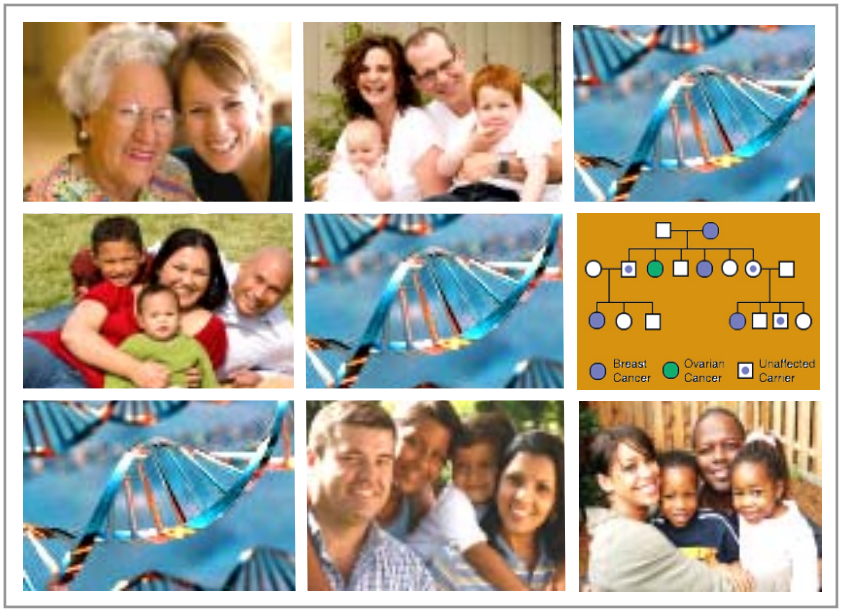
CANCER GENOMICS BEST PRACTICES

for Connecticut Healthcare Providers



Hereditary Breast and Ovarian Cancer Syndrome

Lynch Syndrome

CONNECTICUT DEPARTMENT OF PUBLIC HEALTH
2012

CANCER GENOMICS BEST PRACTICES

for Connecticut Healthcare Providers

The Connecticut Department of Public Health encourages the adoption by clinicians of national guidelines for genetic counseling and testing concerning Lynch syndrome and BRCA-related hereditary breast and ovarian cancer syndrome.

These recommendations reflect increasing scientific evidence supporting the health benefits of using family health history and genetic testing to guide clinical assessments. This initiative is also consistent with the U.S. Department of Health and Human Services' Healthy People 2020 objectives that support appropriate use of genetic counseling and testing for these two syndromes.

U.S. Preventive Services Task Force (USPSTF) Recommendation Statement, 2005*

The USPSTF recommends that women whose family history is associated with an increased risk for deleterious mutations in *BRCA1* or *BRCA2* genes be referred for genetic counseling and evaluation for *BRCA* testing.

The USPSTF recommends against routine referral for genetic counseling or routine breast cancer susceptibility gene (*BRCA*) testing for women whose family history is not associated with an increased risk for deleterious mutations in breast cancer susceptibility gene 1 (*BRCA1*) or breast cancer susceptibility gene 2 (*BRCA2*).

* U.S. Preventive Services Task Force. Genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility: recommendation statement. *Annals of Internal Medicine* 2005;143:355-61.

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group Recommendation Statement, 2009*

The EGAPP Working Group found sufficient evidence to recommend offering genetic testing for Lynch syndrome to individuals with newly diagnosed colorectal cancer to reduce morbidity and mortality in relatives.

We [EGAPP] found insufficient evidence to recommend a specific genetic testing strategy among the several examined.

* Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: Genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. *Genetics in Medicine* 2009; 11:35-41.

Jewel Mullen, MD, MPH, MPA, Commissioner

Developed by the Connecticut Department of Public Health's Genomics Office in partnership with the Connecticut Tumor Registry, and funded through a Healthy People 2020 Action Project grant.

Connecticut Department of Public Health
410 Capitol Avenue, Hartford, CT 06106
(860) 509-8070
www.ct.gov/dph

Connecticut Department of Public Health, Healthy People 2020 Action Project

Cancer Genomics Best Practices
for Hereditary Breast and Ovarian Cancer and Lynch Syndromes

CONTENTS

A. Hereditary Breast and Ovarian Cancer Syndrome (HBOC) Documents

- Potential Cases of HBOC Syndrome in Connecticut, 2008-2009
- Fact Sheet
- Evidence-based Clinical Practice Guidelines Supporting Genetic Susceptibility Testing for HBOC Syndrome
- U.S. Preventive Services Task Force. *Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility: Recommendation Statement*
- NCCN Guidelines™ Version 1.2011, Hereditary Breast and Ovarian Cancer Syndrome

