CHAPTER

6

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Genetic Risk and Hereditary Cancer Syndromes

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INTRODUCTION

The clustering of cancer within families has been recognized for centuries, and over the past 30 years, scientists and geneticists actively debated whether familial cancer syndromes have an inherited genetic basis, in contrast to an environmental basis. During the past two decades, the elucidation of the genetic basis for many of the most prevalent and penetrant hereditary cancer syndromes seen in clinical practice has occurred. As the genetic basis of hereditary cancer syndromes is clarified, the number of hereditary cancer syndromes for which germline mutation testing for one or more genes is available has dramatically increased.[1] Currently, clinical genetic testing is available for more than 50 syndromes, and several online resources exist that provide comprehensive information about these syndromes (Appendix 6-A). As a result, the number of genetic tests ordered for hereditary cancer risk assessment has increased, leading to an improvement in the quantification of individual hereditary cancer risk. The challenge for busy healthcare providers is to select appropriate candidates for hereditary cancer risk assessment and to provide, or identify, comprehensive cancer risk assessment and genetic counseling services for patients. As the number of candidates for genetic services increases, a diverse group of healthcare providers will be called upon to integrate genetic concepts into their daily practice. Oncology nurses are at the forefront of nursing practice, integrating genetic information into patient care services.

CANCER NURSING PRACTICE AND HEREDITARY CANCER SYNDROMES

THE ROLE OF THE ONCOLOGY NURSE IN CANCER RISK ASSESSMENT AND COUNSELING

The need for highly educated, skilled clinicians to perform hereditary cancer risk assessment and cancer risk counseling has accelerated over the past 20 years as new cancer syndromes have been identified and clinical genetic testing has become more widely available. Oncology nurses with expertise in clinical cancer genetics are a key group of healthcare providers who have the knowledge and skills necessary to provide these services to an ever-increasing group of patients. Several nursing professional organizations have developed position statements on this practice—for example, the Oncology Nursing Society (ONS),[2,3] International Society of Nurses in Genetics (ISONG),[4] American Nurses Association,[5] and credentialing programs[4,6] for nurses seeking to practice in genetic health care. The ONS position statement on the role of the oncology nurse in cancer

genetic counseling identifies three levels of oncology nursing practice in cancer genetic counseling: the general oncology nurse, the advanced practice oncology nurse, and the advanced practice oncology nurse with specialty training in cancer genetics. This position statement reflects the need for oncology nurses at all levels to contribute to the following:

- Pedigree construction and evaluation
- Education of patients, families, and the public regarding genetic risks and cancer prevention (risk reduction measures)
- Integration of genetic information into oncology nursing practice as new genetic information becomes available
- Continuing education in cancer genetics and genomics
- Collaboration with other genetic healthcare professionals and organizations to provide comprehensive, culturally sensitive, and evidence-based care to individuals at high genetic risk of cancer

In addition, an advanced practice oncology nurse with specialty training in hereditary cancer genetics may provide comprehensive cancer genetic risk assessment services consisting of the following[3]:

- Comprehensive risk assessment
- Education, facilitation, and interpretation of genetic testing
- Pre- and post-test counseling and follow-up
- Provision of personally tailored cancer risk management options and recommendations
- Psychosocial counseling and support services

The advanced practice oncology nurse's practice must be consistent with the nurse's state practice act, the nurse's educational preparation, the scope of the nurse's role, and the standards of oncology nursing practice. The International Society of Nurses in Genetics[4] has developed two credentialing programs for nurses who wish to document their expertise in genetic health care:

- Nurses with a master's degree in nursing may qualify for the Advanced Practice Nurse in Genetics (APNG) credential.
- Nurses with a baccalaureate degree in nursing may qualify for the Genetics Clinical Nurse (GCN) credential.

The American Nurses Credentialing Center (ANCC) took over the credentialing of genetic nurses in 2014.[6] The International Society of Nurses in Genetics will assist the ANCC to maintain the standards of credentialing and assist in the transition and review of this program.

VOCABULARY OF HEREDITARY CANCER SYNDROMES FOR ONCOLOGY NURSES

The rapid increase in information about hereditary cancer syndromes has created a challenge for oncology nurses as they seek to stay abreast of the patient care issues related to an inherited predisposition to cancer. The language of hereditary cancer syndromes is complicated. Many terms are commonly used in the media, by researchers and healthcare professionals, and as part of daily conversations about discoveries resulting from the Human Genome Project. To effectively deliver care in the field of oncology, a working knowledge of the common vocabulary associated with hereditary cancer syndromes is essential. Many terms are often, yet incorrectly, used interchangeably; it is particularly important to review and understand widely used terms to ensure that the appropriate information is being communicated to patients as well as other healthcare professionals. **Table 6-1** includes a number of common vocabulary terms associated with hereditary cancer syndromes.

TABLE 6-1

Vocabulary Related to the Genetics of Hereditary Cancer Syndromes

De novo mutation	New damage to a germline gene causing a disease to be seen in a family for the first time.
Genotype	The genetic constitution of an organism or cell; also refers to the specific set of alleles inherited at a locus.
Phenocopy	An environmental alteration of a gene such that the resulting phenotype is similar to the expression of a known genetic mutation.
Phenotype	The observable physical and/or biochemical characteristics of the expression of a gene; the clinical presentation of an individual with a particular genotype.
Mutation	A condition in which the DNA of a gene is damaged or changed in such a way that it alters the genetic code carried by that gene. These changes can be caused by mutagens such as chemicals, radiation, environmental factors such as sunlight, and by chance during cell division.
Somatic mutation	A mutation that occurs in any of the cells of the body except the germ cells (sperm and egg). Somatic mutations cannot be passed on to children. These alterations can (but do not always) cause cancer or other diseases.

(continues)

TABLE 6-1

Vocabulary Related to the Genetics of Hereditary Cancer Syndromes (*continued*)

Germline mutation	The presence of an altered gene within the egg or sperm (germ cell) such that the altered gene can be passed to subsequent generations.
Sporadic mutation	The presence of a genetic disorder for the first time in one family member as a result of a mutation in a germ cell (egg or sperm) of one of the parents or in the fertilized egg itself. Also called de novo or new germline mutations. An individual with a new germline mutation will lack a family history of cancer in his or her siblings and ancestors, but the individual's children will be at risk of receiving the altered gene.
Founder mutation	A gene mutation observed in high frequency in a specific population due to the presence of that gene mutation in a single ancestor or a small number of ancestors. These mutations often arise when an ancestral population is decimated by a natural or other type of disaster. If a germline mutation is present among those individuals who survive the event, it will be disproportionately more common among the descendants of the survivors.
Autosomal dominant inheritance	Describes a trait or disorder in which the phenotype is expressed in those individuals who have inherited only one copy of a particular gene mutation (heterozygotes); specifically refers to a gene on 1 of the 22 pairs of autosomes (non-sex chromosomes).
Autosomal recessive inheritance	Describes a trait or disorder requiring the presence of two copies of a gene mutation at a particular locus to express an observable phenotype; specifically refers to genes on 1 of the 22 pairs of autosomes (non-sex chromosomes).
X-linked inheritance	A mode of inheritance in which a mutation in a gene on the X chromosome causes the phenotype to be expressed in males who are hemizygous for the gene mutation.(i.e., they have only one X chromosome) and in females who are homozygous for the gene mutation (i.e., they have a defective copy of the gene on each of their two X chromosomes). Carrier females who have only one copy of the mutation do not usually express the phenotype, although differences in X-chromosome inactivation can lead to varying degrees of clinical expression in carrier females.
Carrier	An individual who has a recessive, disease-causing gene mutation at a particular locus on one chromosome of a pair and a normal allele at that locus on the other chromosome.
Heterogeneity	In cancer genetics, the presence of multiple different genes that cause the same disease (e.g., *BRCA1* and *BRCA2* can both cause breast cancer).
Penetrance	The proportion of individuals with a mutation causing a particular disorder who exhibit clinical symptoms of that disorder; most often refers to autosomal dominant conditions.
Incomplete penetrance	The presence of a mutated gene that is not phenotypically expressed in all members of a family with the genetic mutation.
Incidental finding	A result from sequencing that is not related to the indication of ordering the sequencing but may be of clinical utility.
Expression	The manifestation of a heritable trait.
Variable expressivity	Variation in clinical features (type and severity) of a genetic disorder between affected individuals, even within the same family.
Variant of unknown significance	A variation in a genetic sequence whose association with disease risk versus a healthy individual without the variation in genetic sequence is unknown. Also called variant of uncertain significance (VUS) and unclassified variant.
Next-generation sequencing (NGS)	Second-generation genome sequencing that is able to sequence more fragments of the genome (high-throughput) at a faster (one day versus weeks) and less costly rate. Examples include whole-exome sequencing (WES) and whole-genome sequencing (WGS).
Clinical utility of genetic/genomic testing	The ability of the results of a genetic/genomic test to lead to improvement in health outcomes: morbidity, mortality, and disability.

CHARACTERISTICS OF HEREDITARY CANCER SYNDROMES

The majority of cancer is thought to be sporadic, occurring in individuals as a result of aging and/or environmental exposures. Sporadic cancers develop because of somatic errors in DNA replication, which occur in genes (tumor suppressor genes and proto-oncogenes) that normally function to promote proper cell growth and differentiation.[7]

Hereditary cancers are attributable to changes (or mutations) in specific genes that are passed from either parent (mother and/or father) to their offspring. Approximately

TABLE 6-2

Features Suggestive of a Hereditary Cancer Predisposition Syndrome

In the Individual Patient	In the Patient's Family
Multiple primary tumors in the same organ	One first-degree relative with the same or a related tumor and one of the individual features listed
Multiple primary tumors in different organs	Two or more first-degree relatives with tumors of the same site
Bilateral primary tumors in paired organs (e.g., bilateral breast cancer)	Two or more first-degree relatives with tumor types belonging to a known familial cancer syndrome
Multifocality within a single organ	Two or more first-degree relatives with rare tumors
Younger-than-usual age at tumor diagnosis	Two or more relatives in two generations with tumors of the same site or etiologically related sites
Rare Histology	
In the sex not usually affected (e.g., male breast cancer)	
Associated with other genetic traits	
Associated with congenital defects	
Associated with an inherited precursor lesion	
Associated with another rare disease	
Associated with cutaneous lesions known to be cancer susceptibility	

Source: Data from Lindor et al.[1]

5% to 10% of all cancers are hereditary.[1] Individuals who inherit one of these germline mutations will have a higher likelihood of developing cancer within their lifetime than individuals who have not inherited a germline mutation in a cancer susceptibility gene. The major individual and family features of hereditary cancer syndromes are listed in **Table 6-2**.[1]

A familial cancer pattern is characterized by an increase in the number of cancers within a family—more than what would be expected by chance alone. However, the pattern of cancers observed in such a case does not fit the features of a hereditary cancer syndrome. Genetic testing for known hereditary cancer susceptibility genes is most frequently uninformative in familial cancer clusters. Cancer cases within family clusters most likely represent complex interactions of low-penetrance susceptibility gene(s) and/or environmental factors.[8] Consequently, it is often difficult to adequately quantify the risk of developing cancer in close family members. Nevertheless, unaffected close relatives are considered to be at increased risk of developing the cancers seen within the family, as compared to the general population.

IDENTIFYING HIGH-RISK INDIVIDUALS AND FAMILIES

Identifying individuals who are at high genetic risk of cancer begins with recognizing key characteristics within an individual or family that are suggestive of a hereditary cancer syndrome. The importance of being able to construct and evaluate a three-generation pedigree, on both the maternal and paternal lineage, cannot be overemphasized in the identification of individuals and families at risk of a hereditary cancer syndrome.

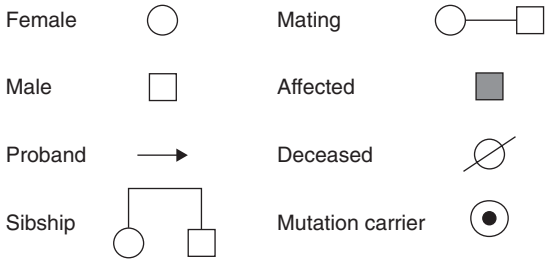

FIGURE 6-1

Basic pedigree symbols.

Basic pedigree symbols and notations are used to construct a visual summary of the proband's and his or her family's health history (**Figure 6-1**). Dominant and recessive inheritance patterns within families can be identified during the construction of a pedigree (**Figure 6-2** and **Figure 6-3**). Individual and family health history information is obtained from all members of the family in both the maternal and paternal lineage and includes information on race and ethnicity, current health status, current age or age at and cause of death, type of each primary cancer, age at diagnosis for each primary cancer, bilaterality for paired organs (e.g., breast,

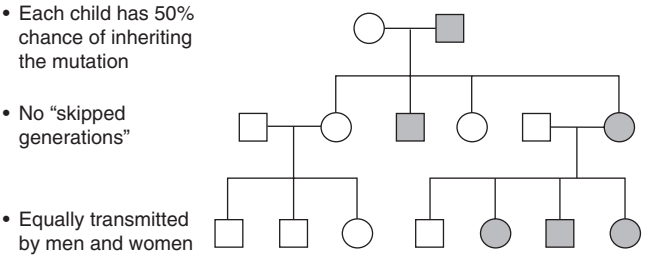

FIGURE 6-2

Pedigree sample of autosomal dominant inheritance (vertical pattern).

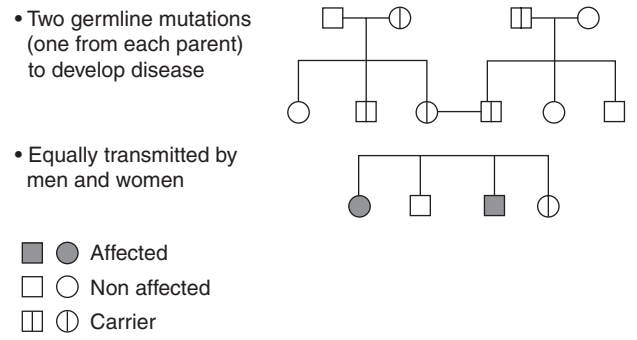

FIGURE 6-3

Pedigree sample of autosomal recessive inheritance (horizontal pattern).

eyes), and exposures (e.g., tobacco exposure and asbestos) (**Figure 6-4**). It is clear that family history is a powerful technique to predict disease when multiple family members are affected, the relationship between affected relatives and unaffected relatives is close (e.g., siblings or parents) and the disease occurs at an earlier age than is typically expected (**Figure 6-5** and **Figure 6-6**).[9]

For several hereditary cancer syndromes (e.g., multiple endocrine neoplasia [MEN] type 2 and familial adenomatous polyposis [FAP]), the benefits of early cancer detection and prevention have been demonstrated; it is assumed that in other syndromes, significant healthcare cost savings could likewise be achieved by identifying high-risk individuals and intervening early.[9] Once identified, these individuals may benefit from cancer genetic risk assessment, counseling, and testing. Family members who are identified as mutation carriers can begin healthcare interventions earlier in the disease process to lower their risk of developing cancer. Conversely, family members who did *not* inherit the mutation associated with the cancers in their family will not have to undergo earlier or increased interventions to lower their risk of developing cancer.

Oncology nurses frequently identify individuals from families at high risk of a hereditary cancer syndrome. The challenge for busy clinicians is to obtain a comprehensive family history in a busy day-to-day practice. "My Family

General medical history
- Tobacco use, alcohol use, and exercise
- Medical conditions such as osteoporosis, thyroid disorder, hypertension, and diabetes
- Medications

Reproductive history (female)
- Age at menarche
- Age at menopause
- Pregnancies: including number of pregnancies, number of live births, number of therapeutic and spontaneous abortions, and age at first pregnancy
- Birth control use, in particular hormonal contraceptives (type, duration and age at time of use)
- Fertility drugs (type, duration and age at time of use)
- Menopausal hormone therapy (type and duration)

Gynecologic history
- Gynecologic surgeries (hysterectomy, oophorectomy, endometrial biopsies)
- History of ovarian cysts, endometriosis, and abnormal Pap smears (including colposcopy, cervical biopsy and cryosurgery, loop electrosurgical excision or cone biopsy procedures)
- Breast biopsies (including age at time of biopsy, right/left breast, results, treatment)

Other cancer history
- Type
- Age at diagnosis
- Treatment
  - Surgery
  - Radiation
  - Chemotherapy
  - Hormonal therapy

Screening practices
- Breast
  - Breast self exam (frequency)
  - Clinical breast exam (frequency)
  - Mammogram (age at baseline and frequency)
  - Ultrasound (frequency)
  - Breast MRI (frequency)
- Colon
  - Sigmoidoscopy
  - Colonoscopy (age at baseline, frequency)
- Skin
  - Biopsies
  - Frequency of exam
- Prostate
  - PSA (frequency)
  - Digital rectal exam (frequency)
- Gynecological
  - Pelvic exam (frequency)
  - Transvaginal ultrasound (frequency)
  - CA-125 (frequency)

FIGURE 6-4

Health information to obtain on all family members.

Abbreviations: MRI: magnetic resonance imaging; PSA: prostate specific antigen.

Source: Data from National Cancer Institute.[10]

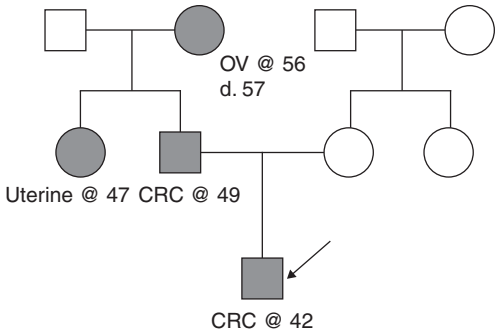

FIGURE 6-5

Sample Lynch syndrome pedigree.
Abbreviations: CRC: colorectal cancer; OV: ovarian cancer.

