of-life issues secondary to estrogen deprivation with cancer risk reduction in these young female BRCA1/2 carriers.

Genetic counseling and testing are also available for many other cancer syndromes, including Lynch syndrome, von Hippel–Lindau, multiple endocrine neoplasias, and FAP. Surveillance and risk reduction for patients who are known mutation carriers for such conditions may decrease the associated morbidity and mortality of these syndromes.
Follow-up

A follow-up letter to the patient is a concrete means of documenting the information conveyed in the sessions so that the patient and his/her family members can review it over time. This letter should be sent to the patient and health care professionals to whom the patient has granted access to this information. A follow-up phone call and/or counseling session may also be helpful, particularly in the case of a positive test result. Some programs provide patients with an annual or biannual newsletter updating them on new information in the field of cancer genetics or patient support groups. It is now recommended that patients return for follow-up counseling sessions months, or even years, after their initial consult to discuss advances in genetic testing and changes in surveillance and risk reduction options. This can be beneficial for individuals who have been found to carry a hereditary predisposition, for those in whom a syndrome/mutation is suspected but yet unidentified and for those who are ready to move forward with genetic testing. Follow-up counseling is also recommended for patients whose life circumstances have changed (e.g., preconception, after childbearing is complete), are preparing for prophylactic surgery, or are ready to discuss the family genetics with their children.

ISSUES IN CANCER GENETIC COUNSELING

Psychosocial Issues

The psychosocial impact of cancer genetic counseling cannot be underestimated. Just the process of scheduling a cancer risk counseling session may be quite difficult for some individuals with a family history who are not only frightened about their own cancer risk, but are reliving painful experiences associated with the cancer of their loved ones.9 Counselees may be faced with an onslaught of emotions, including anger, fear of developing cancer, fear of disfigurement and dying, grief, lack of control, negative body image, and a sense of isolation.21 Some counselees are wrestling with the fear that insurance companies, employers, family members, and even future partners will react negatively to their cancer risks. For many it is a double-edged sword as they balance their fears and apprehensions about dredging up these issues with the possibility of obtaining reassuring news and much needed information.

A person’s perceived cancer risk is often dependent on many “nonmedical” variables. They may estimate that their risk is higher if they look like an affected individual, or share some of their personality traits.21 Their perceived risks will vary depending on if their relatives were cancer survivors, or died painful deaths from the disease. Many people wonder not “if” they are going to get cancer, but “when.”

The counseling session is an opportunity for individuals to express why they believe they have developed cancer, or why their family members have cancer. Some explanations may revolve around family folklore, and it is important to listen to and address these explanations rather than dismiss them.21 In doing this, the counselor will allow the clients to alleviate their greatest fears, and to give more credibility to the “medical” theory. Understanding a patient’s perceived cancer risk is important, in
that fear may decrease surveillance and preventive health care behaviors.\textsuperscript{79} For patients and families who are moving forward with DNA testing, a referral to a mental health care professional is often very helpful. Genetic testing has an impact not only on the patient, but also on his/her children, siblings, parents, and extended relatives. This can be overwhelming for an individual and the family, and should be discussed in detail before testing.

To date, studies conducted in the setting of pre- and postgenetic counseling have revealed that, at least in the short term, most patients do not experience adverse psychological outcomes after receiving their test results.\textsuperscript{80,81} In fact, preliminary data have revealed that individuals in families with known mutations who seek testing seem to fare better psychologically at 6 months than those who avoid testing.\textsuperscript{80} Among individuals who learn they are BRCA mutation carriers, anxiety and distress levels appear to increase slightly after receiving their test results but returned to pretest levels in several weeks.\textsuperscript{82} While these data are reassuring, it is important to recognize that genetic testing is an individual decision and will not be right for every patient or every family.