B. Lynch Syndrome Documents

- Potential Cases of Lynch Syndrome in Connecticut, 2008-2009
- Fact Sheet
- Evidence-based Clinical Practice Guidelines Supporting Genetic Susceptibility Testing for Lynch Syndrome
- Recommendations from the EGAPP Working Group: *Genetic Testing Strategies in Newly Diagnosed Individuals with Colorectal Cancer Aimed at Reducing Morbidity and Mortality from Lynch Syndrome in Relatives*

C. Resources for Health Professionals and Consumers

- Cancer Genetic Counselors in Connecticut
- Handout: Information for Patients and their Families
- Connecticut's Family Health History Pocket Guide
- Additional Resources for Health Professionals and Consumers
- NEW American College of Surgeons Cancer Program Standard 2.3: Risk Assessment and Genetic Counseling

Connecticut

Potential Cases of Hereditary Breast and Ovarian Cancer Syndrome 2008-2009

Cancer site	Number of diagnosed cancers Connecticut
Female breast (≤ 50 yrs of age)	1,127
Ovary (All ages)	533
Male breast	47
Multiple primary sites* (Breast-breast or breast-ovary)	2,085

Source: Connecticut Tumor Registry. * The most recent cancer diagnosis was in 2008-2009.

This table contains the number of cancers diagnosed during 2008-2009 in Connecticut patients who could be predisposed to hereditary breast and ovarian cancer syndrome (HBOC).

WHY THESE DATA ARE IMPORTANT FOR YOU TO KNOW

HBOC is a collective term that describes genetic susceptibility to breast and/or ovarian cancer. Most HBOC cases are attributed to the tumor suppressor genes *BRCA1* and *BRCA2*. HBOC accounts for approximately 5-10% of all breast cancer diagnoses and 10-15% of all ovarian cancer diagnoses.

A woman with HBOC syndrome has an increased risk of certain cancers.

- Up to 80% risk of breast cancer (compared to 12-13% in the general population)
- Up to 60% risk of ovarian cancer (compared to 1-2% in the general population)
- 40% risk of a second primary breast cancer within 10 years of first diagnosis

Patients with any of the following diagnoses might be predisposed to HBOC due to *BRCA1* or *BRCA2* mutations.

- Early onset female breast cancer (diagnosed at or before 50 years of age)
- Ovarian cancer (diagnosed at any age)
- Male breast cancer
- Two or more of any combination of breast and/or ovarian cancers in the same patient

Patients with any of the above diagnoses should be considered for a formal risk assessment and genetic counseling and/or testing.

- Refer patients to a health care provider who is suitably trained in cancer genetics.
- Individuals with breast or ovarian cancer who are diagnosed with HBOC may have a higher risk for developing future cancers and may benefit from closer monitoring or special medical management.
- Family members of these individuals also may be affected.

This report was developed by the Connecticut Department of Public Health's Genomics Office in partnership with the Connecticut Tumor Registry, and was funded through a Healthy People 2020 Action Project grant.

Connecticut Department of Public Health
410 Capitol Avenue, Hartford, CT 06106
(860) 509-8070

January 2012

Hereditary Breast and Ovarian Cancer Syndrome

Fact Sheet for Connecticut Healthcare Professionals

What is Hereditary Breast and Ovarian Cancer (HBOC) syndrome?
HBOC syndrome is a hereditary cancer predisposition condition usually caused by mutations in the *BRCA1* and *BRCA2* (breast cancer susceptibility genes 1 and 2). *BRCA1* and *BRCA2* belong to a class of genes known as tumor suppressors. In normal cells, *BRCA1* and *BRCA2* help ensure the stability of the cell's genetic material (DNA) and help prevent uncontrolled cell growth.

Facts about HBOC syndrome

- Approximately 5%-10% of breast cancer patients have HBOC syndrome.
- Approximately 10%-15% of ovarian cancer patients have HBOC syndrome.
- Women who inherit abnormal *BRCA1* and/or *BRCA2* genes have a 35%-80% risk of being diagnosed with breast cancer during their lifetimes, compared to a 12%-13% chance for women in the general population.
- Women who inherit abnormal *BRCA1* and/or *BRCA2* genes have a 40%-60% risk of being diagnosed with ovarian cancer during their lifetimes, compared to a 1%-2% chance for women in the general population. Although ovarian cancer is less common than breast cancer, it is more often fatal.
- Women with a harmful *BRCA* mutation are more likely than non-carriers to be diagnosed with cancer before age 50.
- Men with harmful *BRCA1* and/or *BRCA2* mutations have a 5%-10% risk of being diagnosed with breast cancer, compared to a 0.1% chance for men in the general population.