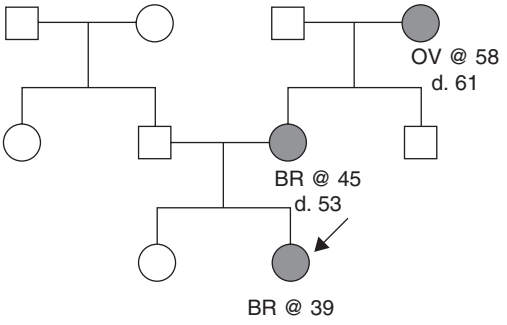

FIGURE 6-6

Sample hereditary breast ovarian cancer (HBOC) pedigree.
Abbreviations: BR: breast cancer; OV: ovarian cancer.

Health Portrait," a patient-oriented, family history tool, was developed for this purpose by the Centers for Disease Control and Prevention, in conjunction with the National Institutes of Health (NIH) and the U.S. Surgeon General's office. It is available for free to the public in English and Spanish at the U.S. Surgeon General's website: http://www.hhs.gov/familyhistory. While it does not produce a comprehensive, three-generation pedigree, "My Family Health Portrait" is simple for the lay public to complete, provides information on the individual and his or her close family members' health history, and alerts clinicians to possibility of the presence of a hereditary cancer syndrome. From this simple family pedigree, a more comprehensive pedigree can be developed to conduct a comprehensive cancer genetic risk evaluation.

ETHICAL, LEGAL, AND SOCIAL IMPLICATIONS OF PREDISPOSITION GENETIC TESTING FOR HEREDITARY CANCER SYNDROMES

Genetic testing for hereditary cancer is thought to reduce cancer mortality by identifying those persons at high genetic risk of cancer, who can then be targeted for increased cancer surveillance and preventive strategies. However, genetic information has the potential to cause significant psychosocial morbidity and can raise questions about the balance between the benefits of knowing one's mutation status and choosing not to know. Certainly, genetic testing for cancer susceptibility stands apart from other forms of cancer risk assessment (e.g., assessment of personal modifiable risk factors), in the sense that there is no ability to alter one's genetic make-up. Many controversial areas also exist in the ethical and social implications of testing for hereditary cancer syndromes in relation to the following questions:

- Who owns DNA?
- Can DNA be patented?
- Should direct-to-consumer testing be made available?
- Should children be screened for hereditary cancer syndromes that will not affect them until adulthood?

Several aspects of the ethical, legal, and social implications of genetic testing for hereditary cancer syndromes and some of the major controversies encountered in the assessment of hereditary cancer susceptibility will be considered here. A variety of resources on the ethical, legal, and social implications of hereditary susceptibility testing are listed in **Table 6-3**.[10]

ETHICAL PRINCIPLES

Four widely accepted fundamental ethical principles guide medical decision making: (1) autonomy, (2) nonmaleficence, (3) beneficence, and (4) justice. These principles may be applied to inform difficult decisions and to allow for a broad range in judgment. Within the realm of genetic testing and genetic information, two of the most important considerations are informed consent and confidentiality.[11] Many ethical dilemmas involve conflicts that arise when establishing measures of informed consent for genetic testing and in protecting individual confidentiality. The following is a brief review of the ethical principles involved in such situations.

Respect for Autonomy

The principle of autonomy underlies the proposition that an adult, with the capacity to make decisions, has the right to determine what may be done to his or her body. This principle requires that even when a medical professional disagrees with a patient's informed decision, his or her opinion does not infringe upon the patient's right to choose.[11] In the field of genetics, it is important to understand that all healthcare providers are obligated to respect the autonomy of individuals insofar as such respect is compatible with the autonomy of all. Therefore, informed consent is a central focus of autonomy when it pertains to genetic information.

TABLE 6-3

Resources on Ethical, Legal, and Social Implications of Cancer Genetics

Resource	Description
Bioethics.net www.bioethics.net	Links to articles on genetics and bioethics.
Bioethics Resources on the Web http://bioethics.od.nih.gov	Links to bioethics resources.
Coalition for Genetic Fairness www.geneticfairness.org/ginaresource.html	Describes GINA's protections, including a history of the legislation, key examples, and definitions.
DNA Patent Database http://dnapatents.georgetown.edu	Searchable database of U.S. DNA-based patents and patent applications issued by the U.S. Patent and Patent Applications Trademark Office.
Ethical, Legal, and Social Issues (from the Human Genome Project) www.ornl.gov/sci/techresources/Human_Genome/elsi/elsi.shtml	Information, articles, and links on a wide range of genetics-related issues.
Genethics.ca www.genethics.ca	Information on the social, ethical, and policy issues associated with genetic and genomic knowledge and technology.
Genetics and Public Policy Center www.dnapolicy.org	Information on public policy related to human genetic technologies for the public, media, and policy makers.
Genome Technology and Reproduction: Values and Public Policy and Communities of Color and Genetics Policy Project www.sph.umich.edu/genpolicy	Two subprojects combined to form a five-year project designed to provide policy recommendations based on public perceptions and responses to the explosion of genetic information and technology.
HumGen International www.humgen.umontreal.ca/int	Comprehensive international database on the legal, social, and ethical aspects of human genetics.
National Conference of State Legislatures (NCSL) Genetic Technologies Project www.ncsl.org/programs/health/genetics.htm	Resources on a variety of genetics public policy and related issues for state legislators, legislative staff, and other policy makers.
National Information Resource on Ethics and Human Genetics www.11.georgetown.edu/research/nrcbl/nirehg	Links to resources and databases on ethics and human genetics.
National Information Resource on Ethics and Human Genetics: Annotated Bibliographies: Scope Note Series www.11.georgetown.edu/research/nrcbl/nirehg/quickbibsgen.htm	Annotated bibliographies on various genetics and ethics issues.
National Human Genome Research Institute (NHGRI) Policy and Legislation Database www.genome.gov/PolicyEthics/LegDatabase/pubsearch.cfm	Searchable database of federal and state laws/statutes, federal legislative materials, and federal administrative and executive materials about privacy of genetic information/confidentiality; informed consent; insurance and employment discrimination; genetic testing and counseling; and commercialization and patenting.
National Society of Genetic Counselors (NSGC) Code of Ethics www.nsgc.org/about/codeEthics.cfm	A statement to clarify and guide the ethical conduct of genetic counselors.
The President's Council on Bioethics www.bioethics.gov	Reports, transcripts, and background material on current bioethical issues.
THOMAS Legislative Information (from Library of Congress) http://thomas.loc.gov	Searchable database of U.S. legislation (current and previous Congresses).
Your Genes, Your Choices http://ehrweb.aaas.org/ehr/books/index.html	Description of the Human Genome Project, the science behind it, and the ethical, legal, and social issues raised by the project.

Source: Data from the National Cancer Institute.[10]

Nonmaleficence

Nonmaleficence is derived from the ancient Latin maxim *primum non nocere*, meaning "first do no harm." Many medical and public health practices strive for a utilitarian approach to achieving the greatest good for the greatest number of people. In cancer genetics, an example of a potential threat to nonmaleficence is when a clinician discloses an uninformative test result. As a consequence of an uninformative test disclosure, a patient may have a false sense of security.[11] If a patient is a member of a family with a cancer history that is suggestive of a hereditary cancer syndrome, and individual mutation testing for the appropriate syndrome(s) does not reveal a deleterious mutation, it is possible that the family's cancers may be caused by a mutation that is not detectable or has not yet been discovered. Communicating the impact of an uninformative, negative genetic test result is clearly a challenge in cancer risk counseling and increases the potential for nonmaleficence on the part of healthcare providers who lack experience in interpreting genetic test results.

Beneficence

The ethical principle of beneficence, in the context of cancer genetic susceptibility testing, can be summarized as a healthcare provider's responsibility to provide an opportunity for benefit. Given that as a society there is an underlying need for self-determination, this principle often comes into conflict with autonomy. Hence, it is not enough that nursing actions avoid harm; they must also strive to distinguish for patients the specific benefits that come from having genetic information.[11] For example, predisposition genetic testing is considered beneficent if enhanced cancer surveillance or cancer prevention strategies decrease the morbidity and mortality associated with a specific hereditary syndrome.[12] There is an ongoing need for evidence-based, safe, and effective management strategies for high-risk individuals. However, the clinical utility and validity of many interventions for rare hereditary cancer syndromes are based on highly selected families.[1] Until evidence of benefits in survival and decreased morbidity is established in these high-risk families, clinicians will continue to rely on cancer screening and prevention guidelines that are based on consensus expert opinion.

Justice/Equity

The principle of justice is often envisioned as being synonymous with equity or fairness. Justice can be conceptualized as a balance between potential harms and benefits. Often, a decision that is equitable may still be considered unjust; it is critical to consider that what might seem just to one person may be perceived differently by another person. A central issue of justice and equity in hereditary cancer genetics is the equitable distribution of resources to individuals. Do individuals who might benefit from predictive genetic testing have access to experts in cancer genetic risk assessment, counseling, and testing? Do individuals who are at high genetic risk of cancer also have the means to pay for these services? As the number of genetic tests for cancer susceptibility and other diseases increases, oncology nurses must be advocates for all patients having equal access to genetic services.

Informed Consent

Prior to obtaining informed consent for genetic testing, it is important that healthcare providers anticipate the decisions a patient may contemplate as a result of the test outcome. Pertinent issues may include understanding the limitations of the genetic test, the accuracy and performance characteristics of the genetic test, the laboratory processing of the specimen, and implications of the results. Healthcare providers have an obligation to offer genetic testing to patients who might benefit from the results, but it is the patient who must decide what is in his or her own best interest. Patients have as much of a right to informed consent as they do informed refusal.[11,13] The requirements of informed consent for cancer predisposition testing include the following:[11]

1. Competence to comprehend the informed consent discussion (including the implications of a positive, negative, and uninformative test result; use of the DNA in future; and plans for follow-up and sharing information with relatives);
2. Disclosure of known procedures, risks, and benefits (including potential fees associated with testing, emotional implications and the potential for discrimination, and loss of confidentiality);
3. Understanding of the information presented (including options and limitations of risk management with and without testing, and heritability of the mutation);
4. The voluntary nature of the decision; and
5. Consent by the individual or appropriate surrogate

Given the nature of cancer predisposition testing and its inherent ability to affect more than just one individual, comprehensive genetic counseling can help to ensure that patients make informed decisions.

Duty to Warn

In some instances, the ethical principles of autonomy and beneficence conflict when a healthcare provider contemplates his or her duty to warn individuals of their risk of inherited cancer. Currently, the American Society of Human Genetics[14] and the American Society of Clinical Oncology[12] posit that it is the clinician's obligation to inform the proband of the risk of inherited cancer and to encourage the sharing of that information among the biologically related family members.[12] However, it is not a

realistic expectation of the practitioner to warn all of those persons at risk.[15] Upon deciding the best course of action, some questions for the healthcare provider to consider include the following[16]:

- Who is the primary client?
- Is there a way to satisfy all parties?
- What is the potential harm in disclosure?
- What is the potential harm in nondisclosure?

These questions may serve as a guide when contemplating a duty to warn. However, ideally, these decisions would be discussed and a consensus established within an interdisciplinary healthcare team.

The Right to Know or Not to Know

In many cases of cancer genetic testing, there are individuals who want to learn their genetic status and others who do not. Again, this may bring up controversial issues in balancing the right to autonomy and privacy of individual family members. When dilemmas in balancing individual rights arise within a family, and the proband decides to undergo predictive genetic testing, a positive result will reveal genetic information that has profound implications for other family members. In general, when testing for hereditary cancer syndromes, an individual's right to know supersedes another individual's right not to know. It is imperative that the individual seeking predictive genetic testing be made aware of the potential for complex psychosocial consequences of testing on other family relationships.

FAIRNESS IN USE OF GENETIC INFORMATION

One of the major controversies surrounding genetic testing for hereditary cancer involves the concept of who is entitled to access and utilize genetic information. Significant legislative actions have been taken at the federal and state levels to prohibit the use of genetic information in any aspect of employment, including hiring, firing, promoting, and offering access to health insurance benefits. In 2000, President Bill Clinton signed an executive order prohibiting federal departments and agencies from using genetic information in any hiring or promotion action.[17] Employment, however, is only one area in which an individual's basic rights may be compromised by the use of genetic information. Other stakeholders may include health and life insurance companies, judicial courts, schools, the military, and adoption agencies.

Who has the right to use a patient's genetic information? Fear of genetic discrimination is still a widespread public concern; there is potential to create a social underclass of individuals based on genetic discrimination—particularly for those who are asymptomatic. The Genetic Information Nondiscrimination Act (GINA) of 2008 was passed to protect the public against genetic discrimination.

GENETIC INFORMATION NONDISCRIMINATION ACT OF 2008

After 13 years of congressional debate, President George W. Bush signed GINA into law on May 21, 2008. The law, enacted in 2009, is now the most comprehensive piece of legislation to protect individuals from genetic discrimination in employment and health insurance settings. Encompassed in this law is a definition of genetic information (including predictive genetic tests, family members' genetic tests, and family history information).[18] Essentially, GINA protects only predictive genetic information—not information from a genetic test that is directly related to an existing condition that could be reasonably detected by a healthcare provider. GINA applies to both individual and group health insurance coverage, prohibits the use of genetic information in health insurance underwriting, and bans employers and insurers from requiring genetic testing as a condition for employment or the issuance of a health insurance policy. There are some limitations to GINA, however: For example, the act does not address issues pertaining to life, disability, or long-term care insurance, nor does it apply to active-duty military personnel.[18] GINA also will not mandate coverage for any particular medical tests or treatments. The most positive outcome of the GINA legislation may, in fact, be that patients will now partake in cutting-edge genetic technology without the fears that have discouraged predisposition genetic testing over the past decade.

RISK ASSESSMENT OF CANCER SUSCEPTIBILITY

Families with a known hereditary cancer syndrome are human models for studying carcinogenesis and susceptibility to neoplasia, including gene–gene interactions, gene–environment interactions, and environmental influences in isolation. Much of what we know about hereditary cancer syndromes today comes from the knowledge we have gained by studying highly susceptible families.

Genetic risk assessment is initiated by obtaining a comprehensive individual and family history. Although it is the family history that often leads to a healthcare provider's suspicion of a hereditary cancer syndrome, several important characteristics of an individual health history can also be highly suggestive of a hereditary cancer syndrome (Table 6-2). It is critical that healthcare providers ask about these characteristics, particularly if the individual is affected with cancer. The same questions can be applied to family members to obtain specific information about

other individuals in the family who are affected with cancer. Pathology reports should be obtained on all reported cancer cases in the family to confirm the patient-reported family cancer history.

In addition to the individual and family features of the proband, the American Society of Clinical Oncology[12] recommends that the following issues be carefully considered prior to offering any genetic test of known cancer susceptibility syndromes:

- Is there evidence that a cancer susceptibility syndrome is present?
- Is the healthcare provider able to interpret the results of the genetic test being considered?
- What is the level of certainty that the testing will yield information to facilitate a diagnosis or be used for medical management?

In 2010, the American Society of Clinical Oncology expanded the first criteria related to evidence of a syndrome being present. The recommendation now supports genomic profiling for individuals with a suspected genomic variance of low penetrance when there is established clinical utility and the results can be interpreted adequately.[12] Of concern to clinicians are the lack of guidelines or expert recommendations for cancer screening and management and/or treatment of the syndrome-associated cancers. In addition, as sequencing technology improves and the cost of sequencing decreases, more people will have full sequencing of their personal genome, which will lead to an increase in secondary and incidental findings (genetic findings that were not the primary purpose of the sequencing).[12] Clinicians are encouraged to anticipate secondary and incidental findings, inform patients about the possibility of such findings, and determine the best course of action when they are encountered.[19]

CANCER RISK ASSESSMENT MODELS

Only a small proportion of cancers can be attributed to hereditary susceptibility; cancer risk assessment models can aid healthcare providers in identifying those individuals who might be most appropriate for genetic testing or increased cancer surveillance. Current cancer risk assessment models help with the following tasks:

- Estimate the probability that an individual has inherited a mutation in a known hereditary susceptibility gene
- Estimate the probability that an individual will develop cancer over a defined period of time

However, cancer risk estimate models are not substitutes for sound clinical judgment. Healthcare providers should select models that have been peer reviewed and validated and should also consider using more than one risk assessment model, if available. Risk assessment models are useful tools to assist clinicians in cancer risk assessment but they are regarded as guides for—*not standards of*—cancer risk assessment, as each model comes with inherent limitations.

GENETIC COUNSELING

The process of genetic counseling is essentially a communication process that deals with the human problems associated with the occurrence, or risk of occurrence, of a genetic disorder in a family.[14] Cancer genetic pre- and post-test counseling involves an attempt to assist the individual or family to become familiar with the following information:

- Facts about the diagnosis, natural history of the disorder, and the current medical management options available, including the risks and benefits associated with genetic testing and management options
- How heredity contributes to the disorder, and to the risk of occurrence (recurrence), in specific relatives
- Alternatives for dealing with the risk associated with the disorder, including the risks and benefits of each alternative intervention
- The optimal adjustment (both physiological and psychological) to the disorder in an affected family member
- The appropriate options available (in view of their risk), their individual and family goals, and their ethical and religious beliefs, including the implications of testing and sharing of test results with other family members

IDENTIFYING THE OPTIMAL FAMILY MEMBER TO TEST AND INTERPRETATION OF TEST RESULTS

Genetic testing for a hereditary cancer syndrome is most informative when the test is performed on a member of the family who has a cancer diagnosis that is known to be associated with a suspected syndrome (e.g., *BRCA1/2* testing in a woman with breast cancer from a family where a hereditary breast and ovarian cancer [HBOC] syndrome is suspected). If a mutation is identified in an affected family member (a "true positive" test result), genetic testing for the presence or absence of the family-specific mutation can then be offered to close relatives. Some of the relatives may undergo testing and learn they have not inherited the family mutation; these members are said to have a "true negative" test result. In the absence of a known mutation associated with cancer in a family, a negative genetic test result (i.e., no mutation detected) in a family member is considered to be "uninformative" for the family. The person tested and that individual's descendants can be assured a "true negative"

result means they will not pass a disease-causing mutation of that gene to their children.