**Presymptomatic Testing in Children**

Presymptomatic testing in children has been widely discussed, and most concur that it is appropriate only when the onset of the condition regularly occurs in childhood or there are useful interventions that can be applied.\textsuperscript{83} For example, genetic testing for mutations in the BRCA genes and other adult-onset diseases is generally limited to individuals who are >18 years of age. The American College of Medical Genetics states that if the “medical or psychosocial benefits of a genetic test will not accrue until adulthood…genetic testing generally should be deferred.”\textsuperscript{84} In contrast, DNA-based diagnosis of children and young adults at risk for hereditary MTC is appropriate and has improved the management of these patients.\textsuperscript{85} DNA-based testing for MTC is virtually 100% accurate and allows at-risk family members to make informed decisions about prophylactic thyroidectomy. FAP is a disorder that occurs in childhood, and in which mortality can be reduced if detection is presymptomatic.\textsuperscript{86} Testing is clearly indicated in these instances.

Questions have been raised about parents’ right to demand testing for adult-onset diseases. Parents may have a constitutionally protected right to demand that unwilling physicians order this test, but there is little risk for liability for damages unless the child suffers physical harm as a direct result of this refusal.\textsuperscript{83} The child’s right not to be tested must be considered. Whenever childhood testing is not medically indicated it is preferable that testing decisions are postponed until the children are adults and can decide for themselves whether or not to be tested.

**Confidentiality**

The level of confidentiality surrounding cancer genetic testing is paramount due to concerns of genetic discrimination. Some programs opt to keep shadow files, keep their databases off-line, limit patient information in e-mails, and take precautions
to protect confidentially when leaving voice mail messages for patients. Genetic counseling summary letters are often sent directly to patients and are copied to the referring physicians only with the explicit permission of the patient. These measures are taken because confidentiality and genetic discrimination are a grave concern for many of the patients seen in the cancer genetic counseling clinic. Careful consideration should be given to the confidentiality of family history information, pedigrees, genetic test results, pathology reports, and the carrier status of other family members, as many hospitals and medical centers transition to electronic medical record systems. The goal of electronic records is to share information about the patient with his/her entire health care team. However, genetics is a unique specialty that involves the whole family. Patient’s charts often contain HIPAA (Health Insurance Portability and Accountability Act)-protected health information and genetic test results for many other family members. This information may not be appropriate to enter into an electronic record. In addition, the hand-drawn pedigrees that genetics professionals rely on are difficult to translate into an electronic medical record. The unique issues of genetics services need to be considered when designing electronic medical record standards.

Confidentiality of test results within a family can also be of issue, as genetic counseling and testing often reveal the risk status of family members other than the patient. Under confidentiality codes, the patient needs to grant permission before at-risk family members can be contacted. It has been questioned whether or not a family member could sue a health care professional for negligence if they were identified at high risk yet not informed. Most recommendations have stated that the burden of confidentiality lies between the provider and the patient. However, more recent recommendations state that confidentiality should be violated if the potential harm of not notifying other family members outweighs the harm of breaking a confidence to the patient. There is no patent solution for this difficult dilemma, and situations must be considered on a case-by-case basis with the assistance of the in-house legal department and ethics committee.

Patients should be counseled about the benefits to other family members of knowing testing results, but, at the present time, the decision is ultimately the patient’s. Extended family members who are notified, with the patient’s consent, may not always be grateful to receive this information, and may feel that their privacy has been invaded by being contacted.

**Insurance and Discrimination Issues**

When genetic testing for cancer predisposition first became widely available, the fear of health insurance discrimination—by both patients and providers—was one of the most common concerns. It appears that the risks of health insurance discrimination were overstated and that almost no discrimination by health insurers has been reported. The HIPAA of 1996 banned the use of genetic information as a pre-existing condition. In May 2008, Congress passed the Genetic Information Nondiscrimination Act (GINA) (HR 493) that provides broad protection of an individual’s genetic information against health insurance and employment
discrimination. In addition, the 2010 Heath Care Reform (HR 4872) prohibits group health plans from denying insurance based on pre-existing conditions and from increasing premiums based on health status. Health care providers can now more confidently reassure their patients that genetic counseling and testing will not put them at risk of losing group or individual health insurance.

More and more patients are choosing to submit their genetic counseling and/or testing charges to their health insurance companies. In the past few years, more insurance companies have agreed to pay for counseling and/or testing, perhaps in light of decision analyses that show these services and subsequent prophylactic surgeries to be cost-effective. The risk of life or disability insurance discrimination, however, is more realistic. Patients should be counseled about such risks before they pursue genetic testing.