How common are *BRCA1* and *BRCA2* mutations?

- In the general population, between 1 in 300 and 1 in 800 individuals carries a *BRCA1* or *BRCA2* mutation.
- For individuals of Ashkenazi (Eastern European) Jewish ancestry, 1 in 40 individuals carries a *BRCA1* or *BRCA2* mutation.

Who is most likely to have a *BRCA1* or *BRCA2* mutation?
The likelihood is highest in families with a history of multiple cases of breast cancer, cases of both breast and ovarian cancer, one or more family members with two primary cancers (original tumors that develop at different sites in the body), or Ashkenazi Jewish ancestry. However, not every woman in such families carries a harmful *BRCA1* or *BRCA2* mutation, and not every cancer in such families is linked to a harmful mutation in one of these genes but instead may be the result of a sporadic mutation. Furthermore, not every woman who has a harmful *BRCA1* or *BRCA2* mutation will develop breast and/or ovarian cancer.

Specific indications for genetic counseling and testing vary among professional organizations. Guidelines are not a substitute for clinical judgment. Not all clinical scenarios can be anticipated, such as when there is a limited family structure or family medical history.

Why is genetic counseling important?
Genetic counseling helps people better understand their risk for hereditary cancer in order to make informed decisions about genetic testing and follow-up care.

Developed by the Connecticut Department of Public Health's Genomics Office in partnership with the Connecticut Tumor Registry, and funded through a Healthy People 2020 Action Project grant.

Connecticut Department of Public Health
410 Capitol Avenue, Hartford, CT 06106
(860) 509-8070 *www.ct.gov/dph*

What does genetic counseling entail?

Genetic counseling is a process that encompasses the following services:

- Reviewing an individual's personal and detailed family medical history
- Assessing and explaining risk for hereditary cancers and the chance of finding a mutation through genetic testing
- Discussing the benefits, limitations, and other possible consequences of genetic testing
- Outlining medical implications of a positive or a negative test result
- Determining which family member is most appropriate to begin the genetic testing process in a family
- Interpreting genetic test results and explaining what they mean for individuals and their relatives
- Providing referrals to experts for follow-up screening and risk management
- Providing referrals to support resources and research opportunities (including research on genetic testing, screening, treatment, etc.)
- Discussing risks and medical management options with a patient's other health care provider(s)
- Addressing common concerns about the privacy and confidentiality of personal genetic information

What are some of the benefits of genetic testing for breast and ovarian cancer risk?

- A positive test result can bring relief from uncertainty and allow people to make informed decisions about their futures. They can take steps to reduce their cancer risk through increased surveillance or other medical and lifestyle choices.
- A positive test result may help to explain why individuals or family members had cancer in the past, and, should they choose to share test results, may provide their family members with useful information.
- Those who have a positive test result may be able to participate in medical research that could, in the long run, help reduce deaths from breast cancer.
- A negative test result may provide a sense of relief and preclude the need for special preventive checkups, tests, or surgeries.

What are the disadvantages of genetic testing?

Test results may affect a person's emotions, family relationships, finances, privacy, and medical choices.

- A positive result may make a person feel anxious, angry, or depressed. Medical treatments, such as surgery to try to prevent the cancer, could have serious, long-term implications and uncertain effectiveness.
- A negative result may make a person feel guilty because they escaped a disease that affected a loved one. They may also get a false sense of security that they have no chance of getting cancer, when, in fact, their cancer risk is the same as that of the general population.
- Because genetic testing can reveal information about more than one family member, the emotions caused by the results can create tension within families. The results also can affect personal choices, such as marriage and childbearing.
- Privacy and confidentiality of genetic test results are additional potential concerns. There is no guarantee that a person's test results will remain private.
- Genetic testing can be expensive, costing about $300 to $4,000, depending on the extent of testing. Although many insurance plans cover the cost of the testing for women at high risk, coverage is unlikely for women not considered to be at high risk.

Evidence-based Practice Guidelines Supporting Genetic Susceptibility Testing for Hereditary Breast and Ovarian Cancer Syndrome

Individuals who meet the following criteria should be suspected as having HBOC syndrome and referral to genetic counseling and testing should be considered. Criteria have been adapted from the U.S. Preventive Services Task Force Clinical Guidelines[1] and the National Comprehensive Cancer Network (NCCN) Practice Guidelines[2] (with permission from NCCN.)