If other hereditary syndromes are being considered, genetic testing for the syndromes under consideration may continue in an affected family member. However, if the cancer pattern within the family is consistent with only one known hereditary cancer syndrome, no further testing of the unaffected family members is routinely indicated. Theoretically, it is always possible that the person selected for testing has, by chance, a sporadic occurrence of the familial cancer under evaluation (i.e., phenocopy). Thus, if there is a strong probability of a mutation being present, one may elect to test a second family member to be certain that a detectable syndrome has not been overlooked. **Figure 6-7** represents the genetic testing algorithm for cancer susceptibility.[20]

If there is no living affected family member in a family suspected of having a hereditary cancer syndrome, consideration may be given to testing either stored tissue samples or unaffected family members. Testing stored tissue can be technically difficult and may lead to results that cannot be clearly interpreted. Testing an unaffected family member may also yield uninformative test results for the family. Failing to detect a mutation in an unaffected individual could happen because that person did not inherit the mutation associated with the cancer in the family or because the mutation associated with the cancer in the family is not detectable by the technology used by the laboratory. For an individual who receives an uninformative test result when he or she has a diagnosis of cancer, the presence of a cancer susceptibility gene and an increased risk of developing cancer have not been excluded for either the individual or his or her family. Genetic counseling in the post-test disclosure session focuses on alternative ways to perform risk assessment, if any, and management of cancer risk based on the family's cancer history.

GENETIC TESTING FOR CANCER SUSCEPTIBILITY IN MINORS

As previously discussed, genetic risk assessment, counseling, and testing are grounded in the ethical principles of beneficence, nonmaleficence, and respect for autonomy. A primary goal when providing genetic services to individuals and families at high genetic risk of cancer is to protect the individuals and family members from harm, including emotional harm. Family members who are minors (individuals younger than age 18) are not typically offered genetic testing for hereditary cancer syndromes until they become adults.[21,22] Many of the most common hereditary cancer syndromes are associated with cancers that do not occur until adulthood; therefore, it is appropriate to wait until individuals have reached adulthood so that they can make their own decisions about genetic testing. This practice allows minors to achieve majority and make an autonomous decision about whether to undergo genetic testing. However, when there is evidence of an increased risk of cancer developing in childhood (**Table 6-4**), or there are benefits of (or consensus for) early cancer screening and prevention[23] of hereditary cancer syndromes in minors, genetic testing for the suspected cancer syndrome is appropriate in childhood.

SELECTED HEREDITARY CANCER SYNDROMES

The following featured hereditary cancer syndromes are presented to provide information about common hereditary cancer syndromes for which there is clinical genetic testing available, and to provide an introduction to the management of individuals with hereditary cancer syndromes. The syndromes chosen are examples of hereditary cancer syndromes where either evidence has demonstrated that intervention improves overall survival or there is broad consensus about the value of early cancer detection and cancer prevention interventions. A more comprehensive approach is beyond the scope of this chapter; however, several textbooks are available for those who would like to delve more deeply into hereditary cancer syndromes.[23–26]

HEREDITARY BREAST AND OVARIAN CANCER SYNDROMES

Individuals who are at risk of carrying a mutation that predisposes them to an hereditary breast and ovarian cancer (HBOC) syndrome are the patients most commonly referred for cancer genetic risk assessment, counseling, and testing. As many as 10% of breast cancer cases and 14% of ovarian cancer cases are associated with a mutation in a cancer susceptibility gene.[27–29] Hereditary causes of breast and ovarian cancers are primarily due to the *BRCA1* and *BRCA2* mutations.[30–34] Cowden syndrome (*PTEN*), Li-Fraumeni syndrome (*p53*), and Fanconi anemia (*PALB2*) are other hereditary cancer syndromes that are also associated with an increase in the lifetime risk of breast and/or ovarian cancer.[1] In addition, some germline mutations in DNA damage response pathways (e.g., *CHEK2, ATM, BIRP1*) are known to be associated with a modest increase in breast cancer risk and are now included in cancer susceptibility test panels.[35]

BRCA1, located at chromosome 17q21, and *BRCA2*, located at chromosome 13q12.3, are tumor suppressor genes that are inherited in an autosomal dominant pattern. In normal cellular physiology, their protein products initiate a response to DNA damage by slowing the cell cycle and recruiting other proteins involved in DNA damage

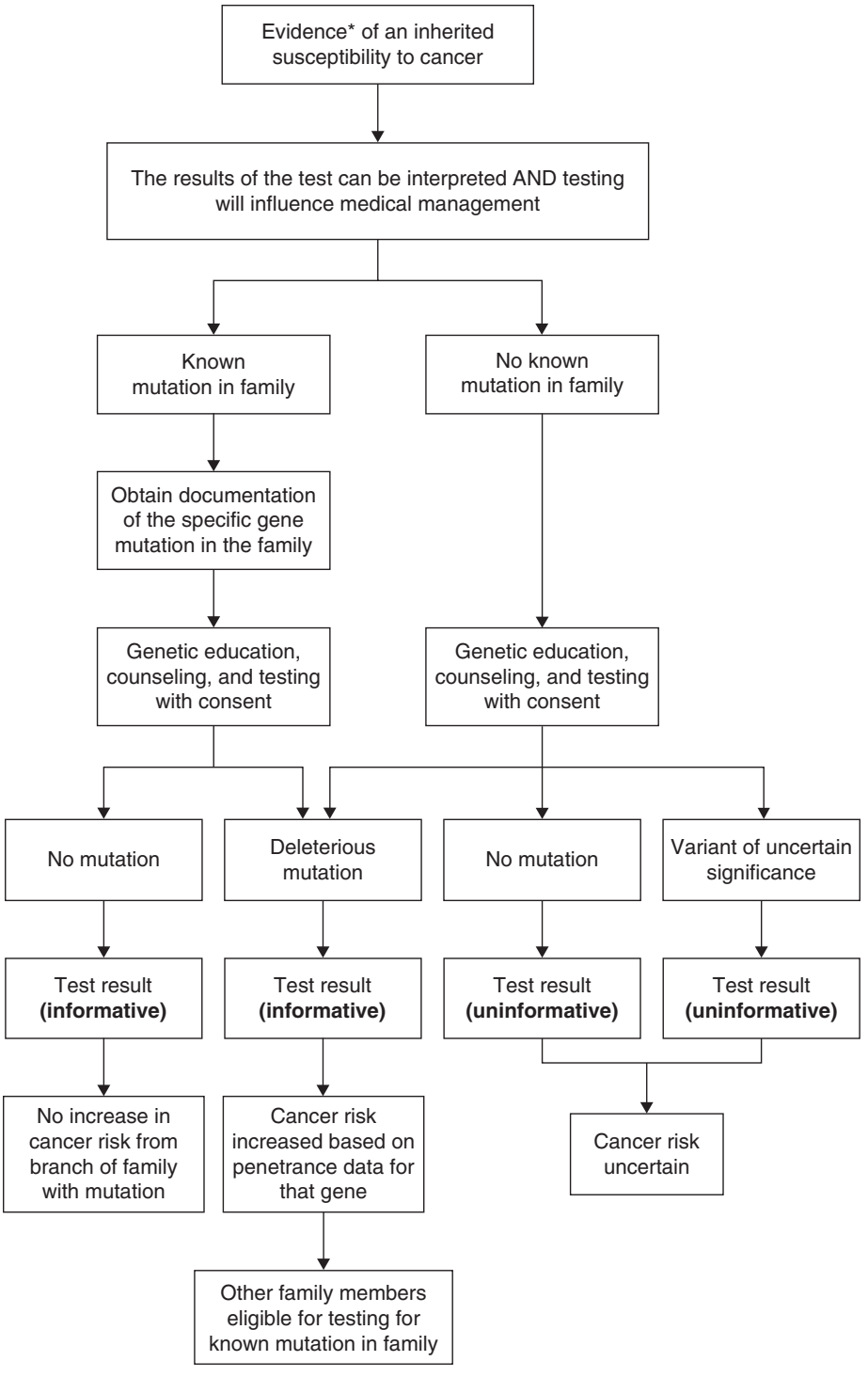

FIGURE 6-7

Genetic testing algorithm for cancer susceptibility.

*Families with evidence of an inherited susceptibility that have not had any genetic testing or in which genetic testing has not identified a mutation or families with a documented deleterious mutation.[20]

Source: Reproduced from National Cancer Institute. Genetic testing algorithm for cancer susceptibility. http://www.cancer.gov/cancertopics/pdq/genetics/risk-assessment-and-counseling/HealthProfessional/page6.[20]

TABLE 6-4

Autosomal Dominant Cancer Syndromes and Risk in Childhood

Syndrome	Probable Earliest Tumor	Risk in Childhood (%)
Familial adenomatous polyposis	First year	80
Neurofibromatosis	First year (meningioma)	30
Von Hippel-Lindau	1–2 years (retinal)	15
MEN1	5 years	5
MEN2A	3 years	2.5
MEN2B	1 year	< 50
Li-Fraumeni	First year	30
HBOC/*BRCA1*	> 16 years	< 0.1
HBOC/*BRCA2*	> 16 years	< 0.1
Hereditary nonpolyposis colorectal cancer	> 16 years	< 0.1

Source: Data from Lindor et al.[1]

repair.[30–34] *BRCA1* and *BRCA2* are not genetically related to each other, and each mutation has a unique mechanism of action in repair of DNA damage.[35] The *BRCA* genes have been shown to have more than 2180 pathogenic mutations (*BRCA1*, 1064; *BRCA2*, 1120), with other variants of unknown significance requiring further evaluation.[36,37]

Both traditional and new laboratory methods are used to detect *BRCA1* and *BRCA2* mutations. While traditional methods, such as Sanger sequencing, continue to be used to confirm accuracy of results, newer methods, such as next-generation sequencing (NGS), can provide faster results and have the ability to create vast amounts of data at a fraction of the cost.[35] Some methods can provide for whole-genome sequencing (WGS) of an individual or sequencing of only the protein-coding regions of the genome, known as whole-exome sequencing (WES). The diagnostic accuracy for each method has been reviewed.[35–37]

Estimates of the carrier frequency of a *BRCA* mutation in the general population (except women of Ashkenazi heritage) is about 1/400 (approximately 0.25%).[38] Approximations of the prevalence of the *BRCA1* mutations in the general population vary depending on the type of mutation, age at onset of cancer, and type of cancer.[38–41] Founder mutations in *BRCA1* and *BRCA2* have been reported in several populations, including groups of Dutch, French Canadian, Hungarian, Icelandic (*BRCA2* 999del5), French Canadian, and Swedish descent.[41] In Ashkenazi Jewish (AJ) population, three founder mutations have been reported (*BRCA1* 185delAG, *BRCA1* 5382insC, and *BRCA2* 617delT); together they account for 80% to 90% of all *BRCA* mutations found in AJ hereditary breast/ovarian cancer families.[42]

Female carriers of a *BRCA1* mutation are at much greater risk of developing breast and ovarian cancer than individuals in the general population. They are also at higher than average risk of developing fallopian tube carcinoma and primary serous carcinoma of the peritoneum.[1] Breast cancers associated with *BRCA1* mutations tend to be estrogen-receptor negative, progesterone-receptor negative and HER2/neu negative adenocarcinomas of the breast. The lifetime risks (to 70 years of age) of developing breast and ovarian cancer for women with *BRCA1* mutations have been estimated to be 60% to 65% and 39% to 60%, respectively.[39]

Other penetrance estimates have been reported and vary considerably, emphasizing the impact of the environment on breast cancer incidence.[43] A large Canadian group reported *BRCA1* penetrance estimates to age 80 years to be 90% for breast cancer and 24% for ovarian cancer.[41] A meta-analysis of 10 *BRCA1* studies reported a cumulative cancer risk to age 70 years to be 57% for breast cancer and 40% for ovarian cancer. In the Canadian AJ population, the penetrance of the two *BRCA1* mutations for breast cancer by age 70 are 64% for *BRCA1* 185delAG and 67% for *BRCA1* 5382insC.[41] For ovarian cancer, the penetrance estimates are 14% for *BRCA1* 185delAG and 33% for *BRCA1* 5382insC by age 70.[41] Among the U.S. population, the penetrance for breast cancer to age 70 is estimated to be 46% for breast cancer and 39% for ovarian cancer, based on 676 AJ families and 1272 families of other ethnicities.[44]

Like *BRCA1* mutation carriers, *BRCA2* mutation carriers are at much greater risk of developing breast and ovarian cancer than the general population. The breast cancer risk is lower than that seen in *BRCA1* mutation carriers (*BRCA1*, 55% to 65%; *BRCA2*, 45%), but the risk of ovarian cancer is significantly lower (and the age at diagnosis is significantly older) than that reported for *BRCA1* carriers (*BRCA1*, 39%; *BRCA2*, 11% to 17%).[45] Breast cancers associated with *BRCA2* mutations tend to be estrogen-receptor positive adenocarcinomas of the breast, much like postmenopausal breast cancer in non-*BRCA* carriers. Lifetime risks of developing cancer to age 70 years for persons with *BRCA2* mutations have been estimated to be 45% for breast cancer and 11% to 17% for ovarian cancer.[45] Penetrance estimates for the Ashkenazi *BRCA2* 6174delT mutation are 43% for breast cancer and 20% for ovarian cancer to age 70 years.[29] Male breast cancer is more common among *BRCA2* carriers; the cumulative probability to age 70 ranges between 6% and 6.8%.[46,47] Other cancers associated with mutations in *BRCA2* include fallopian tube carcinoma, primary serous carcinoma of the peritoneum, prostate cancer, pancreatic cancer, and melanoma.[47–49]

Recently, researchers combined single-nucleotide polymorphisms (SNPs), alone or in combination with both or

other alleles in women with *BRCA1* or *BRCA2* mutations plus other known breast cancer risk factors (i.e., breast density, age at menarche, parity), to more effectively determine the risk of developing a female cancer. Female *BRCA2* carriers with the highest tertile of risk and seven specific SNPs have four times higher risk of breast cancer than those in the lowest tertile. There were no significant results for *BRCA1* carriers when analyzed in terms of only four SNPs.[34]

More than 20 genes have been identified that have an intermediate to high penetrance in breast cancer.[44] Two of these genes, which are associated with an increased lifetime risk of breast cancer, have been linked to other hereditary cancer syndromes (e.g., Li-Fraumeni syndrome and Cowden syndrome) and will be reviewed later in the chapter.

IDENTIFYING INDIVIDUALS AT HIGH RISK OF HBOC

Hereditary cancer risk assessment and genetic counseling are indicated for individuals and families who have been identified as being at high genetic risk of HBOC. Through cancer genetic risk assessment and counseling, individuals and family members learn about hereditary cancer, the individual and family risk of cancer, and options for risk reduction, cancer screening, and cancer management.[48,49] Often preliminary cancer genetic risk assessment is performed by oncology nurses, oncologists, primary care providers, and other healthcare providers, many of whom lack formal training and certification in genetic health care. In an effort to encourage busy clinicians to integrate cancer risk assessment into their daily practice, guidelines to identify high-risk individuals have been developed.[50–52] These guidelines are based on the United States Preventive Services Task Force (USPSTF) clinical guidelines on genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer genetic susceptibility; they include important questions to ask about the family's cancer history and suggest when to recommend genetic counseling. Once individuals from high-risk families have been identified, formal cancer genetic risk assessment and genetic counseling can be initiated.

In general, the following factors increase an *affected* (a person with a cancer diagnosis) individual's risk of being a *BRCA1* or *BRCA2* mutation carrier:

- Breast cancer diagnosed prior to menopause (age younger than 50 years)
- Ovarian cancer at any age
- Triple negative (ER–, PR–, HER2–) markers
- Two or more primary breast cancers in the same individual
- Breast and ovarian cancer in the same individual
- Two or more individuals in the family with breast and/or ovarian cancer or other cancer (pancreatic cancer, prostate cancer [Gleason score > 7], sarcoma, adrenocortical carcinoma, brain tumors, endometrial cancer, leukemia/lymphoma, thyroid cancer, diffuse gastric cancer, dermatologic manifestations and/or macrocephaly, hamartomatous polyps of the GI tract)
- Male breast cancer
- AJ ancestry[52]

Unaffected individuals with a family history may also receive further genetic evaluation. These individuals are required to have one or more of the following factors:

- An individual with more than two breast primary cancers
- More than two individuals on the same side of the family with breast primary cancers
- At least one ovarian primary cancer on the same side of the family
- First- or second-degree relative with a history of breast cancer diagnosis at an age younger than 45
- A known breast cancer susceptibility gene mutation within the family
- At least one family member on the same side of the family with a combination of breast cancer and at least one of the following:
  - A breast and/or ovarian cancer
  - Other cancer (pancreatic cancer, prostate cancer [Gleason score > 7], sarcoma, adrenocortical carcinoma, brain tumors, endometrial cancer, leukemia/lymphoma, thyroid cancer, diffuse gastric cancer, dermatologic manifestations and/or macrocephaly, hamartomatous polyps of the GI tract)
- Male breast cancer[52]

For primary care providers, the USPSTF recommendation is to provide cancer risk assessments to individuals who are members of families with patterns of breast, ovarian, fallopian tube, or peritoneal cancer. Useful risk assessment tools are those designed to identify a familial cancer pattern that is associated with an increased risk for deleterious mutations in breast cancer susceptibility genes (e.g., *BRCA1* or *BRCA2*). Women whose results of a risk assessment screening are suggestive of a known hereditary cancer syndrome should be offered genetic counseling and testing for the identified syndrome.[53]

BRCA1 and *BRCA2* Carrier Probability

As noted earlier, mutations in *BRCA1* and *BRCA2* account for only a small proportion (approximately 5% to 10%) of all breast cancers.[27,28] Several cancer risk assessment tools have been published to guide healthcare providers in making decisions about when to recommend genetic testing or increased surveillance, or whether to follow consensus

guidelines for syndrome-specific cancer screening for individuals who are at high genetic risk of cancer. Certainly, there are advantages to making predictions based on known hereditary patterns using family history and pedigree construction as risk assessment tools. Family history can be used as a surrogate marker of shared environmental and genetic risk. Reassuringly, comprehensive cancer risk assessment was found to be a better predictor of carrier probability than computerized modeling.[52,53]

The U.S. Preventive Services Task Force and the National Comprehensive Cancer Network (NCCN) have published guidelines for cancer genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility in high-risk individuals.[52,54] More than a dozen different models have been published that use various statistical methods, study populations, personal and family history features, and outcomes. In addition, several models have been published for estimating breast cancer risk and *BRCA1/2* carrier probability. The appropriate predictive model is chosen based on an individual's health history and the cancer pattern (and other associated features) within the family.