**Future Directions**

The field of cancer genetic counseling and testing has grown tremendously over the past 15 years. Although cancer genetic counseling has traditionally been targeted at individuals with strong personal or family histories of cancer, this focus has broadened. Genetic counseling and testing is now offered to patients diagnosed with early-onset breast and colon cancer as a critical tool to guide surgical and radiation decision making, as the risk of new primaries is greater in individuals who carry germline mutations.

Clinicians should be aware that technology to perform gene panels, whole exome and whole genome sequencing, has exploded onto the marketplace. Gene panels simultaneously analyze groups of genes that contribute to increased risk for breast, colon, ovarian, uterine, and other cancers while whole exome and genome sequencing deliver enormous amounts of data related to the entire exome/genome. These tests can identify mutations associated with rare and common disorders that may be overlooked by targeted, single gene testing; however, each have risks and benefits that should be weighed carefully. The cost of this technology continues to decrease and now costs, roughly, just a few hundred dollars more than full testing for **BRCA1** and **BRCA2**. Testing by whole exome and whole genome sequencing presents unique advantages and challenges that are further detailed in the chapter entitled “Whole-Genome and Whole-Exome Sequencing in Hereditary Cancer.”

A remarkable limitation of this technology in the field of cancer genetics is specific gene patents that prohibit testing and reporting of genetic mutations found in these regions. In particular, the US Patent and Trademark Office issued patents on the **BRCA1** and **BRCA2** genes. Although various researchers contributed to the identification of these genes, patent rights were granted to the privately owned biotech firm Myriad Genetics. As the exclusive patent holder, Myriad has opted to strictly enforce its monopoly rights and is the only laboratory in the country where diagnostic testing can be performed. In 2009, the American Civil Liberties Union filed suit against Myriad and the US Patent and Trademark Office, arguing that the patents are illegal because genes are “products of nature.” According to the lawsuit, researchers and scientists are prevented from studying, testing, and developing alternative tests because of the strict control of these genes. Several of the patents were overturned.
in a March 29, 2010 ruling. Judge Robert Sweet stated that purification of DNA does not change the essential characteristic of DNA and is therefore not a patentable product.99 This ruling has since been overturned and the Supreme Court is scheduled to hear this case in Spring 2013. If the patents are overturned, precedent will be set about how gene patents are issued and genetic counselors, clinicians, and researchers will be able to engage freely in research, testing, and clinical practice involving these genes. Patients would also have access to genetic testing services from multiple, and perhaps more affordable, sources.

New developments are also emerging in the treatment and possibly prevention of BRCA-related cancers. Several small studies have evaluated the effect of poly adenosine diphosphate (ADP) ribose polymerases (PARP) inhibitors in combination with chemotherapy for cancer treatment. It appears that PARP inhibitors are particularly effective in patients with BRCA mutations.100,101 Future studies will focus on the use of PARP inhibitors in earlier stage cancers in BRCA carriers, cancers in women with triple-negative breast cancers, and BRCA carriers in the prevention setting.

Reproductive technology in the form of preimplantation genetic diagnosis is also an option102 for men and women with a hereditary cancer syndrome, but one that is requested by few patients for adult-onset conditions in which there are viable options for surveillance and risk reduction. The option of sperm selection to increase the likelihood of having a male fetus (or vice versa for a condition that affects mostly males) can be discussed if parents are looking for preconception options. If a BRCA2 carrier is considering having a child, it is important to assess the spouse’s risk of also carrying a BRCA2 mutation. If the spouse is of Jewish ancestry, or has a personal or family history of breast, ovarian, or pancreatic cancer, BRCA testing should be considered and a discussion of the risk of Fanconi anemia in a child with two BRCA2 mutations should take place.103

The combination of technologic advances in genetic testing, new pharmacologic developments for cancer risk reduction, and increased utility for testing in high- and moderate-risk populations will result in a significant expansion in the field of cancer genetic counseling. Maintenance of high standards for thorough genetic counseling, informed consent, and accurate result interpretation will be paramount in reducing potential risks and maximizing the benefits of this technology in the next century.

REFERENCES

6. Rosenthal ET. Shortage of genetics counselors may be anecdotal, but need is real. Oncol Times. 2007;29(19):34,36.