Women without a personal history of breast or ovarian cancer and any of the following:[1]

Three or more close relatives* on the same side of the family with breast cancer regardless of age at diagnosis

Two close relatives* on the same side of the family with any of the following:

- Ovarian cancer‡ regardless of age at diagnosis
- Breast cancer in two 1st-degree relatives, one of whom was diagnosed at age 50 or younger
- Breast cancer in one relative and ovarian cancer‡ in another relative

One close relative* with any of the following:

- Male breast cancer
- Bilateral breast cancer in a 1st degree relative
- Both breast and ovarian cancer‡ regardless of age at diagnosis
- Known deleterious *BRCA1* or *BRCA2* mutation

Of Ashkenazi (Eastern European) Jewish ancestry with any of the following:

- Two 2nd-degree relatives on same side of the family with breast or ovarian cancer‡
- One 1st-degree relative with breast or ovarian cancer‡

Men with any of the following:[2]

- A personal history of breast cancer
- One close† relative with a known deleterious *BRCA1* or *BRCA2* mutation

Women with a personal history of breast cancer and any of the following:[2]

Breast cancer diagnosed at age 45 years or younger

Breast cancer diagnosed at age 50 years or younger and any of the following:

- At least one close relative† with breast cancer diagnosed at age 50 years or younger
- At least one close relative† with ovarian cancer‡ at any age
- Two primary breast cancers with first primary diagnosed at age 50 years or younger

Developed by the Connecticut Department of Public Health's Genomics Office in partnership with the Connecticut Tumor Registry, and funded through a Healthy People 2020 Action Project grant.

Connecticut Department of Public Health
410 Capitol Avenue, Hartford, CT 06106
(860) 509-8070 *www.ct.gov/dph*

- Limited family history (<2 close female relatives† or <2 female relatives surviving beyond 45 years)

Breast cancer diagnosed at age 60 years or younger and is triple negative (cancer cells test negative for estrogen receptors, progesterone receptors, and human epidermal growth factor receptors)

Breast cancer diagnosed at any age with any of the following:

- Two close relatives† on the same side of the family with breast and/or ovarian cancer‡ at any age
- One close male relative† with breast cancer
- One close relative† with a known deleterious *BRCA1* or *BRCA2* mutation
- Two close relatives† on the same side of the family with pancreatic cancer at any age
- Of Ashkenazi Jewish ancestry or other ethnic descent associated with deleterious BRCA mutations (for example, Icelandic, Dutch, Swedish, or Hungarian)

Women with a personal history of ovarian cancer[2]

Women with a personal history of pancreatic cancer with 2 close relatives† on the same side of the family with breast cancer, ovarian cancer, ‡ and/or pancreatic cancer at any age.[2]

---

* Close relative = 1st or 2nd degree blood relative

† Close relative = 1st, 2nd, or 3rd degree blood relative

1st degree relative includes parent, sibling, or child

2nd degree relative includes aunt, uncle, niece, nephew, grandparent, grandchild, or half-sibling

3rd degree relative includes first cousin, great grandparent, great-aunt, great-uncle, or great-grandchildren

‡ Ovarian cancer also includes fallopian tube cancer and primary peritoneal cancer

REFERENCES

1. U.S. Preventive Services Task Force. Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: recommendation statement. Ann Intern Med. 2005;143:355-361.

2. National Comprehensive Cancer Network. The NCCN 1.2011 clinical practice guidelines in oncology genetic/familial high-risk assessment: breast and ovarian. Available at: http://www.nccn.org. Accessed August 18, 2011. Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Genetic/Familial High-Risk Assessment: Breast and Ovarian V.1.2011. © 2010 National Comprehensive Cancer Network, Inc. [NCCN guidelines are updated periodically, so a more recent version may be available.]

Genetic Risk Assessment and *BRCA* Mutation Testing for Breast and Ovarian Cancer Susceptibility: Recommendation Statement

U.S. Preventive Services Task Force*

This statement summarizes the U.S. Preventive Services Task Force (USPSTF) recommendations on genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility, along with the supporting scientific evidence. The complete information on which this statement is based, including evidence tables and references, is included in the evidence synthesis available through the USPSTF Web site (www.preventiveservices.ahrq.gov). The recommendation is also posted on the Web site of the National Guideline Clearinghouse (www.guideline.gov).

Ann Intern Med. 2005;143:355-361. www.annals.org

For author affiliation, see end of text.

Individuals who wish to cite this recommendation statement should use the following format: U.S. Preventive Services Task Force. Genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility. Ann Intern Med. 2005;143:355-61.

*For a list of the members of the U.S. Preventive Services Task Force, see the Appendix.