Mutation Carrier Prediction Models: BRCAPRO and BOADICEA

BRCA mutation carrier prediction models aim to identify individuals who are likely to be *carriers* of a *BRCA1* or *BRCA2* mutation. Several models are available, and comparison of the different models suggests that BRCAPRO has the best performance characteristics, though all models performed adequately in clinical use.[1,55,56]

BRCAPRO (http://astor.som.jhmi.edu/BayesMendel/brcapro.html) is a computerized, statistical Bayesian model that calculates *BRCA1* and *BRCA2* carrier probability based on history of breast or ovarian cancer, and age(s) at diagnosis in the proband and in the first-degree relative (FDR) and second-degree relative (SDR).[55,56] It also accounts for current age and age at death of unaffected relatives. The model is derived from published estimates of gene prevalence and penetrance; these are updated periodically, but estimates may be inaccurate. Other limitations include the following: (1) The model accounts only for first- and second-degree relatives of the index case; (2) it does not incorporate prostate or pancreatic cancer; and (3) it considers only the *BRCA1* and *BRCA2* genes. Therefore, some individuals with increased BRCAPRO carrier probability will have mutations in other genes but will test negative for *BRCA1* and *BRCA2*.[55,56] Healthcare providers must also take care in selecting the family member or proband who will produce the most accurate estimates based on the distribution of affected relatives. A recent study determined that while the BRCAPRO model is highly sensitive, it missed an estimated 15% of mutations.[55] The BRCAPRO software contains the Gail and Claus models for breast cancer risk prediction embedded within its software.

The BRCAPRO and BOADICEA breast/ovarian mutations and cancer risk assessment models have been updated. Researchers using the BOADICEA and BRCAPRO genetic models found they had sensitivity of 76% and 77%, respectively, and specificity of 70% and 69%, respectively, for mutation detection. Previously reported specificity for both tools was less than 50%.[57,58] In addition, the newest version of BOADICEA includes an assessment of whether key breast cancer molecular markers (e.g., estrogen receptor, progesterone receptor, HER2/neu, and CK5/6 and CK14) were detected in affected family members.[58,59]

While mutation and risk assessment models can aid in determining the best use of genetic testing for individuals at risk, healthcare providers must use caution when relying on these estimates to make clinical decisions about increased cancer surveillance and risk-reducing surgeries such as prophylactic mastectomy and/or bilateral oophorectomy.[59,60]

Breast Cancer Risk Models: Gail, Claus, and Tyrer-Cuzick

The most frequently used model for estimating breast cancer risk in clinical practice is the Gail Model (http://www.cancer.gov/bcrisktool).[61] This tool is based on a case-control analysis of the Breast Cancer Detection Demonstration Project, which was a joint American Cancer Society (ACS) and National Cancer Institute (NCI) breast cancer screening study that involved 280,000 women between the ages of 35 and 74 years. The Gail Model takes into account variables including a woman's own personal history of prior breast biopsies and the presence of atypical hyperplasia, known *BRCA* mutation, or diagnosis of a genetic syndrome associated with elevated risk of breast cancer; her reproductive history (age at menarche and age at the first live birth of a child); and the history of breast cancer among her FDRs (mother, sisters, daughters). These variables are then used to estimate the 5-year and lifetime risk of breast cancer. Factors that correlate with an increased risk of developing breast cancer include nulliparity, early age of menarche, later age of menopause, history of previous breast biopsy, and positive family history in a FDR. The Gail Model is advantageous in that it accounts for other risk factors besides family history, and can provide comparison of an individual's risk *versus* women in the same age group from the general population. However, it does not account for paternal family history, SDRs, age at onset of cancer, bilateral cancers, multiple primary cancers, or other cancers. The Gail Model has been updated to include factors related to African American, Asian, and Pacific Islander ethnic backgrounds.[59,60]

Investigators explored the impact of adding an extended family history of breast cancer to the existing Gail Model in a case-control study conducted among 1765 women

recruited in Italy between 1997 and 2000.[61] The investigators modeled risk estimates based on extended family history grouped according to (1) women with no reported FDRs or SDRs with breast cancer, (2) women with one or more FDRs with breast cancer, (3) women with one or more SDRs with breast cancer, and (4) women with one or more FDRs and/or one or more SDRs with breast cancer. The findings demonstrated that the extended family history information could be a useful supplement to the existing standard model in predicting breast cancer risk estimates.[58–61]

The Claus Model is another commonly used model for estimating the cumulative probability of breast cancer.[27] The foundation for this model was a population-based case-control study involving 4730 breast cancer patients and matched controls. First- and second-degree family history of breast cancer with age at diagnosis is incorporated into the Claus Model to estimate the probability that a woman will develop breast cancer. This model accounts for paternal contributions to breast cancer risk, which adds to its strengths. Its limitations include that it does not account for bilateral cancers, multiple primary cancers, or other cancers, and it does not account for other breast cancer risk factors. Further, only two relatives with a breast cancer diagnosis can be selected to determine risk estimates, making it confusing for healthcare providers to choose the most informative case. Additionally, healthcare providers require access to the Claus Model's data tables, since this model has not been implemented as an online tool. Recent research revealed that the extended Claus Model predicted twice as many mutation carriers as observed, suggesting the revised model requires more research prior to its introduction into the clinical setting.[59,60]

Investigators of the International Breast Intervention Study (IBIS) and the Mayo Clinic Benign Breast Disease cohort studied a group of 9736 women age 18 to 55 to evaluate whether the Tyrer-Cuzick Model was a useful tool to determine whether there was benefit to adding breast magnetic resonance imaging (MRI) to annual mammography for the early detection of breast cancer in high-risk women. Similar to the Gail Model, the Tyrer-Cuzick Model includes family history but adds paternal information, breast cancer status of FDRs and SDRs, half-siblings, Ashkenazi Jewish family history, hormone replacement usage, and age at menopause.[57,59–61] The results indicate that for women with a lifetime risk of more than 20%, based on the American Cancer Society guidelines, it is appropriate to consider adding breast MRI to annual breast cancer screening.

BRCA1/2 CANCER RISK MANAGEMENT

During genetic test disclosure, all *BRCA* mutation carriers are advised of the genetic risk of cancer to relatives and are strongly encouraged to alert family members to the value of genetic risk assessment. Although the major cancers associated with *BRCA* mutations are breast and ovarian, other cancers are considered to be part of the syndrome. However, for most of these cancers, no proven cancer prevention or early detection strategies are currently available. It is imperative to educate *BRCA* mutation carriers about the signs and symptoms of *BRCA*-related cancers so they do not delay seeking care for persistent symptoms that may be associated with the development of cancer.[51]

Breast Cancer Surveillance in Female *BRCA1* or *BRCA2* Mutation Carriers, or in Untested Females From Families With Known *BRCA1* or *BRCA2* Mutations or Women With a Risk Assessment Calculation > 20%

Recommendations for breast cancer screening in women at high genetic risk include the following:[52,53]

- Monthly breast self-exam beginning at age 18[52]
- Clinical breast exam performed by a clinician every 6 months starting at age 30
- Screening mammogram once a year beginning at age 30 or at an individualized timetable based on the earliest age at which breast cancer has been diagnosed in the family[52]
- Breast MRI once a year starting at the same age as the mammogram to be scheduled on days 7–15 of the menstrual cycle in premenopausal women[52]
- Consider risk reduction strategies outlined in the NCCN's *Guidelines for Breast Cancer Risk Reduction*[53]

A prospective screening cohort study found MRI of the breast to be more sensitive than mammography (94% versus 9%; $p < 0.0001$) in unaffected women with known *BRCA1/2* mutations aged 25 to 65.[62] In addition, the researchers reported that no distant recurrences in the cancers were detected in 24 of 28 women with *BRCA* mutations diagnosed at an early stage with MRI with 8.4 years of follow-up.[62] MRI has also been found to detect breast cancer at an earlier stage than mammography alone.[63–65] In a European analysis of three nationwide studies (GENEPSO, EMBRACE, and HEBON) of women with *BRCA1/2* mutations, exposure to diagnostic radiation before age 30 was associated with an increased risk of breast cancer at dose levels considerably lower than those at which increased incidence has been found in other cohorts exposed to radiation. These study results suggest MRI and other non-ionizing radiation imaging techniques could be used as the primary technology employed for breast surveillance in young women with *BRCA1/2* mutations.[34,62–65] However, there is no consensus at present to change the recommendation of annual MRI with annual mammography or to screen with only MRI for women who are known carriers of a *BRCA* mutation or untested women from families with a known *BRCA* mutation.[52]

Risk-Reducing Bilateral Mastectomy

Risk-reducing bilateral mastectomy (RRBM), the prophylactic removal of both breasts removed before a breast cancer is detected, lowers breast cancer risk by approximately 90%.[66–68] Women who are considering RRBM should discuss surgical and reconstruction options with a breast surgeon and a plastic surgeon. A small risk of breast cancer remains after RRBM. RRBM removes primarily visible breast tissue, leaving behind a small amount of residual breast tissue after surgery. This clinically undetectable breast tissue may give rise to a breast cancer. Although screening with mammogram and MRI are not recommended following RRBM, periodic examination of the chest can be performed.[66–68]

Hormonal Prevention of *BRCA1/2* Breast and Ovarian Cancers

Bilateral oophorectomy (BO) in women who are *BRCA1* or *BRCA2* mutation carriers reduces the risk of breast cancer by approximately 50% and the risk of ovarian cancer by 90%. Bilateral oophorectomy should be recommended for premenopausal women older than age 35, once these high-risk women have completed childbearing, and/or individualized for the earliest age of onset of ovarian cancer within the family.[52]

The reduction in risk of breast cancer by BO appears to apply to both *BRCA1* mutation carriers and *BRCA2* mutation carriers.[69,70] However, preliminary data suggest that *BRCA2* mutation carriers may obtain a greater reduction in risk than *BRCA1* mutation carriers.[71]

Limited data are available to support the use of chemoprevention of breast cancer in *BRCA1* or *BRCA2* mutation carriers. A significant (approximately 50%) reduction in the risk of contralateral breast cancer was observed in *BRCA1* and *BRCA2* mutation carriers who had used tamoxifen for at least 2 years following a diagnosis of unilateral breast cancer.[72] A follow-up study to the original investigation confirmed a significant decrease in the risk of a contralateral breast cancer was associated with the use of tamoxifen in *BRCA* mutation carriers.[73]

Two different medications can lower the risk of breast cancer among women at increased risk; however, they have not been adequately studied in women who have a *BRCA* mutation.[74] The Study of Tamoxifen and Raloxifene (STAR) compared the effectiveness of these two drugs among women with elevated breast cancer risk, whereas an earlier study, the Breast Cancer Prevention Trial (BCPT), demonstrated tamoxifen reduced breast cancer incidence by about 50%.[75] The STAR trial revealed raloxifene is as effective as tamoxifen in reducing the number of invasive breast cancer cases and has fewer serious side effects. However, the benefit of these medications in unaffected women with known *BRCA* mutations is not well established. There are no data regarding the benefits of raloxifene in *BRCA* mutation carriers, and only a limited amount of information regarding tamoxifen use by *BRCA* carriers. The largest studies of tamoxifen as a breast cancer prevention agent in mutation carriers without a prior breast cancer diagnosis have yielded conflicting results, although there is some suggestion that the risk of contralateral breast cancer may be reduced in *BRCA* carriers; nevertheless, there are no data regarding tamoxifen's benefit in primary prevention of breast cancer in this group of women.[66,76,77] Therefore, tamoxifen may be a reasonable option for high-risk women to consider in the future after further research is completed.

Ovarian Cancer Surveillance

For women with a *BRCA* mutation who have not had their ovaries removed, the following measures are currently recommended:[52] transvaginal ultrasound and CA-125 blood test every 6 to 12 months starting at age 35, or 5 to 10 years earlier than the youngest age of onset of ovarian cancer diagnosis in the family. However, several studies have demonstrated that screening for ovarian cancer using transvaginal ultrasound and serum CA-125 is ineffective and inefficient.[78–80] Routine use of transvaginal ultrasound and serum CA-125 does not prevent the diagnosis of late-stage ovarian cancer and leads to a high number of false-positive findings. For that reason, risk-reducing oophorectomy (RRO), after childbearing is completed, is considered the most powerful intervention available to *BRCA1* or *BRCA2* mutation carriers to reduce the risk of ovarian and fallopian tube cancer.

Prophylactic Removal of the Ovaries and Fallopian Tubes

Risk-reducing oophorectomy has been shown to lower the risk of developing ovarian cancer among high-risk women by 85% to 95%[81–83] and to provide a 77% reduction in all-cause mortality.[84] The fallopian tubes must be removed because of the increased risk of fallopian tube malignancies among *BRCA* mutation carriers.[71,83] However, this surgical procedure does not completely protect against ovarian cancer-like malignancy. After a woman has undergone risk-reducing salpingo-oophorectomy (RRSO), there is still a 1% to 4% chance that she may develop a cancer in the abdomen that resembles ovarian cancer; such disease appears to occur more frequently in *BRCA1* carriers compared with *BRCA2* carriers.[71] Designated primary peritoneal carcinoma (PPC), this malignancy is thought to arise from other tissues in the abdomen that are related to the ovaries. There are no recommendations for routine screening following RRSO to detect PPC at this time.

Risk-reducing salpingo-oophorectomy is usually recommended starting at ages 35 to 40 years, or once childbearing

is completed.[52,85] Before making a decision regarding RRSO, mutation carriers must pursue a thorough discussion about the age of the earliest ovarian cancer in the family, their personal reproductive plans, the degree of risk reduction expected from RRSO, management of menopausal symptoms, and the possibility of other medical conditions that may occur more frequently among women who have undergone surgical menopause. The most common symptoms associated with RRSO in premenopausal women are hot flashes and dyspareunia. Fortunately, menopausal hormone therapy (MHT), when used for short periods of time (2–3 years), is not associated with an increased risk of breast cancer[86] and can be safely used to relieve menopausal symptoms caused by surgical menopause. Further research is needed to determine whether there are differences in the risk of developing breast cancer based on the precise hormonal preparation and duration of MHT in *BRCA1/2* mutation carriers. The Women's Health Initiative[87,88] demonstrated that women taking estrogen-only MHT did not have an increased risk of developing breast cancer. Therefore, it may be worth considering hysterectomy at the time of RRSO, in carefully selected women, if either estrogen-only MHT is contemplated for the relief of menopausal symptoms, or if tamoxifen is being considered for breast cancer risk reduction.[87]

Chemoprevention of Ovarian Cancer

For women who are not ready to have RRSO to lower their risk of ovarian cancer, oral contraceptives (OCs) may be considered. The use of OCs has been shown to decrease the risk of ovarian cancer by approximately 50% in regard to both sporadic and hereditary ovarian cancer.[88–91] With continued use of OCs, there is a 36% decrease in ovarian cancer risk for each decade of use.[88] Of note, the overall research findings involving *BRCA1/2* carriers taking OC formulations prior to 1975 suggested that there is a positive association between OC use and breast cancer risk. However, compared with today's OC preparations, OC formulations prior to 1975 included a higher dosage of estrogens; there is no correlation between increased risk of breast cancer and the current OC formulations.[88]

A recent retrospective case-control study evaluating affected (cases) and unaffected (unaffected) *BRCA1* mutation carriers reported that *BRCA1* mutation carriers who *ever* used OCs had a greater likelihood of developing breast cancer (odds ratio [OR], 1.18; 95% confidence interval [CI], 1.03–1.36; $p \geq 0.02$) than women who *never* used OCs.[92] This effect was limited to *BRCA1* carriers diagnosed with breast cancer *prior* to the age of 40. There was also an increased risk of early-onset breast cancer (OR, 1.1; 95% CI, 1.02–1.2) for each year of OC use prior to the age of 20.[92] *BRCA1* mutation carriers interested in using contraceptive pills to reduce their risk of ovarian cancer need to balance the potential increase in breast cancer risk with the prevention of unintended pregnancy and the clear benefit of OCs in the prevention of ovarian cancer.

CANCER RISK MANAGEMENT IN MALE *BRCA* MUTATION CARRIERS

It is recommended that male *BRCA* mutation carriers learn and perform breast self-examination monthly, undergo clinical breast examination, and consider baseline mammography. If gynecomastia or glandular breast density is seen on the baseline mammogram, annual mammography is indicated.[1,93]

Male *BRCA* mutation carriers are also at higher than average risk of developing prostate cancer. Being a *BRCA2* mutation carrier has been associated with an 8.6-fold increased risk of prostate cancer in men, while *BRCA1* carrier status is associated with a 3.7-fold increased risk of this cancer.[94,95] A recently published retrospective cohort study reported that 2% of men with early-onset prostate cancer (before 55 years of age) carry a germline *BRCA2* mutation and are more likely to develop early-onset prostate cancer (23-fold higher relative risk) than men with prostate cancer but without a *BRCA2* mutation.[96,97] In addition, the results from the first 300 patients enrolled in the IMPACT (identification of men with a genetic predisposition to prostate cancer) trial group reported a prostate cancer-specific prevalence of 3.3%, prostate-specific antigen (PSA) screening having a 48% positive predictive value in male *BRCA1/2* mutation carriers.[97] These results suggest that targeted PSA screening for male *BRCA* carriers, especially those with a family history of young onset, may be associated with better identification of aggressive disease.[97]

Aspirin has drawn some attention as a chemoprevention agent for prostate cancer, including male *BRCA* mutation carriers.[98,99] A recent study reported a lower likelihood of prostate cancer in male *BRCA* mutation carriers who used aspirin daily (OR, 0.091; 95% CI, 0.011–0.467; $p = 0.003$).[99] However, given the study's small sample size ($n = 74$ responders) and relatively low power, this finding, while intriguing, is neither conclusive nor ready for clinical application.

HEREDITARY COLORECTAL CANCER SYNDROMES

Colorectal cancer is the fourth most commonly diagnosed cancer among adults in the United States.[100] Approximately 134,490 new cases were expected to be diagnosed in 2016, with approximately 49,190 deaths occurring because of the disease.[100] The majority of colorectal cancers (75%) are the sporadic form of cancer, which shows no evidence of an autosomal dominant inheritance pattern.[101] Among all individuals diagnosed with colorectal cancer,

approximately 25% have a family history of cancer that is suggestive of genetic risk or perhaps common exposures among family members associated with an increased risk of developing colorectal cancer. The hereditary colorectal cancer syndromes, Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer [HNPCC]) and familial adenomatous polyposis (FAP) account for approximately 5% to 6% of all colorectal cancers. Unique features of family history, characteristics of disease presentation, and histopathological findings in tumor tissue and polyps enhance the ability to identify family members affected by these rare syndromes. While both Lynch syndrome (2–3% incidence) and FAP (1–2% incidence) are rare, it is important to identify mutation carriers so that early detection and cancer prevention strategies can be employed.

LYNCH SYNDROME

Mutations associated with Lynch syndrome are inherited in an autosomal dominant pattern with incomplete penetrance. Several genes are associated with Lynch syndrome: *MLH1* at 3p21.3, *MSH2* at 2p21-22, *PMS2* at 7p22, and *MSH6* at 2p16.[1] These genes function in the DNA mismatch-repair complex within the cell. *MLH1* and *MSH2* are associated with more than 90% of the mutations identified in Lynch syndrome families; *MSH6* is associated with 7% of the mutations identified in such families.[102] Three deletions in the *EPCAM* gene also appear to lead to hypermethylation of the *MSH2* promoter and subsequent *MSH2* silencing.[103,104] These deletions are thought to account for the 20% to 25% of Lynch syndrome cases in which the MSH2 protein is not detected by immunohistochemistry (IHC).[104] Three additional genes have also been found to be associated with Lynch syndrome: *MLH3*, *PMS1*, and *EXO1*.[105]

Lynch syndrome is characterized by the development of colorectal cancer in the right side of the colon and several other extracolonic cancers (gastric, small intestine [ampulla of Vater], biliary tract, urinary tract, ovarian, brain, and endometrial), which present at an earlier age than in the general population.[101] Turcot syndrome consists of colorectal and brain cancer and is a variant of both Lynch syndrome and FAP. In Lynch syndrome, the brain cancers tend to be glioblastomas; in FAP, the brain cancers are usually medulloblastomas.[106] Another variant of Lynch syndrome, known as Muir-Torre syndrome, is characterized by cutaneous lesions (sebaceous adenomas, epitheliomas, carcinomas, or keratoacanthomas) and other malignancies.[1] The risk of colon cancer appears to be greatest in *MLH1* mutation carriers; however, the overall risk of all cancers appears to be greatest in individuals who carry a mutation in the *MSH2* gene.[1]

The lifetime cancer risks of individuals with Lynch syndrome are 50% to 80% for colorectal cancer, 40% to 60% for endometrial cancer, 9% to 12% for ovarian cancer, 11% to 19% for gastric cancer, 1% to 4% for small bowel cancer, 4% to 5% for urinary tract cancer, 1% to 3% for brain cancer, 3% to 4% for pancreatic cancer, and 2% to 7% for hepatobiliary cancer.[101,107–109] Colorectal cancer pathologic features in Lynch syndrome include a solid growth pattern, mucin production, poor differentiation, and lymphoid infiltration of tumor.[106] Endometrial and ovarian cancers associated with Lynch syndrome are diagnosed an average of 10 years earlier than in the general population; however, the survival does not seem to differ significantly from that observed with the sporadic forms of cancer when matched by stage of disease at diagnosis.[109]

Colorectal Cancer Risk Assessment: Lynch Syndrome

Identification of individuals who are likely to carry a mutation associated with Lynch syndrome has relied on the use of family history with the Amsterdam Criteria serving as a guide (discussed later in this section). However, these criteria were initially developed for the purpose of consistent classification of research subjects.[110] The Bethesda criteria were later developed and modified to assist in identifying the risk of Lynch syndrome among patients already diagnosed with HNPCC-related tumors. Subsequently, researchers at Dana Farber Cancer Institute[31] developed a model to help healthcare professionals estimate the probability that an affected individual carries a mutation in a *MLH1* or *MSH2* gene.

Amsterdam Criteria (Revised)

The Amsterdam Criteria were originally created in 1991 and later revised after there was broad agreement that the initial criteria were too restrictive for clinical use (AC-II). The current criteria require that the following conditions be met:

- At least two relatives have an HNPCC-associated cancer: colorectal cancer, or cancer of the endometrium, small intestine, ureter, or renal pelvis.
- One patient should be a FDR of the other two.
- At least two successive generations should be affected.
- At least one tumor should be diagnosed in a relative younger than 50 years of age.
- Familial adenomatous polyposis should be excluded in the colorectal cancer case (if any).
- Tumors should be verified by histopathological examination.

These criteria were not intended to assist with selection of individuals for genetic testing or enhanced cancer surveillance, but instead to unify the selection of families at high risk for research studies. It is important to note that a significant percentage of mutation-positive families with Lynch syndrome do not meet the AC-II; therefore, caution must be applied when using these guidelines, as there

is strong suggestion that other inherited mutations may remain to be identified.

Bethesda Criteria (Modified)

The Bethesda Guidelines were developed to help identify Lynch syndrome families by categorizing colorectal cancer cases via molecular evaluation using microsatellite instability testing (MSI) and immunohistochemistry (IHC) analysis if criteria were met in patients already affected with HNPCC-associated malignancies.[111] The most recent guidelines posit that MSI and/or IHC testing of Lynch syndrome-associated tumors is indicated if any of the following criteria are met:

- The patient is younger than age 50.
- The patient has multiple HNPCC-associated tumors (metachronous or synchronous).
- The patient has at least one FDR who had an HNPCC-related tumor at 50 years of age or younger.
- The patient has at least two FDRs or SDRs with HNPCC-related tumors at any age.
- The patient is younger than 60 years and has colorectal cancer that has microscopic characteristics that are indicative of MSI.

In the clinical setting, the Bethesda Guidelines constitute a useful approach to identify patients at risk of Lynch syndrome. In patients meeting the guidelines, both MSI testing and IHC staining are effective strategies (from both clinical and economic standpoints) to further select patients who can be tested for *MSH2/MLH1* germline mutations.

PREMM 1,2,6 Model

The PREMM 1,2,6 Model (http://www.dfci.org/premm) is an online risk assessment calculator designed to estimate the probability that an individual carries a mutation in *MLH1*, *MSH2*, or *MSH6*; its results guide clinical management.[112,113] The model was derived from a logistic regression analysis of 4539 probands who provided family history data, including FDRs and SDRs, and had full gene sequencing of the three genes. PREMM 1,2,6 is an extension of the PREMM 1,2 models and includes the same variables defined in the previous model:[113,114]

- Diagnosis of and age at diagnosis of colorectal cancer (CRC)
- Colonic adenomas
- Endometrial cancer and other Lynch syndrome–associated cancers (ovary, stomach, kidney/urinary tract, bile ducts, small bowel, brain tumors [glioblastoma multiforme], pancreas, and sebaceous gland tumors)
- Presence of CRC or other Lynch syndrome–associated cancers in the proband's FDRs or SDRs and their ages at diagnosis

External validation and comparison with the previous PREMM 1,2 model was conducted on a second cohort of 1827 individuals.[113] The differences identified gender as an additional predictor in the updated PREMM 1,2,6 model. All other variables being equal, men were two times more likely than women to have an *MMR* mutation, and that adenomas in the proband were not a predictor as indicated in the previous model.[113]

Additional models for identifying HNPCC risk include HNPCC (http://hnpccpredict.hgu.mrc.ac.uk/), MMRpro (https://www4.utsouthwestern.edu/breasthealth/cagene/), and MMRpredict.[115,116]

Cancer Surveillance in Individuals With Known Lynch Syndrome or in Untested Individuals From Known Lynch Syndrome Families

Colorectal cancer surveillance recommendations are based on the specific mutation detected. For individuals with a *MLH1*, *MSH2*, or *EPCAM* mutation, screening guidelines include a colonoscopy every 1 to 2 years beginning between the ages of 20 to 25 years of age or 2 to 5 years prior to the earliest colorectal cancer diagnosed in the family, if diagnosed before the age of 20 years.[117–119] For individuals with an *MSH6* or *PMS2* mutation (associated with a lower risk for colon cancer up to age 70), screening colonoscopy is recommended every 1 to 2 years between the ages of 25 to 30 or 2 to 5 years prior to the earliest colon cancer in the family, if diagnosed before age 30 years.[117–119] Early and increased surveillance and removal of colon polyps have been shown to reduce the incidence of colorectal cancer in individuals with Lynch syndrome.[120]

Evidence does not exist to support the efficacy of screening for gastric, duodenal, and small bowel cancer in Lynch syndrome at this time. Depending on their specific findings, selected individuals or families may be advised to begin upper gastrointestinal and duodenal cancer screening between 30 and 35 years of age, consisting of an upper gastrointestinal endoscopy, to be repeated every 3 to 5 years.[118]

Ovarian, Endometrial, and Urinary Tract Cancer Risk Management of Lynch Syndrome

As with *BRCA1* and *BRCA2*, the efficacy of screening for ovarian cancer in conjunction with high risk for Lynch syndrome has not yet been demonstrated. However, in women at high genetic risk of Lynch syndrome who are not ready for prophylactic bilateral oophorectomy, annual transvaginal ultrasound and serum CA-125 is recommended.[120,121] In the general population, use of oral contraceptive pills has been associated with a substantial reduction in the risk of ovarian cancer; however, this effect has not been demonstrated in Lynch syndrome.[1]

Endometrial cancer surveillance includes annual Pap smear, pelvic examination, annual transvaginal ultrasound, and/or endometrial biopsy and CA-125 beginning between 25 and 30 years of age. These recommendations are based on expert consensus opinion. Increased surveillance of the endometrium leads to early detection of endometrial cancer; however, whether this improves survival has not yet been demonstrated.[121,122] The benefit of the prophylactic removal of the uterus and ovaries, after a woman has completed childbearing, almost completely eliminates the risk of developing ovarian and endometrial cancer[122,123] in women at high genetic risk of Lynch syndrome. Since endometrial cancer is the second most frequent malignancy occurring in Lynch syndrome, prophylactic hysterectomy after completion of childbearing warrants consideration.

The penetrance estimate for urinary tract cancers associated with Lynch syndrome is quite variable. Nevertheless, annual urinalysis is recommended starting at 25 to 30 years of age in individuals who are at high genetic risk of Lynch syndrome to screen for urinary tract cancers.[118]

FAMILIAL ADENOMATOUS POLYPOSIS

Familial adenomatous polyposis is an autosomal dominantly inherited disorder with an incidence of 1 in 8000 to 15,000 live births.[124] Protein truncation mutations in the *APC* gene 5q21-q22 account for 70% to 80% of reported mutations, and approximately 25% of FAP cases are due to new germline mutations (de novo mutations). Clinical diagnosis of the disease is most frequently based on the presence of large numbers (more than 100) of adenomatous colorectal polyps. In untreated individuals, the risk of developing colon cancer (most frequently left-sided) is nearly 100% by the fourth or fifth decade of life if prophylactic colectomy is not performed.[125,126] After an affected family member has tested positive for a deleterious mutation in the *APC* gene, genetic testing is offered to close family members. Colon adenomas will develop in nearly 100% of individuals who test positive for a mutation in the *APC* gene and commonly develop in the teen years. For this reason, once an informative family member has been identified, genetic testing is offered to children. When polyps are identified, risk-reducing colectomy is recommended to prevent colon cancer.

Other cancers have been associated with FAP, including medulloblastoma (lifetime risk < 2%), papillary carcinomas of the thyroid (lifetime risk < 2%), hepatoblastoma (lifetime risk < 5%), pancreatic cancer (lifetime risk < 2%), and gastric cancer (lifetime risk < 1%). Benign neoplasms have also been associated with FAP, such as congenital hypertrophy of retinal pigment epithelium (CHRPE), osteomas, supernumerary teeth, odontomas, desmoids, epidermoid cysts, duodenal and other small bowel adenomas, and gastric fundic gland polyps.[1]

Cancer Risk Management in FAP

For those persons at high genetic risk of FAP, cancer screening guidelines include early detection efforts related to cancers associated with the syndrome and colectomy once polyps are detected. Expert guidelines for surveillance and prevention of cancers associated with FAP are updated frequently as new research about the efficacy of interventions evolves. Management should be individualized based on genotype, phenotype, and other personal considerations taken into account by the physician or center that is managing the patient.[118] Decisions about the timing and the type of surgery are complex and require thoughtful discussions between the patient and his or her surgeon.

OTHER COLON CANCER HEREDITARY SYNDROMES

Attenuated FAP (AFAP) is a milder form of the FAP and may be difficult to distinguish from *MUTYH*-associated polyposis and Lynch syndrome. Carriers of a mutation in the AFAP portion of the *APC* gene (before codon 157, after 1595, and in the alternatively spliced region of exon 9)[1] develop fewer than 100 colonic adenomas; these adenomas tend to be smaller and flatter than FAP polyps and develop on the right side of the colon.[125,126] In AFAP, colorectal cancer occurs later in life, with a mean age at diagnosis of 50 to 52 years.[127] If germline *APC* testing is negative in individuals who are suspected of having AFAP, genetic testing for *MYH* mutations can be contemplated.

MYH-associated polyposis has an autosomal recessive inheritance pattern, and homozygous mutations in the *MYH* gene have been associated with multiple colorectal adenomas with or without cancer. The *MYH* gene is located at 1p32.1-p34.3. It is a base-excision repair gene that participates in the repair of mutations caused by reactive oxygen species.[128] The incidence of the monoallelic *MYH* mutation is approximately 1% in the general population. Approximately 7% to 17% of individuals who have an FAP phenotypic expression of polyposis but without a detectable *APC* germline mutation carry biallelic mutations in the *MYH* gene.[129–132] Biallelic mutations have shown to carry an increased risk of cancer, up to 28-fold greater than the risk associated with monoallelic mutations.[133,134] Associated benign neoplasms include colonic and duodenal adenomas, gastric fundic glad polyps, osteomas, sebaceous gland adenomas, and pilomatricomas.[135]

Cancer risk management in *MYH*-associated polyposis consists of starting colonoscopy at age 25 to 30 years and repeating this procedure every 3 to 5 years if no polyps are found. Upper gastrointestinal endoscopy with side-viewing duodenoscopy beginning at age 30 to 35 and repeated every 3 to 5 years may also be considered. If adenomas are detected, patients should be managed according the FAP

guidelines.[118] Carriers of monoallelic *MYH* mutations are recommended to begin colonoscopy at age 40 and repeat colonoscopy every 5 years, based on expert opinion.[1]

MULTIPLE ENDOCRINE NEOPLASIA

Multiple endocrine neoplasia (MEN) syndromes are rare autosomal dominant inherited disorders that predispose individuals to benign and malignant tumors of the pituitary, thyroid, parathyroids, adrenals, endocrine pancreas, paraganglia, and nonendocrine organs. MEN type 1 (MEN1) and MEN type 2 (MEN2) are examples of classic MEN syndromes. However, von Hippel-Lindau syndrome (VHL) and Cowden syndrome may also be considered as examples of MEN.[136]

MEN1

MEN1 is caused by a mutation in the *MEN1* gene, which is located at chromosome 11q13. This mutation is thought to affect gene transcription, cell proliferation, apoptosis, and genome stability.[137] The incidence of the mutation is estimated to be 1 in 5000 to 50,000 in Caucasian populations. Penetrance is estimated to be 80% by age 50.[136] Hyperparathyroidism either is the presenting symptom or is diagnosed simultaneously as the presenting symptom in the majority of cases.[1] Cancers associated with *MEN1* mutations include parathyroid, pancreas, pituitary, adrenal, and neuroendocrine carcinoid.

Genetic testing for *MEN1* should be offered to patients with MEN1 disease and to any first-degree relatives, even if they are asymptomatic.[138] Testing at an early age is recommended because it allows patients to be monitored for the development of subsequent MEN1-related tumors in individuals identified to be carriers of a mutation in the *MEN1* gene. Several commercial laboratories offer germline *MEN1* mutation testing for patients in whom a diagnosis of MEN1 is suspected. Approximately 10% of all mutations detected are found to be de novo mutations.

Patients need to be managed by a multidisciplinary team with experience in endocrine tumors. If untreated, these patients have a decreased life expectancy.[138] The efficacy, risk, and benefits of early detection in MEN1 are unknown. **Table 6-5** summarizes the current recommendations for early cancer detection in known carriers of a *MEN1* mutation.

MEN2

MEN2 is associated with the *RET* proto-oncogene located at chromosome 10q11.2. The incidence of MEN2 is 1 in 30,000 births. Three distinct subtypes of MEN2 exist: MEN2A, MEN2B, and familial medullary thyroid cancer (FMTC). Each subtype has strong genotype–phenotype correlations. MEN2A is the most common subtype and is associated with medullary thyroid cancer in nearly all cases, pheochromocytoma in 50% of cases, and hyperparathyroidism in 15% to 30% of cases.[1] In MEN2B, the onset of medullary thyroid cancer occurs at a younger age (before 10 years), hyperparathyroidism is infrequent, and patients often have mucosal neuromas of the eyelids, lips, and tongue.[136] For individuals who are diagnosed with FMTC, medullary thyroid cancer is usually the only malignancy in the family, and the age at diagnosis is generally older than with MEN2A or MEN2B. FMTC has shown a 50% penetrance by 36 years of age. [139]

Cancer Risk Assessment and Surveillance in Individuals Suspected of Being MEN2 Mutation Carriers

For affected individuals who test positive for an *MEN2* mutation, experts recommend efforts that lead to early diagnosis (Table 6-5). Genetic testing is recommended for at-risk relatives so that early cancer screening can be initiated if a mutation is detected. Most commonly, physical examination, surgery to remove at-risk organs, and biochemical screening to detect pheochromocytoma and hyperparathyroidism are included in management recommendations.