SUMMARY OF RECOMMENDATIONS

The U.S. Preventive Services Task Force (USPSTF) recommends against routine referral for genetic counseling or routine breast cancer susceptibility gene (*BRCA*) testing for women whose family history is not associated with an increased risk for deleterious mutations in breast cancer susceptibility gene 1 (*BRCA1*) or breast cancer susceptibility gene 2 *(BRCA2).*

This is a **grade D recommendation**. (See **Appendix Table 1** for a description of the USPSTF classification of recommendations.)

The USPSTF found fair evidence that women without certain specific family history patterns, termed here "increased-risk family history" (see Clinical Considerations for a definition), *have a low risk for developing breast or ovarian cancer associated with* BRCA1 *or* BRCA2 *mutations. Thus, any benefit to routine screening of these women for* BRCA1 *or* BRCA2 *mutations, or routine referral for genetic counseling, would be small or zero.*

The USPSTF found fair evidence regarding important adverse ethical, legal, and social consequences that could result from routine referral and testing of these women. Interventions such as prophylactic surgery, chemoprevention, or intensive screening have known harms. The USPSTF estimated that the magnitude of these potential harms is small or greater.

The USPSTF concluded that the potential harms of routine referral for genetic counseling or BRCA *testing in these women outweigh the benefits.* (See **Appendix Table 2** for a description of the USPSTF classification of levels of evidence.)

The USPSTF recommends that women whose family history is associated with an increased risk for deleterious mutations in *BRCA1* or *BRCA2* genes be referred for genetic counseling and evaluation for *BRCA* testing.

This is a **grade B recommendation.**

The USPSTF found fair evidence that women with certain specific family history patterns (increased-risk family history) have an increased risk for developing breast or ovarian cancer associated with BRCA1 *or* BRCA2 *mutations. The USPSTF determined that these women would benefit from genetic counseling that allows informed decision making about testing and further prophylactic treatment. This counseling should be done by suitably trained health care providers. There is insufficient evidence to determine the benefits of chemoprevention or intensive screening in improving health outcomes in these women if they test positive for deleterious* BRCA1 *or* BRCA2 *mutations. However, there is fair evidence that prophylactic surgery for these women significantly decreases breast and ovarian cancer incidence. Thus, the potential benefits of referral and discussion of testing and prophylactic treatment for these women may be substantial.*

The USPSTF also found insufficient evidence regarding important adverse ethical, legal, and social consequences that could result from referral and testing of high-risk women.

See also:

Print
Editorial comment. 388
Related article. 362
Summary for Patients. I-47

Web-Only
Conversion of tables into slides

Prophylactic surgery is associated with known harms. The USPSTF estimated that the magnitude of these potential harms is small.

The USPSTF concluded that the benefits of referring women with an increased-risk family history to suitably trained health care providers outweigh the harms.

CLINICAL CONSIDERATIONS

These recommendations apply to women who have not received a diagnosis of breast or ovarian cancer. They do not apply to women with a family history of breast or ovarian cancer that includes a relative with a *known* deleterious mutation in *BRCA1* or *BRCA2* genes; these women should be referred for genetic counseling. These recommendations do not apply to men.

Although there currently are no standardized referral criteria, women with an increased-risk family history should be considered for genetic counseling to further evaluate their potential risks.

Certain specific family history patterns are associated with an increased risk for deleterious mutations in the *BRCA1* or *BRCA2* gene. Both maternal and paternal family histories are important. For non–Ashkenazi Jewish women, these patterns include 2 first-degree relatives with breast cancer, 1 of whom received the diagnosis at age 50 years or younger; a combination of 3 or more first- or second-degree relatives with breast cancer regardless of age at diagnosis; a combination of both breast and ovarian cancer among first- and second- degree relatives; a first-degree relative with bilateral breast cancer; a combination of 2 or more first- or second-degree relatives with ovarian cancer regardless of age at diagnosis; a first- or second-degree relative with both breast and ovarian cancer at any age; and a history of breast cancer in a male relative.

For women of Ashkenazi Jewish heritage, an increased-risk family history includes any first-degree relative (or 2 second-degree relatives on the same side of the family) with breast or ovarian cancer.

About 2% of adult women in the general population have an increased-risk family history as defined here. Women with none of these family history patterns have a low probability of having a deleterious mutation in *BRCA1* or *BRCA2* genes.

Computational tools are available to predict the risk for clinically important *BRCA* mutations (that is, *BRCA* mutations associated with the presence of breast cancer, ovarian cancer, or both), but these tools have not been verified in the general population. There is no empirical evidence concerning the level of risk for a *BRCA* mutation that merits referral for genetic counseling.