Endocrine tumors are rare in the general population. If they are identified in more than one family member, or if more than one endocrine tumor is identified in a single individual, formal cancer genetic risk assessment is recommended. Furthermore, certain endocrine tumors (pheochromocytoma, paraganglioma, medullary thyroid cancer, and parathyroid carcinoma) are "red flags" for a hereditary cancer syndrome. Even in the absence of a personal or family history suggestive of a hereditary cancer syndrome, individuals who are diagnosed with any one of these cancers should be referred for comprehensive cancer risk assessment.[136]

COWDEN SYNDROME

Cowden syndrome is a rare hereditary cancer syndrome associated with mutations in the *PTEN* gene at chromosome 10q23.3. The mode of inheritance is autosomal dominant, and its incidence is estimated to be approximately 1 in 200,000 births.[140] Cowden disease is most commonly recognized based on clinical findings of benign skin lesions (trichilemmomas) and intestinal hamartomas.[141] Individuals who inherit a *PTEN* mutation are at high risk of developing female breast cancer (85% lifetime risk), which occurs approximately 10 years earlier than in the general population.[142] Male breast cancer has also been reported.[1] Other cancers associated with Cowden syndrome include thyroid cancer (primarily follicular type), endometrial cancer, and renal cancer.[143] Colorectal and renal cell cancers

TABLE 6-5

Summary of Cancer Risk Management

Hereditary Cancer Syndrome Gene (Chromosome Location)	Major Associated Malignant Neoplasms	Associated Benign Neoplasms	Primary Cancer Prevention	Cancer Syndrome Screening[a]
Hereditary breast and ovarian cancer AD TSG *BRCA1* (17q21) *BRCA2* (13q12.3)	Breast, ovary, fallopian tube cancer, prostate Basal phenotype breast cancer, pancreatic cancer Estrogen-receptor positive breast cancer	None known	Breast • RRBPM • Consider chemoprevention of breast cancer Ovarian • Consider chemoprevention of ovarian cancer with oral contraceptives Ovarian/fallopian tube • RRSO (between age 35 and 40 or upon completion on childrearing)	Breast • BSE training and monthly exams starting at age 18 • CBE semiannually, starting at age 25 • Annual mammography and breast MRI at age 25 or 5–10 years before the earliest breast cancer in family Ovarian • Twice yearly transvaginal ultrasound with CA-125 starting at age 35 years or 5–10 years prior to the earliest ovarian cancer in family Male breast • BSE training and monthly exams starting when identified as high risk • Semiannual CBE • Consider baseline mammogram and annual mammogram if gynecomastia or dense breasts on baseline study Prostate
Hereditary colon cancer syndromes *MLH1* (3p21.3) *MSH2* (2p21-p22) *PMS* (2q31-q33) *PMS2* (7p22) *MSH6* (2p16) *MSH3* (5q11-q12) *EPCAM* AD DMRG	Colorectal, endometrial, gastric, biliary tract, urinary tract, ovarian, small bowel	Sebaceous adenomas, colonic adenomas, keratoacanthomas, Fordyce granules, epitheliomas	Endometrial/ovarian • RRSO and hysterectomy after childbearing	Colon • Colonoscopy and polypectomy every 1–2 years, starting at ages 20–25 or 2–5 years before the earliest age of CRC in family, if diagnosed before age 25 Endometrial/ovarian • Annual Pap smear, pelvic exam, annual transvaginal ultrasound, and/or endometrial biopsy and CA-125 Gastric and small bowel • EGD with extended duodenoscopy every 3–5 years, starting at ages 30–35 Urothelial • Yearly urinalysis starting at ages 25–30 CNS • Physical with neurologic exam starting at ages 25–30

Familial adenomatous polyposis *APC* (5q21-q22) AD DMRG	Colon adenocarcinoma, duodenal carcinomas thyroid, brain, childhood hepatoblastoma	Adenomatous polyps of the colon, duodenal polyps, hamartomatous gastric polyps, adenomatous gastric polyps, desmoid tumors, lipomas, sebaceous or epidermoid cysts, dental abnormalities	Colorectal • Colectomy after adenomas develop • Consider NSAIDs on clinical trial	Colorectal • Colonoscopy every 2–3 years beginning in late teens; annually once polyps are detected Hepatoblastoma • Physical examination with or without abdominal ultrasound, and serum alpha-fetoprotein from birth to 6 years Thyroid • Annual palpation of the thyroid gland Gastric/duodenal • Esphagogastroduodenoscopy with a side-viewing endoscope by age 25 or when colonic polyps appear; repeat every 1–3 years • Consider small bowel x-ray or CT or abdomen/pelvis every 1–3 years after duodenal adenomas are detected
Cowden syndrome *PTEN* (10q23.3) AD TSG	Breast, thyroid, endometrial, renal	Verrucous skin lesions of the face and limbs, facial trichilemmomas, oral fibromas, hyperkeratosis, hamartomatous polyps of the stomach, small bowel and colon; lipomas, cerebellar gangliocytomatosis, hemangiomas and uterine leiomyomas; vascular abnormalities; benign breast histopathological findings	Breast • Consider RRBPM	Annual physical exam • Starting at 18 years or 5 years before the earliest cancer diagnosis in family, with attention to thyroid and breast exam Breast • BSE training and monthly starting at age 18 • CBE semiannually, starting at age 25 • Annual mammography and breast MRI at age 35 or 5–10 years before the earliest breast cancer in family Endometrial • Consider endometrial cancer screening starting at 35–40 years and participation in a clinical trial to determine the effectiveness of screening Thyroid • Clinical exam beginning in adolescence (monograph) • Baseline thyroid ultrasound at 18 years; consider annually Renal • Annual urinalysis • Renal ultrasound if family history of renal cancer is present (monograph) Skin • Consider annual dermatologic exam

(continues)

TABLE 6-5

Summary of Cancer Risk Management (*continued*)

Hereditary Cancer Syndrome Gene (Chromosome Location)	Major Associated Malignant Neoplasms	Associated Benign Neoplasms	Primary Cancer Prevention	Cancer Syndrome Screeninga
Li-Fraumeni *TP53* (17p13.1) AD TSG	Osteogenic and chondrosarcoma, rhabdomyosarcoma, breast, brain (glioblastomas) leukemia, lymphoma, adrenocortical carcinoma	None known	Breast • Consider RRBPM on a case-by-case basis	Breast • BSE training and monthly starting at age 18 • CBE semiannually starting at age 20–25 • Mammogram and breast MRI annually starting at age 20–25
Multiple endocrine neoplasia type 1 *MEN1* (11q13) AD TSG	Pancreatic, duodenal, gastrinomas, carcinoids of the thymus, bronchus, or stomach	Hyperparathyroidism, anterior pituitary adenomas, adrenal cortical adenomas, lipomas, collagenomas, facial angiofibromas		Annual serum glucose, insulin, proinsulin, prolactin, IGF-1, and brain imaging every 3 years starting at age 5 Age 8: Start serum parathyroid hormone and ionized calcium annually Age 20: Consider annual fasting serum gastrin, pancreatic polypeptide, fasting VIP and glucagons, and SRS/CT of thorax and abdomen every 2–3 years
Multiple endocrine neoplasia type 2A/2B and familial medullary thyroid cancer (FMTC) *RET* (10q11.2) AD OG	Medullary thyroid cancer, papillary thyroid cancer	Hyperparathyroidism (MEN2A) Ganglioneuromas of the gastrointestinal tract and mucosal neuromas (MEN2B) Pheochromocytomas	• Prophylactic thyroidectomy before 6 months of age for MEN2B, before 6 years for MEN2A, and between 6 and 10 years for FMTC • Consider the removal of 3.5 parathyroid glands at the time of thyroidectomy in *MEN2A* carriers	Annual screening for pheochromocytomas starting at same age as thyroidectomy; screening for hyperparathyroidism starting at 6 years for *MEN2A* carriers
Von Hippel-Lindau *VHL* (3p25-p26) AD TSG	Renal carcinoma (RCC, clear cell type), pancreatic islet cell carcinomas, carcinoid (occasionally), endolymphatic sac tumors	Hemangioblastomas, retinal angiomas, pancreatic cysts, renal cysts, pheochromocytomas, adrenal adenomas, paragangliomas, epididymal cysts, hepatic cysts		Annually: • Ophthalmological exam, starting by age 5 years • Physical exam, with blood pressure and neurologic exam, starting at 5 years • CBC, urinalysis • Ultrasound of kidneys and pancreas, starting no later than 16 years MRI of CNS and spinal cord, biennially starting at 11 years CT or MRI of kidneys and pancreas in adults, every 2–3 years

[a]Or individualized based on the earliest age of onset in family.

Abbreviations: AD: autosomal dominant; AR: autosomal recessive; BSE: breast self-exam; CBC: complete blood count; CBE: clinical breast exam; CNS: central nervous system; CRC: colorectal cancer; CT: computed tomography; DMRG: DNA mismatch-repair gene; EGD: esophagogastroduodenoscopy; IP: incomplete penetrance; MRI: magnetic resonance imaging; NSAID: nonsteroidal anti-inflammatory drug; OG: oncogene; P: penetrance; RRBPM: risk-reducing bilateral prophylactic mastectomy; RRSO: risk-reducing bilateral salpingo-oophorectomy; TSG: tumor suppressor gene; VIP: vasoactive intestinal peptide.

Source: Data from Lindor et al.[1]

occur around age 40, with the lifetime risk of renal cell carcinoma estimated at 34%.[142] Kidney cancer and melanoma have also been reported and shown some association in individuals with Cowden syndrome.[142]

Cancer Surveillance of Individuals With Known Cowden Syndrome

Currently, the benefit of early detection and cancer prevention in Cowden syndrome is unknown.[1] However, based on expert consensus opinion, the ACS recommends annual breast MRI and annual mammography in women with Cowden syndrome. Table 6-6 provides other current recommendations for early detection and cancer prevention in individuals with Cowden syndrome.

VON HIPPEL-LINDAU SYNDROME

Individuals who inherit a mutation in the *VHL* gene are at high genetic risk of developing renal cell carcinoma (typically, clear-cell histology) as well as pancreatic islet cell carcinomas, carcinoid tumors, pheochromocytomas, endolymphatic sac tumors, and nonmalignant neoplasms including hemangioblastomas of the central nervous system and/or the retina.[1,144] The *VHL* tumor suppressor gene is located on chromosome 3p25-p26, and the incidence of this mutation is approximately 1 per 30,000 to 40,000.[1,144] Penetrance of the diseases associated with the *VHL* mutation is nearly 100% by the age of 65 years. Genetic testing is available[1,144] and is an effective method to identify or exclude VHL in individuals who are suspected of having the disease.[144]

Several subtypes of VHL may be distinguished based on the presence (VHL type 2: 7%–20% of families) or absence (VHL type 1) of pheochromocytomas within a family. VHL type 2 is further subclassified depending on the absence (2A) or presence (2B) of a predisposition to renal cell cancer and (2C) with pheochromocytomas only within the family.[145]

A series of hereditary renal cancer syndromes has been identified and their causative genes determined. Identification of these disorders has been driven by the recognition that there are numerous subtle histologic subtypes of renal cancers, each of which is associated with a different disorder.[146]

Cancer Surveillance and Cancer Risk Assessment of Individuals Suspected of Being VHL Mutation Carriers

Affected individuals suspected of being *VHL* mutation carriers are recommended to undergo comprehensive cancer risk assessment. If a *VHL* mutation is identified, all FDRs can also be offered cancer risk assessment and genetic testing.

Cancer surveillance is initiated in childhood if an individual is identified as a *VHL* mutation carrier (see Table 6-6). The timing, duration, risks, and benefits of cancer screening for individuals at risk of VHL syndrome are not known.[145] VHL cancer screening recommendations are frequently modified and updated regularly by the VHL Family Alliance (http://www.vhl.org).

LI-FRAUMENI SYNDROME

Li-Fraumeni syndrome (LFS) is caused by a germline mutation in the tumor suppressor gene *TP53*, also known as *p53*, located at chromosome 17p13.1.[147] LFS is thought to be rare, with approximately 400 families having this syndrome being reported in the literature. The precise incidence of the syndrome is unknown. The major cancers associated with the LFS include osteosarcoma, chondrosarcoma, rhabdomyosarcoma, breast cancer, brain cancer (glioblastoma), leukemia, lymphoma, and adrenocortical carcinoma. The penetrance of the diseases associated with LFS is approximately 50% by age 30 and approaches 100% by age 70.[147] The risk of developing early breast cancer among women who inherit a mutated copy of the germline *p53* gene is 100 times greater than the risk seen in the general population.[148] Classic LFS is identified based on the following criteria: one patient with sarcoma diagnosed before age 45, a FDR diagnosed with cancer (any type) before age 45, and a third affected family member (FDR or SDR) with either sarcoma at any age or cancer before age 45.[149] Malignancies that are part of the "classic" form of LFS account for approximately 80% of all cancers that occur in LFS families.[150]

The Chompret criteria are most commonly used to determine risk and need for further genetic screening. Further support for the revised Chompret criteria was reported by Gonzalez et al.,[151] who used a cohort of 525 families in their assessment.

CANCER SURVEILLANCE OF INDIVIDUALS AT HIGH GENETIC RISK OF LFS

Annual comprehensive physical exams should be performed starting in childhood when a family history of LFS is present. Breast cancer screening, including monthly breast self-examination, every 6 months' clinical breast examination, annual mammography, and breast MRI, is recommended for known LFS mutation carriers and their female FDRs.[1,52,93] Mammography and MRI should begin at 20 to 25 years or be based on earliest age of onset; annual MRI may be the only screening performed on young (20- to 30-year-old) patients.[52] Prophylactic mastectomy can be discussed on an individual basis. A colonoscopy is suggested beginning at age 25 and repeated every 2 to 5 years.[52] The risk and benefits of screening for other malignancies

associated with LFS are not known and should be tailored to the phenotype of individual families. A summary of the current cancer screening and prevention strategies for LFS is included in Table 6-6.

FUTURE DIRECTION OF NURSING PRACTICE AND RESEARCH

Integrating emerging genetic findings into evidence-based healthcare recommendations is a challenge for all healthcare providers. Oncology nurses practice at the nexus of genetic discoveries and oncology care. They provide patient services that are driven by new discoveries, leading to improvements in cancer risk prediction, prevention, and treatment. Oncology nurses work to enhance patient understanding, decision making, and treatment outcomes in oncology by integrating genetic information into their daily practice. They maintain state-of-the-art cancer genetic practice through participation in ongoing continuing educational programs offered by professional groups specializing in genetics, such as ONS, ISONG, the American Society of Human Genetics (ASHG), and the American Society of Clinical Oncology (ASCO). Organizations that provide nurses with opportunities to further expand their professional practice and understanding of cancer genetics through intensive training programs include the City of Hope,[152] Fox Chase Cancer Center,[153] and Cincinnati Children's Hospital.[154]

At the basic educational level of nursing, nursing students need exposure to clinical genetics that is more comprehensive and clinically relevant than traditional Mendelian genetics courses provide. To ensure that future nurses are well educated in genetic health care, genetics, and genomics, subject-specific content has been integrated into the American Association of Colleges of Nursing documents: *Essentials of Baccalaureate Education for Professional Nursing Practice*,[155] for all baccalaureate nursing programs in the United States, and *Essentials of Master's Education in Nursing*,[156] for those obtaining their master's degree in nursing.

Changes in the genetic knowledge base will continue to influence healthcare decisions and lead to changes in nursing practice over time. The ONS developed position statements for oncology nurses practicing at the general oncology nurse level and the advanced practice level to respond to thisenvironment of changing healthcare needs.[2,3] The previous professional credentialing in genetics offered through ISONG will be administered by the American Nurses Credentialing Center (ANCC) by 2015. This credentialing recognizes the new subspecialty of genetic nursing. In this way, professional nursing practice has responded yet again to the ever-changing needs of patient care.

Oncology nurses deliver oncology care by improving patient outcomes through evidence-based interventions and research to define best practices. Oncology nursing research will continue to contribute to better understanding of nursing-sensitive, patient-specific outcomes of oncology patients, and hereditary cancer genetics, including the following areas:

- Patient outcomes of oncology nursing interventions geared toward providing cancer genetic services
- How healthcare systems deliver hereditary cancer genetic services
- The effects of implementing screening to identify those in need of hereditary genetic services at the population level
- How genetic information affects individuals and families
- How genetic policy affects access to health care and the use of cancer genetic services
- Whether there are barriers to, or facilitators of, patient access to genetic services
- The potential risks and benefits of pharmacogenetics and pharmacogenomics in cancer care

CONCLUSION

Oncology nurses will continue to provide state-of-the-art cancer genetic care as new genetic information is discovered or refined. As the technologies underlying genomic research change, leading to new research methods that further refine our understanding of how genetic information influences health and healthcare decision making, nurses will seek and obtain education in genetics to ensure they can continue to provide excellent health care. On the near horizon, nurses must expand their understanding of genome-wide association studies, candidate gene association studies, and next-generation sequencing so that they can knowledgeably participate in the broad healthcare discussion regarding the following questions:

- Whether specific genetic polymorphisms are meaningfully associated with cancer risk
- Why personal genome scans may or may not be ready for integration into healthcare decision making[157]
- Why there may be emotional or psychological risk associated with particular findings of genetic association studies and disease prediction
- How to protect individuals' rights while maximizing scientific discovery
- How new genetic and genomic information affects the ethics of health care, especially related to privacy and confidentiality
- Whether there is an obligation to report incidental and secondary findings from genomic tests with variable or unknown clinical utility to patients[35,158]
- Whether some particular results might be considered clinically actionable and, therefore, warrant patient disclosure[158]
- Whether individuals and families intend to learn of incidental and secondary findings[158,159]

Nurses will continue to advocate for high-quality patient care during the transition from pre-genomic health care to post-genomic health care. As electronic medical records improve the safety and efficiency of health care, nurses will safeguard patient privacy rights and protect against discrimination. Healthcare delivery systems will continue to change as evidence for practice is established and implemented. Nurses will help patients understand and interpret complex cancer genetic information as applied to cancer diagnosis, treatment, or susceptibility testing as new genetic information emerges from research and is translated into practice. Nursing practice in genetic health care will continue to evolve in response to the needs of society and rapid changes in health care, as nursing practice has done since the beginning of the profession.

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REFERENCES

1. Lindor NM, McMaster ML, Lindor CJ, Greene MH. Concise handbook of familial cancer susceptibility syndromes. 2nd ed. *J Natl Cancer Inst Monogr*. 2008;38:1-93.
2. Oncology Nurses Society. The role of the oncology nurse in cancer genetic counseling. Oncol Nurs Forum. 2000;27(9): 1348.
3. Oncology Nurses Society. Oncology nursing: the application of cancer genetics and genomics throughout the oncology care continuum. https://www.ons.org/advocacy-policy/positions/education/genetics. Accessed May 26, 2016.
4. International Society of Nurses in Genetics. What is a Genetics Nurse? http://www.isong.org/ISONG_genetic_nurse.php. Accessed May 19, 2015.
5. Badzek L, Turner M, Jenkins JF. Genomics and nursing practice: advancing the nursing profession. *OJIN*. 2008;1. http://www.nursingworld.org/MainMenuCategories/ANAMarketplace/ANAPeriodicals/OJIN/TableofContents/vol132008/No1Jan08/GenomicsandAdvancingNursing.html. Accessed May 19, 2016.
6. Genetic Nursing Credentialing Commission (GNCC). Advanced Genetics Nursing. http://www.nursecredentialing.org/AdvancedGenetics. Accessesd May 19, 2016
7. Vogelstein B, Kinzler KW. The multistep nature of cancer. *Trends Genet*. 1993;9:138-141.
8. Hemminki K, Rawal R, Chen B, Bermejo JL. Genetic epidemiology of cancer: from families to heritable genes. *Int J Cancer.* 2004;111: 944-950.
9. Yoon PW, Scheuner MT, Peterson-Oehlke KL, Gwinn M, Faucett A, Khoury MJ. Can family history be used as a tool for public health and preventive medicine? *Genet Med.* 2002;4:304-310.
10. National Cancer Institute. Genetics overview (PDQ). 2014. http://www.cancer.gov/about-cancer/causes-prevention/genetics/overview-pdq. Accessed June 14, 2016.
11. Beauchamp TL, Childress JF. *Principles of Biomedical Ethics*. 7th ed. Boston, MA: Oxford University Press; 2012.
12. Robson ME, Storm CD, Weitzel J, Wollins, DS, Offit, K. American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. *J Clin Oncol.* 2010;*28*(5): 893-901.
13. Cluff CA. California Supreme Court expands the informed consent doctrine; physicians have a duty to obtain an informed refusal: *Truman v. Thomas*. *Brigh Young Univ Law Rev*. 1980;4:933-947.
14. Knoppers BM, Strom C, Wright Clayton E, et al. ASHG Social Issues Subcommittee on Familial Disclosure. ASHG statement: professional disclosure of familial genetic information; The American Society of Human Genetics Social Issues Subcommittee on Familial Disclosure. *Am J Hum Genet*. 1998;62:474-483.
15. Offit K, Groeger E, Turner S, Wadsworth EA, Weiser MA. The "duty to warn" a patient's family members about hereditary disease risks. *JAMA*. 2004;292:1469-1473.
16. Schneider K, ed. *Counseling About Cancer: Strategies for Genetic Counseling*. 3rd ed. New York: Wiley-Liss; 2012.
17. Jefferson D. Clinton outlaws genetic discrimination in federal jobs. *BMJ.* 2000;320:468.
18. Leib JR, Hoodfar E, Haidle JL, Nagy R. The new genetic privacy law. *Comm Oncol*. 2008;5:351-354.
19. Presidential Commission for the Study of Bioethical Issues. *Anticipate, Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research and Direct-to-Consumer Contexts.* Washington, DC: Presidential Commission for the Study of Bioethical Issues; 2013. http://bioethics.gov/node/3183. Accessed May 19, 2015.
20. National Cancer Institute. Genetic testing algorithm for cancer susceptibility. http://www.cancer.gov/cancertopics/pdq/genetics/risk-assessment-and-counseling/HealthProfessional/page6. Accessed May 19, 2015.
21. Anderson JA, Hayeems RZ, Shuman C, Szego MJ, Monfared N, Bowdin S, Zlotnik Shaul R, Meyn MS. Predictive genetic testing for adult-onset disorders in minors: a critical analysis of the arguments for and against the 2013 ACMG guidelines. *Clin Genet*. 2015 ;87(4):301-303.
22. Mand C, Gillam L, Delatycki MB, Duncan RE. Predictive genetic testing in minors for late-onset conditions: a chronological and analytical review of the ethical arguments. *J Med Ethics*. 2012 ;38(9):519-524.
23. Mendelsohn J, Howley PM, Israel MA, Gray JW. *The Molecular Basis of Cancer*. 4th ed. Philadelphia, PA: Elsevier Saunders; 2014.
24. Jenkins JF, Lea DH. *Nursing Care in the Genomic Era: A Case Based Approach*. Sudbury, MA: Jones and Bartlett; 2004.
25. Matloff ET. *Cancer Principles and Practice of Oncology: Handbook of Clinical Cancer Genetics*. Philadelphia, PA: Lippincott Williams & Wilkins; 2013.
26. Devita VT, Lawrence TS, Rosenberg SA. *DeVita, Hellman and Rosenberg's Cancer: Principles and Practice of Oncology*. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2014.
27. Adaniel C, Kirchhoff T. Introduction to epidemiology of breast and ovarian cancers. *Ann Oncol*. 2013;24S(8):viii61-viii62.
28. Turnball C, Rahman N. Genetic predisposition to breast cancer: past, present, and future. *Annu Rev Genom Hum Genetics*. 2008;9:321-345.
29. Zhang S, Royer R, Li S, et al. Frequencies of *BRCA1* and *BRCA2* mutations among 1,342 unselected patients with invasive ovarian cancer. *Gynecol Oncol*. 2011;121:352-357.
30. Ramus SJ, Kartsonaki C, Gayther SA, et al. & Consortium of Investigators of Modifiers of *BRCA1/2*. Genetic variation at 9p22.2 and ovarian cancer risk for *BRCA1* and *BRCA2* mutation carriers. *J Natl Cancer Inst.* 2011;103:105-116.
31. Rebbeck TR, Mitra N, Domchek SM, Wan F, Friebel TM, Tran TV, Singer CF. Modification of *BRCA1*-associated breast and ovarian cancer risk by *BRCA1*-interacting genes. *Cancer Res.* 2011;71:5792-5805.
32. Narod SA, Feunteun J, Lynch HT, et al. Familial breast–ovarian cancer locus on chromosome 17q12-q23. *Lancet.* 1991;338:82-83.
33. Wooster R, Neuhausen SL, Mangion J, et al. Localization of a breast cancer susceptibility gene, *BRCA2*, to chromosome 13q12-13. *Science*. 1994;265:2088-2090.
34. Mavaddat N, Peock S, Frost D, et al. Cancer risks for *BRCA1* and *BRCA2* mutation carriers: results from prospective analysis of EMBRACE. *J Natl Cancer Inst.* 2013;105(11):812-822.
35. Stadler ZK, Schrader KA, Vijai J, Robson ME, Offit K. Cancer genomics and inherited risk. *J Clin Oncol*. 2014;32:1-12.

36. National Center for Biotechnology Information. Genetic database. http://www.ncbi.nlm.nih.gov/clinvar/docs/clinsig/. Accessed May 19, 2015.
37. Couch FJ, Nathanson KL, Offit K. Two decades after *BRCA:* setting paradigms in personalized cancer care and prevention. *Science.* 2014:343(6178):1466-1470.
38. Milne RL, Antoniou AC. Genetic modifiers of cancer risk for *BRCA1* and *BRCA2* mutation carriers. *Ann Oncol.* 2011;22(suppl 1):i11-i17.
39. Whittemore AS, Gong G, John EM, et al. Prevalence of *BRCA1* mutation carriers among U.S. non-Hispanic whites. *Cancer Epidemiol Biomarkers Prev.* 2004;13:2078-2083.
40. Nelson-Moeseke AC, Jeter JM, Cui H, et al. An unusual *BRCA* mutation distribution in a high risk cancer genetics clinic. *Familial Cancer.* 2013;12:83-87.
41. Risch HA, McLaughlin JR, Cole DE, et al. Population *BRCA1* and *BRCA2* mutation frequencies and cancer penetrance: a kin-cohort study in Ontario, Canada. *J Natl Cancer Inst.* 2006;98:1694-1706.
42. Ferla R, Calo V, Cascio S, et al. Founder mutations in *BRCA1* and *BRCA2* genes. *Ann Oncol.* 2007;18(suppl 6):vi93-vi98.
43. Goodwin PJ, Phillips K, West DW, et al. Breast cancer prognosis in *BRCA1* and *BRCA2* mutation carriers: an international prospective breast cancer family registry population-based cohort study. *J Clin Oncol*. 2012;30(1):19-26.
44. Bogdanova N, Helbig S, Dörk T. Hereditary breast cancer: ever more pieces to the polygenic puzzle. *Hered Cancer Clin Pract*. 2013;11:12.
45. Howlader N, Noone AM, Krapcho M, et al., eds. *SEER Cancer Statistics Review, 1975–2011*. Bethesda, MD: National Cancer Institute; April 2015. http://seer.cancer.gov/csr/1975_2012/. Accessed May 26, 2015.
46. Ravi A, Bang H, Karsif K, Nori D. Breast cancer in men: prognostic factors, treatment patterns, and outcome. *Am J Men's Health*. 2012; 6:5158.
47. Johansson I, Killander F, Linderholm B, Hedenfalk I. Molecular profiling of male breast cancer: lost in translation? *Int J Biochem Cell Biol*. 2014;53:526-535.
48. Petrucelli N, Daly MB, Feldman GL. *BRCA1* and *BRCA2* hereditary breast and ovarian cancer. *GeneReviews.* September 26, 2013. http://www.ncbi.nlm.nih.gov/books/NBK1247/. Accessed May 19, 2015.
49. Levy-Lahad E, Friedman E. Cancer risks among *BRCA1* and *BRCA2* mutation carriers. *Br J Cancer*. 2007;96:11-15.
50. Nelson HD, Pappas M, Zakher B, et al. Risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer in women: a systematic review to update the U.S. Preventive Services Task Force recommendation. *Ann Intern Med*. 2014;160:255-273.
51. Prucka SK, McIlvried DE, Korf BR. Cancer risk assessment and the genetic counseling process: using hereditary breast and ovarian cancer as an example. *Med Princ Pract*. 2008;17:173-189.
52. National Comprehensive Cancer Network. Version 1.2014. http://www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf. Accessed May 19, 2015.
53. deHoog CL, Porteglis PJ, Stoffers HE. Family history tools for primary care are not ready yet to be implements: a systematic review. *Eur J Gen Pract.* 2014;20:125-133.
54. Moyer VA. Risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer in women: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;160(4):271-281.
55. Laresco L, Viassolo V, Viel A, et al. Performance of BOADICEA and BRCAPRO genetic models and of empirical criteria based on cancer family history for predicting *BRCA* mutation carrier probabilities: a retrospective study in a sample of Italian cancer genetics clinics. *Breast*. 2013;22(6):1130-1135.
56. Mazzola E, Chipman J, Cheng S, Parmigiani G. Recent BRCAPRO upgrades significantly improve calibration. *Cancer Epidemiol Biomarkers Prev.* 2014;23(8):1689-1695.
57. Antoniou AC, Hardy R, Walker L, et al. Predicting the likelihood of carrying a *BRCA1* or *BRCA2* mutation: validation of BOADICEA, BRCAPRO, IBIS, Myriad, and the Mancheester scoring system using data from UK genetics clinics. *J Med Genet*. 2008;45:425-431.
58. Weitzel JN, Lagos VI, Cullinane CA, et al. Limited family structure and *BRCA* gene mutation status in single cases of breast cancer. *JAMA*. 2007;297:2587-2595.
59. Fischer C, Kuchenbacker K, Engel C, et al. Evaluating the performance of the breast cancer genetic risk models BOADICDEA, IBIS, BRCAPRO and Claus for predicting *BRCA1/2* mutation carrier probabilities: a study based on 7352 families from the German Hereditary Breast and Ovarian Cancer Consortium. *J Med Genet*. 2013;50(6):360-367.
60. Millstine D, David P, Pruthi S. Tools of the trade: individualized breast cancer risk assessment. *J Womens Health.* 2014;23(5):434-436.
61. Crispo A, D'Aiuto G, De Marco M, et al. Gail model risk factors: impact of adding an extended family history for breast cancer. *Breast J*. 2008;14:221-227.
62. Passaperuma K, Warner E, Causer PA, et al. Long-term results of screening with magnetic resonance imaging in women with *BRCA* mutations. *Br J Cancer.* 2012;107(1):24-30.
63. Moller P, Stormorken A, Jonsrud C, et al. Survival of patients with *BRCA1*-associated breast cancer diagnosed in an MRI-based surveillance program. *Breast Cancer Res Treat*. 2013;139(1):155-161.
64. Rijnsburger AJ, Obdeijn IM, Kaas R, et al. *BRCA1*-associated breast cancers present differently from *BRCA2*-associated and familial cases: long-term follow-up of the Dutch MRISC Screening Study. *J Clin Oncol.* 2010;28(36):5265-5273.
65. Pijpe A, Andrieu N, Kesminiene A, et al. Exposure to diagnostic radiation and risk for breast cancer among carriers of *BRCA1/2* mutations: retrospective cohort study (GENE-RAD-RISK). *BMJ*. 2012;345:e5660.
66. Balmana J, Diez O, Rubio IT, Cardoso F. *BRCA* in breast: ESMO clinical practice guidelines. *Ann Oncol*. 2011;22(suppl 6):vi31-vi34.
67. Domchek SM, Friebel TM, Singer CF, et al. Association of risk reducing surgery in *BRCA1* or *BRCA2* mutation carriers with cancer risk and mortality. *JAMA.* 2010;304:967-975.
68. Pierce LJ, Phillips KA, Griffith KA, et al. Local therapy in *BRCA1* and *BRCA2* mutation carriers with operable breast cancer: comparison of breast conservation and mastectomy. *Breast Cancer Res Treat*. 2010;121: 389-398.
69. Eisen A, Lubinski J, Klijn J, et al. Breast cancer risk following bilateral oophorectomy in *BRCA1* and *BRCA2* mutation carriers: an international case-control study. *J Clin Oncol*. 2005;23:7491-7496.
70. Kramer JL, Velazquez IA, Chen BE, Rosenberg PS, Struewing JP, Greene MH. Prophylactic oophorectomy reduces breast cancer penetrance during prospective, long-term follow-up of *BRCA1* mutation carriers. *J Clin Oncol*. 2005;23:8629-8635.
71. Finch A, Beiner M, Lubinski J, et al. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a *BRCA1* or *BRCA2* mutation. *JAMA*. 2006;296:185-192.
72. Nazarali S, Narod SA. Tamoxifen for women at high risk of breast cancer. *Breast Cancer*. 2014;6:29-36.
73. Gronwald J, Tung N, Foulkes WD, et al. Tamoxifen and contralateral breast cancer in *BRCA1* and *BRCA2* carriers: an update. *Int J Cancer*. 2006;118:2281-2284.
74. Gulati AP, Domchek SM. The clinical management of *BRCA1* and *BRCA2* mutation carriers. *Curr Oncol Rep*. 2008;10:47-53.
75. Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA*. 2006;295:2727-2741.
76. Phillips KA, Lindeman GJ. Breast cancer prevention for *BRCA1* and *BRCA2* mutation carriers: is there a role for tamoxifen. *Future Oncol*. 2014;10(4):499-502.
77. King MC, Wieand S, Hale K, et al. Tamoxifen and breast cancer incidence among women with inherited mutations in *BRCA1* and *BRCA2*: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. *JAMA.* 2001;286(18):2251-2256.
78. Gaarenstroom KN, van der Hiel B, Tollenaar RA, et al. Efficacy of screening women at high risk of hereditary ovarian cancer: results of an 11-year cohort study. *Int J Gynecol Cancer*. 2006;16(suppl 1):54-59.