Not all women with a potentially deleterious *BRCA* mutation will develop breast or ovarian cancer. In a woman who has a clinically important *BRCA* mutation, the probability of developing breast or ovarian cancer by age 70 years is estimated to be 35% to 84% for breast cancer and 10% to 50% for ovarian cancer.

Appropriate genetic counseling helps women make informed decisions, can improve their knowledge and perception of absolute risk for breast and ovarian cancer, and can often reduce anxiety. Genetic counseling includes elements of counseling; risk assessment; pedigree analysis; and, in some cases, recommendations for testing for *BRCA* mutations in affected family members, the presenting patient, or both. It is best delivered by a suitably trained health care provider.

A *BRCA* test is typically ordered by a physician. When done in concert with genetic counseling, the test assures the linkage of testing with appropriate management decisions. Genetic testing may lead to potential adverse ethical, legal, and social consequences, such as insurance and employment discrimination; these issues should be discussed in the context of genetic counseling and evaluation for testing.

Among women with *BRCA1* or *BRCA2* mutations, prophylactic mastectomy or oophorectomy decreases the incidence of breast and ovarian cancer; there is inadequate evidence for mortality benefits. Chemoprevention with selective estrogen receptor modulators may decrease incidence of estrogen receptor–positive breast cancer; however, it is also associated with adverse effects, such as pulmonary embolism, deep venous thrombosis, and endometrial cancer. Most breast cancer associated with *BRCA1* mutations is estrogen receptor–negative and thus is not prevented by tamoxifen. Intensive screening with mammography has poor sensitivity, and there is no evidence of benefit of intensive screening for women with *BRCA1* or *BRCA2* gene mutations. Magnetic resonance imaging (MRI) may detect more cases of cancer, but the effect on mortality is not clear.

Women with an increased-risk family history are at risk not only for deleterious *BRCA1* or *BRCA2* mutations but potentially for other unknown mutations as well. Women with an increased-risk family history who have negative results on tests for *BRCA1* and *BRCA2* mutations may also benefit from surgical prophylaxis.

The USPSTF has made recommendations on mammography screening for breast cancer, screening for ovarian cancer, and chemoprevention of breast cancer, which can be accessed at www.preventiveservices.ahrq.gov.

DISCUSSION

Breast and ovarian cancer are associated with a family history of these conditions. Approximately 5% to 10% of women with breast cancer have a mother or sister with breast cancer, and up to 20% have a first-degree or a second-degree relative with breast cancer (1–6). Germline mutations in 2 genes, *BRCA1* and *BRCA2*, have been associated with an increased risk for breast cancer and ovarian cancer (7, 8). Specific *BRCA* mutations (founder mu-

tations) are clustered among certain ethnic groups, such as Ashkenazi Jews, and among families in the Netherlands, Iceland, and Sweden (1).

Several characteristics are associated with an increased likelihood of *BRCA* mutations (1, 9–12). These include breast cancer diagnosed at an early age, bilateral breast cancer, history of both breast and ovarian cancer, presence of breast cancer in 1 or more male family members, multiple cases of breast cancer in the family, both breast and ovarian cancer in the family, 1 or more family members with 2 primary cases of cancer, and Ashkenazi Jewish background. No direct measures of the prevalence of clinically important *BRCA1* or *BRCA2* mutations in the general, non-Jewish U.S. population have been published; however, models have estimated it to be about 1 in 300 to 500 (13–16). Prevalence estimates in a large study of individuals from referral populations with various levels of family history ranged from 3.9% (no breast cancer diagnosed in relatives <50 years of age and no ovarian cancer) to 16.4% (breast cancer diagnosed in a relative <50 years of age and ovarian cancer diagnosed at any age) (17).

Penetrance is the probability of developing breast or ovarian cancer in women who have a *BRCA1* or *BRCA2* mutation. Published reports of penetrance describe estimates of *BRCA1* and *BRCA2* mutations ranging from 35% to 84% for breast cancer and 10% to 50% for ovarian cancer, calculated to age 70 years, for non–Ashkenazi Jewish women or those unselected for ethnicity (1, 13, 14, 18–22). Among Ashkenazi Jewish women, penetrance estimates range from 26% to 81% for breast cancer and 10% to 46% for ovarian cancer (1, 23–29). Estimates are higher for relatives of women with cancer diagnosed at younger ages, for women from families with greater numbers of affected relatives (when based on data from families selected for breast and ovarian cancer), and when certain methods of analysis are used.

A systematic review of the evidence found no population-based randomized, controlled trials of risk assessment and *BRCA* mutation testing using the outcomes of incidence of breast and ovarian cancer or cause-specific mortality (1). The USPSTF therefore examined the chain of evidence for accuracy of risk assessment tools, efficacy of preventive interventions, and the harms of screening and interventions.

Although several tools to predict risk for deleterious *BRCA* mutations have been developed from data on previously tested women, no studies of their effectiveness in a primary care screening population are available (30). These risk tools include the Myriad Genetic Laboratories model, the Couch model, BRCAPRO, and the Tyrer model (1). Much of the data used to develop the models are from women with existing cancer, and their applicability to asymptomatic, cancer-free women in the general population is unknown. Three tools have been developed to guide primary care clinicians in assessing risk and guiding referral: the Family History Risk Assessment Tool (FHAT), the Manchester scoring system, and the Risk Assessment in Genetics (RAGs) tool (31). The sensitivity and specificity of FHAT for a clinically important *BRCA1* or *BRCA2* mutation were 94% and 51%, respectively. The Manchester scoring system was developed in the United Kingdom to predict deleterious *BRCA1* or *BRCA2* mutations at the 10% likelihood level and had an 87% sensitivity and a 66% specificity (32). The RAGs tool, a computer program designed to support assessment and management of family breast and ovarian cancer in primary care settings (33), is used to assign patients to categories of low risk (<10%), moderate risk (10% to 25%), and high risk (>25%). Primary care clinicians can then manage recommendations of reassurance, referral to a breast clinic, or referral to a geneticist on the basis of the patient's respective risk categories (34).

The interventions that can be offered to a woman with a deleterious *BRCA1* or *BRCA2* mutation or other increased risk for hereditary breast cancer include intensive screening, chemoprevention, prophylactic mastectomy or oophorectomy, or a combination. Overall, evidence on the efficacy of intensive surveillance of *BRCA1* and *BRCA2* carriers to reduce morbidity or mortality is insufficient. Recent descriptive studies report increased risk for interval cancer (cancer occurring between mammograms) in *BRCA*–positive patients with and without previous cancer who were receiving annual mammographic screening. This indicates that annual mammography may miss aggressive cancer in carriers of the *BRCA* mutation (1).

Good evidence shows that MRI has higher sensitivity for detecting breast cancer among women with a *BRCA1* or *BRCA2* mutation than does mammography, clinical breast examination, or ultrasonography. One study compared these screening methods in 236 Canadian women 25 to 65 years of age who had *BRCA1* or *BRCA*2 mutations (35). The women underwent 1 to 3 annual screening examinations, including MRI, mammography, and ultrasonography, and received clinical breast examinations every 6 months. The researchers found that MRI was more sensitive for detecting breast cancer (sensitivity, 77%; specificity, 95.4%) than mammography (sensitivity, 36%; specificity, 99.8%), ultrasonography (sensitivity, 33%; specificity, 96%), or clinical breast examination alone (sensitivity, 9%; specificity, 99.3%). However, use of MRI, ultrasonography, and mammography in combination had the highest sensitivity, 95%. The effect of this increased detection on morbidity and mortality remains unclear. Expert groups recommend intensive screening for breast cancer in patients with the *BRCA* mutation (36).

The evidence is also insufficient to determine the morbidity and mortality effects of intensive screening for ovarian cancer among women with *BRCA1* or *BRCA2* mutations. One study in which 1610 women with a family history of ovarian cancer were screened with transvaginal ultrasonography showed a high rate of false-positive results

(only 3 of 61 women with abnormal scans had ovarian cancer) (37).

Good-quality evidence from 4 randomized, controlled trials shows that prophylactic tamoxifen reduces the risk for estrogen receptor–positive breast cancer in women without previous breast cancer (38, 39). A meta-analysis of these trials showed a relative risk for total breast cancer of 0.62 (95% CI, 0.46 to 0.83) (1). Further analysis of the largest of these trials showed a possible reduction in breast cancer incidence for women with *BRCA2* mutations but not those with *BRCA1* mutations, possibly because women with *BRCA1* mutations had predominantly estrogen receptor–negative tumors. Conclusions are difficult to draw because of the small number of breast cancer cases in this analysis (40).

Fair-quality evidence is available on the effectiveness of prophylactic surgery to prevent breast and ovarian cancer. Cohort studies of prophylactic surgery have several methodologic limitations that should be considered when interpreting and generalizing their results, such as selection bias, retrospective study design, lack of a control group for estimation of benefit-attributable outcome in the untreated group, and inability to define risk reduction attributable to mastectomy in patients electing to have both mastectomy and oophorectomy (41). Four published studies (2 of fair quality and 2 that did not meet USPSTF quality criteria) of prophylactic bilateral mastectomy in high-risk women show a consistent 85% to 100% reduction in risk for breast cancer despite differences in study designs and comparison groups (for example, sisters [42], matched controls [43], a surveillance group [44], and penetrance models [45]). Four studies of prophylactic oophorectomy reported reduced risks for ovarian and breast cancer (46–49), although the number of cases was small and the confidence intervals for the only prospective study crossed 1.0 for both outcomes (50). Overall, oophorectomy reduced ovarian cancer risk by 85% to 100% and reduced breast cancer risk by 53% to 68%.