79. Oei AL, Massuger LF, Bulten J, Ligtenberg MJ, Hoogerbrugge N, de Hullu JA. Surveillance of women at high risk for hereditary ovarian cancer is inefficient. *Br J Cancer.* 2006;94:814-819.
80. Olivier RI, Lubsen-Brandsma MA, Verhoef S, van Beurden M. CA125 and transvaginal ultrasound monitoring in high-risk women cannot prevent the diagnosis of advanced ovarian cancer. *Gynecol Oncol*. 2006; 100(1):20-26.
81. Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of *BRCA1* or *BRCA2* mutations. *N Engl J Med*. 2002; 346:1616-1622.
82. Kauff ND, Satagopan JM, Robson ME, et al. Risk-reducing salpingo-oophorectomy in women with a *BRCA1* or *BRCA2* mutation. *N Engl J Med*. 2002;346:1609-1615.
83. Domchek SM, Friebel TM, Neuhausen SL, et al. Mortality after bilateral salpingo-oophorectomy in *BRCA1* and *BRCA2* mutation carriers: a prospective cohort study. *Lancet Oncol*. 2006;7:223-229.
84. Finch AP, Lubinski J, Moller P, et al. Impact of oophorectomy on cancer incidence and mortality in women with a *BRCA1* or *BRCA2* mutation. *J Clin Oncol*. 2014;32:1547-1553.
85. Society of Gynecologic Oncologists. Society of Gynecologic Oncologists Clinical Practice Committee: statement on prophylactic salpingo-oophorectomy. *Gynecol Oncol*. 2005;98:179-181.
86. Rebbeck TR, Friebel T, Wagner T, et al. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in *BRCA1* and *BRCA2* mutation carriers: the PROSE Study Group. *J Clin Oncol*. 2005;23:7804-7810.
87. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004;291:1701-1712.
88. Iodice S, Barile M, Rotmensz N, et al. Oral contraceptive use and breast or ovarian cancer risk in *BRCA1/2* carriers: a meta-analysis. *Euro J Cancer.* 2010;46:2275-2284.
89. Friebel TM, Domchek SM, Rebbeck TR. Modifiers of cancer risk in *BRCA1* and *BRCA2* mutation carriers: systematic review and meta-analysis. *J Natl Cancer Inst.* 2014;106(6):1-16.
90. McLaughlin JR, Risch HA, Lubinski J, et al. Reproductive risk factors for ovarian cancer in carriers of *BRCA1* or *BRCA2* mutations: a case-control study. *Lancet Oncol.* 2007;8:26-34.
91. Dolle JM, Daling JR, White E, et al. Risk factors for triple-negative breast cancer in women under the age of 45 years. *Cancer Epidemiol Biomarkers Prev*. 2009;18(4):1157.
92. Kotsopolous J, Lubinski J, Moller P, et al. Timing of oral contraceptive use and the risk of breast cancer in *BRCA1* mutation carriers. *Breast Cancer Res Treat*. 2014;143(3):579-586.
93. Daly MB, Axilbund JE, Bryant E, et al. Genetic/familial high-risk assessment: breast and ovarian. *J Natl Compr Canc Netw.* 2006;4:156-176.
94. Kote-Jarai K, Leongamornlet D, Saunders E, et al. *BRCA2* is a moderate penetrance gene contributing to young-onset prostate cancer: implications for genetic testing in prostate cancer patients. *Br J Cancer*. 2011;105(8):1230-1234.
95. Leongamornlert D, Mahmud N, Tymrakiewicz M, et al. Germline *BRCA1* mutations increase prostate cancer risk. *Br J Cancer*. 2012; 106(10):1697-1701.
96. Edwards SM, Kote-Jarai Z, Meitz J, et al. Two percent of men with early-onset prostate cancer harbor germline mutations in the *BRCA2* gene. *Am J Hum Genet*. 2003;72(1):1-12.
97. Mitra AV, Bancroft EK, Barbachano Y, et al. Targeted prostate cancer screening in men with mutations in *BRCA1* and *BRCA2* detects aggressive prostate cancer: preliminary analysis of the results of the IMPACT study. *BJU Int*. 2011;107(1):28-39.
98. De Nunzio C, Kramer G, Marberger M, et al. The controversial relationship between benign prostatic hyperplasia and prostate cancer: the role of inflammation. *Euro Urol*. 2011;60:106-117.
99. Cossack M., Ghaffary C., Watson P, Snyder C, Lynch H. Aspirin use is associated with lower prostate cancer risk in male carriers of *BRCA* mutations. *J Genet Couns.* 2014;23(2):187-191.
100. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin.* 2016;66(1):7-30.
101. Al-Sukhni W, Aronson M, Gallinger S. Hereditary colorectal cancer syndromes: familial adenomatous polyposis and lynch syndrome. *Surg Clin North Am.* 2008;88(4):819-844.
102. Peltomaki P, Vasen H. Mutations associated with HNPCC predisposition: update of ICG-HNPCC/INSiGHT mutation database. *Dis Markers*. 2004;20(4-5):269-276.
103. Kempers MJ, Kuiper RP, Ockeloen CW, et al. Risk of colorectal and endometrial cancers in *EPCAM* deletion-positive Lynch syndrome: a cohort study. *Lancet Oncol.* 2011;12(1):49-55.
104. Rumilla K, Schowalter KV, Lindor NM, et al. Frequency of deletions of *EPCAM* (*TACSTD1*) in *MSH2*-associated Lynch syndrome cases. *J Mol Diagn.* 2011;13(1):93-99.
105. Boland CR, Goel A. Microsatellite instability in colorectal cancer. *Gastroenterology.* 2010;138(6):2073-2087.
106. Merg A, Howe JR. Genetic conditions associated with intestinal juvenile polyps. *Am J Med Genet C Semin Med Genet*. 2004; 129(1):44-55.
107. Stoffel E, Mukherjee B, Raymond VM, et al. Calculation of risk of colorectal and endometrial cancer among patients with Lynch syndrome. *Gastroenterology.* 2009;137(5):1621-1627.
108. Kastrinos F, Mukherjee B, Tayob N, et al. Risk of pancreatic cancer in families with Lynch syndrome. *JAMA.* 2009;302(16):1790-1795.
109. Vasen HF, Moslein G, Alonso A, et al. Guidelines for the clinical management of Lynch syndrome (HNPCC). *J Med Genet*. 2007; 44(6):353-362.
110. Vasen HF, Mecklin JP, Khan PM, Lynch HT. The International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer (ICG-HNPCC). *Dis Colon Rectum*. 1991;34:424-425.
111. Umar A, Boland CR, Terdiman JP, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst*. 2004;96:261-268.
112. $PREMM_{1,2,6}$ model: prediction model for *MLH1*, *MSH2*, and *MSH6* gene mutations. http://premm.dfci.harvard.edu/. Accessed May 19, 2015.
113. Kastrinos F, Steyerberg EW, Mercado R, et al. The PREMM(1,2,6) model predicts risk of *MLH1*, *MSH2*, and *MSH6* germline mutations based on cancer history. *Gastroenterology*. 2011;140(1):73-81. Erratum in: *Gastroenterology.* 2012;143(5):1399.
114. Balmaña J, Stockwell DH, Steyerberg EW. Prediction of *MLH1* and *MSH2* mutations in Lynch syndrome. *JAMA*. 2006;296:1469-1478.
115. Chen S, Wang W, Lee S, et al. Prediction of germline mutations and cancer risk in the Lynch syndrome. *JAMA.* 2006;296(12):1479-1487.
116. Barnetson RA, Tenesa A, Farrington SM, et al. Identification and survival of carriers of mutations in DNA mismatch-repair genes in colon cancer. *N Engl J Med.* 2006;354(26):2751-2763.
117. Burke W, Petersen G, Lynch P, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. 1. Hereditary nonpolyposis colon cancer. *JAMA*. 1997;277:915–919.
118. National Comprehensive Cancer Network. (2014). NCCN Clinical practice guidelines in oncology: genetic/familial high-risk assessment: colorectal [v.2.2014]. http://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf. Accessed May 19, 2015.
119. Lindor NM, Petersen GM, Hadley DW, et al. Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. *JAMA*. 2006;296:1507-1517.
120. Jarvinen HJ, Aarnio M, Mustonen H, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. *Gastroenterology*. 2000;118:829-834.
121. Lecuru F, Metzger U, Scarabin C, et al. Hysteroscopic findings in women at risk of HNPCC: results of a prospective observational study. *Fam Cancer*. 2007;6:295-299.
122. Renkonen-Sinisalo L, Kivisaari A, Kivisaari L, Sarna S, Jarvinen HJ. Utility of computed tomographic colonography in surveillance for hereditary nonpolyposis colorectal cancer syndrome. *Fam Cancer*. 2007;6:135-140.

123. Schmeler KM, Lynch HT, Chen LM, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. *N Engl J Med.* 2006;354:261-269.
124. Gryfe R. Clinical implications of our advancing knowledge of colorectal cancer genetics: inherited syndromes, prognosis, prevention, screening and therapeutics. *Surg Clin North Am.* 2006; 86(4):787-817.
125. Merg A, Lynch HT, Lynch JF, et al. Hereditary colorectal cancer: part I. *Curr Probl Surg*. 2005;42(5):195-256.
126. Merg A, Lynch HT, Lynch JF, et al. Hereditary colorectal cancer: part II. *Curr Probl Surg*. 2005;42(5):267-333.
127. Bresinger JD, Laken SJ, Muce MC, et al. Variable phenotype of familial adenomatous polyposis in pedigrees with 3′ mutation in the APC gene. *Gut.* 1998;43:548-552.
128. Lipton L, Tomlinson I. The multiple colorectal adenoma phenotype and *MYH*, a base excision repair gene. *Clin Gastroenterol Hepatol*. 2004;2(8):633-638.
129. Sieber OM, Lipton L, Crabtree M, et al. Multiple colorectal adenomas, classic adenomatous polyposis, and germ-line mutations in *MYH*. *N Engl J Med.* 2003;348(9):791-799.
130. Al-Tassan N, Chmiel NH, Maynard J, et al. Inherited variants of *MYH* associated with somatic G:C-T:A mutations in colorectal tumors. *Nat Genet.* 2002;30:227-232.
131. Aretz S, Uhlhaas S, Goergens H, et al. *MUTYH*-associated polyposis: 70 of 71 patients with biallelic mutations present with an attenuated or atypical phenotype. *Int J Cancer*. 2006;119(4):807-814.
132. Sampson JR, Dolwani S, Johes S, et al. Autosomal recessive colorectal adenomatous polyposis due to inherited mutations of *MYH*. *Lancet.* 2003;362(9377):39-41.
133. Grover S, Kastrinos F, Steyerberg EW, et al. Prevalence and phenotypes of *APC* and *MUTYH* mutations in patients with multiple colorectal adenomas. *JAMA.* 2012;308(5):485-492.
134. Theodoratou E, Campbell H, Tenesa A, et al. A large-scale meta-analysis to refine colorectal cancer risk estimates associated with *MUTYH* variants. *Br J Cancer.* 2010;103(12):1875-1884.
135. Ponti G, de Leon P, Pedroni MS, et al. Attenuated familial adenomatous polyposis and Muir-Torre syndrome linked to compound biallelic constitutional *MYH* gene mutations. *Clin Genet*. 2005:68(5): 442-447.
136. Callender GG, Rich TA, Perrier ND. Multiple endocrine neoplasia syndromes. *Surg Clin North Am*. 2008;88:863-895.
137. Yang Y, Hua X. In search of tumor suppressing functions of menin. *Mol Cell Endocrinol*. 2007;265-266:34-41.
138. Thakker RV, Newey PJ, Walls GV, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). *J Clin Endocrinol Metab.* 2012;97(9):2990-3011.
139. Frank-Raue K, Rybicki LA, Erlic Z, et al. Risk profiles and penetrance estimations in multiple endocrine neoplasia type 2A caused by germline *RET* mutations located in exon 10. *Hum Mut.* 2011;32(1): 51-58.
140. Nelen MR, Kremer H, Konings IB, et al. Novel PTEN mutations in patients with Cowden disease: absence of clear genotype–phenotype correlations. *Eur J Hum Genet.* 1999;7:267-273.
141. Schreibman IR, Baker M, Amos C, McGarrity TJ. The hamartomatous polyposis syndromes: a clinical and molecular review. *Am J Gastroenterol*. 2005;100:476-490.
142. Tan MH, Mester J, Peterson C, et al. A clinical scoring system for selection of patients for *PTEN* mutation testing is proposed on the basis of a prospective study of 3042 probands. *Am J Hum Genet.* 2011;88(1): 42-56.
143. Zbuk KM, Eng C. Cancer phenomics: *RET* and *PTEN* as illustrative models. *Nat Rev Cancer.* 2007;7:35-45.
144. Lonser RR, Glenn GM, Walther M, et al. Von Hippel-Lindau disease. *Lancet.* 2003;361:2059-2067.
145. Hes FJ, van der Luijt RB, Lips CJ. Clinical management of von Hippel-Lindau (VHL) disease. *Neth J Med*. 2001;59:225-234.
146. Rosner I, Bratslavsky G, Pinto PA, Linehan WM. The clinical implications of the genetics of renal cell carcinoma. *Urol Oncol*. 2009;27:131-136.
147. Lustbader ED, Williams WR, Bondy ML, Strom S, Strong LC. Segregation analysis of cancer in families of childhood soft-tissue-sarcoma patients. *Am J Hum Genet.* 1992;51:344-356.
148. Hwang SJ, Lozano G, Amos CI, Strong LC. Germline *p53* mutations in a cohort with childhood sarcoma: sex differences in cancer risk. *Am J Hum Genet*. 2003;72:975-983.
149. Li FP, Fraumeni JF Jr. Soft-tissue sarcomas, breast cancer, and other neoplasms: a familial syndrome? *Ann Intern Med*. 1969;71:747-752.
150. Olivier M, Goldgar DE, Sodha N, et al. Li-Fraumeni and related syndromes: correlation between tumor type, family structure, and *TP53* genotype. *Cancer Res.* 2003;63:6643-6650.
151. Gonzalez KD, Noltner KA, Buzin CH, et al. Beyond Li-Fraumeni syndrome: clinical characteristics of families with *p53* germline mutations. *J Clin Oncol.* 2009;27(8):1250-1256.
152. City of Hope, Department of Clinical Cancer Genetics. Community cancer genetics and research training. http://www.infosci.coh.org/ccgp/. Accessed May 19, 2015.
153. Fox Chase Cancer Center. Personalized cancer risk assessment: genetics and genomics in nursing practice. http://www.fccc.edu/healthProfessionals/continuingNursingEducation/index.html. Accessed May 19, 2015.
154. Cincinnati Children's. Genetic education program. http://www.cincinnatichildrens.org/education/clinical/nursing/genetics/default/. May 19, 2015.
155. American Association of Colleges of Nursing. *Essentials of Baccalaureate Education for Professional Nursing Practice.* Washington, DC: Author. http://www.aacn.nche.edu/education-resources/baccessentials08.pdf. May 19, 2015.
156. American Association of Colleges of Nursing. *Essentials of Master's Education in Nursing.* Washington, DC: American Association of Colleges of Nursing; 2011. http://www.aacn.nche.edu/education-resources/MastersEssentials11.pdf. May 19, 2015.
157. Khoury MJ, McBride C, Schully SD, et al. The scientific foundation for personal genomics: recommendations from a National Institutes of Health–Centers for Disease Control and Prevention Multidisciplinary Workshop. *Genet Med.* 2009;11:1-9.
158. Fernandez CV, Bouffet E, Malkin D, et al. Attitudes of parents toward the return of targeted and incidental genomic research findings in children. *Genet Med.* 2014;16:633-640.
159. Hitch K, Joseph G, Guiltinan J, Kianmahd J, Youngblom J, Blanco A. Lynch syndrome: patients' views of and preferences for return of research results following hole exome sequencing. *J Genetic Couns.* 2013:23:539-551.

APPENDIX 6-A

Cancer Genetics Resources: An Organizational Guide

Category	Organization	Description/Materials	Contact Information
Cancer genetics	National Cancer Institute	The official website of the National Cancer Institute provides a variety of resources such as the following: • Cancer facts • Cancer prevention, genetics, and causes • Cancer literature • Clinical trials • Research programs • Cancer dictionary • Educational resources	www.cancer.gov
	Centers for Disease Control and Prevention	Office of Genomics and Disease Prevention Provides information about human genomic discoveries	www.cdc.gov/genomics
	Gene Clinics	Genetics Web-based information resource on genetic syndromes, genetic testing, and clinical resources	www.geneclinics.org
	OMIM: Online Mendelian Inheritance in Man	An online catalog of information on human genes and genetic disorders	www.ncbi.nlm.nih.gov/sites/entrez?db=omim
	Physician's Database Query (PDQ)	PDQ cancer information summaries in genetics	www.cancer.gov/cancerinfo/pdq/genetics
	U.S. National Library of Medicine (NLM), Genetics Home Reference	"The Genetics Home Reference: Your Guide to Understanding Genetic Conditions"; intended to enhance understanding of genetic conditions; includes a glossary of genetic terms and resources and patient support	http://ghr.nlm.nih.gov
	Genetic Alliance	The leading support, education, and advocacy organization in the United States for all those living with genetic conditions	www.geneticalliance.org
	National Society of Genetic Counselors (NSGC)	Provides information on genetic counseling; has a family tree link, lists of conferences, resources, publications, consumer information, career information, news, and a link to the *Journal of Genetic Counseling* for members	www.nsgc.org
	American College of Medical Genetics (ACMG)	The U.S. organization that certifies medical geneticists to practice. In addition to the usual educational content, it has sections on the *Standards and Guidelines for Clinical Genetics Laboratories*, the manual for reimbursement of genetic services, and a link to the journal *Genetics in Medicine*.	www.acmg.net
	American Society of Human Genetics (ASHG)	The largest organization of human genetics researchers and clinicians. In addition to research, it is involved in applications of genetics to health care, health policy, training, and educating the public.	www.ashg.org

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APPENDIX 6-A

Cancer Genetics Resources: An Organizational Guide (*continued*)

Category	Organization	Description/Materials	Contact Information
	Directory of Cancer Genetics Professionals	Lists professionals who provide services related to cancer genetics. These genetic counselors, nurses, and physicians have applied to and been accepted into the directory based on published eligibility criteria linked to the website. One may search by type of cancer, cancer syndrome, or geographic location for a provider.	www.cancer.gov/search/genetics_services
	National Human Genome Research Institute (NHGRI)	Provides information on legislation for all sites related to genetic privacy, discrimination for insurance, and other genetics-related issues	www.genome.gov/PolicyEthics/LegDatabase/pubMapSearch.cfm
	Genes and Disease	A collection of articles that discuss genes and diseases that they cause	www.ncbi.nlm.nih.gov/disease
Resources for genetic nursing practice	American Society of Clinical Oncology	The world's leading professional organization representing physicians who treat people with cancer. *Policy Statement Update: Genetic Testing for Cancer Susceptibility*	www.asco.org
	International Society of Nurses in Genetics	Statement on the scope and standards of genetics clinical nursing practice Position statements: • Access to genomic health care: the role of the nurse • Privacy and confidentiality of genetic information: the role of the nurse • Genetic counseling for vulnerable populations: the role of nursing	www.isong.org
	National Coalition of Health Care Professional Education in Genetics	Recommendations of core competencies in genetics for all health professionals continue to be available through a collaboration with the Jackson Laboratory	www.nchpeg.org
	Oncology Nursing Society	A professional organization of nurses and other healthcare providers dedicated to excellence in patient care, education, research, and administration in oncology nursing. *Position Statement: Oncology Nursing: The Application of Cancer Genetics and Genomics Throughout the Oncology Care Continuum*	www.ons.org/about-ons/ons-position-statements/education-certification-and-role-delineation/oncology-nursing