No studies have described cancer incidence or mortality outcomes associated with genetic counseling, although 10 fair- to good-quality randomized, controlled trials reported psychological and behavioral outcomes (1). These studies examined the impact of genetic counseling on worrying about breast cancer, anxiety, depression, perception of cancer risk, and intention to participate in genetic testing. Studies were conducted in highly selected samples of women, and results may not be generalizable to a screening population. Five of 7 trials showed that breast cancer worry decreased after genetic counseling, and 2 studies showed no significant effect (1). Three studies reported decreased anxiety after genetic counseling, and 3 reported no significant effect. One study reported decreased depression after genetic counseling, and 4 found no significant effect (1). Results of a meta-analysis showed that genetic counseling significantly decreased generalized anxiety, although the reduction in psychological distress was not significant (51). There is poor evidence (conflicting studies) regarding whether genetic counseling increases or decreases the accuracy of patients' risk perception.

The USPSTF examined the available evidence on harms of screening and intervention. Approximately 12% of high-risk families without a *BRCA1* or *BRCA2* coding-region mutation may have other clinically important genomic rearrangements (52). Approximately 13% of tests report mutations of unknown significance; however, the harms associated with such test results are not known (53). Routine referral for genetic counseling and consideration of *BRCA1* and *BRCA2* testing clearly has important psychological, ethical, legal, and social implications, although they are not well quantified in the literature. Among these are the potential for burdening patients with the knowledge of mutations of unknown importance and the potential for affecting family members other than the individual patient. The potential harms of intensive screening include overdiagnosis and overtreatment. There is good-quality evidence on the harms of prophylactic tamoxifen (1), including thromboembolic events, endometrial cancer, and hot flashes. Fair-quality evidence shows that prophylactic mastectomy can cause hematoma, infection, contracture, or implant rupture (with reconstruction) and that prophylactic oophorectomy can cause infection, bleeding, urinary tract or bowel injury, and premature menopause. Overall, the USPSTF estimates that the magnitude of these potential harms is at least small.

Research Gaps

Population studies are needed to determine the prevalence and penetrance of various mutations in the *BRCA* gene and the factors that influence penetrance for women with these mutations. Research has focused on highly selected women in referral centers and has generally reported short-term outcomes. Issues requiring additional study include the effectiveness of risk stratification and genetic counseling when delivered in different settings and by different types of providers, appropriate training for counselors, use of system supports, and patient acceptance of educational strategies. The impact of *BRCA* testing on ethical, legal, and social issues needs to be better clarified. We also need to understand the effect of genetic counseling on the emotions and behavior of the patient and her first-degree female relatives.

Enhanced screening with such methods as MRI needs to be better studied in high-risk women. Future studies should examine the impact of intensive MRI screening on breast cancer mortality and on possible overtreatment. Studies specifically designed to examine the potential benefit of chemoprophylaxis in women with known deleterious *BRCA* mutations are essential to establish whether there are any effective alternatives to prophylactic surgery. There is a paucity of data on *BRCA*-associated ovarian cancer; further research in screening and management of

women at high risk for ovarian cancer is needed. It would be helpful to develop and validate tools feasible for use in primary care practice that would help clinicians make appropriate referrals for genetic counseling.

RECOMMENDATIONS OF OTHER GROUPS

A few organizations have made recommendations on genetic susceptibility testing. The American College of Medical Genetics (ACMG) recommends risk assessment and genetic counseling before testing for *BRCA1*/*BRCA2* mutations in individuals at increased risk, based on a personal or family history of breast cancer, ovarian cancer, or both (54). In a previous guideline published in 1996, the ACMG recommended testing for *BRCA1* mutations in high-risk families and population screening of Ashkenazi Jewish individuals after discussion of test limitations and appropriate informed consent (55). The National Comprehensive Cancer Network recommends offering genetic susceptibility testing (after risk assessment and counseling) to individuals who meet the criteria for hereditary breast or ovarian cancer or both (56). The American Society of Clinical Oncology recommends that genetic testing be offered when 1) an individual has a personal or family history that suggests a genetic cancer susceptibility and 2) the test can be adequately interpreted and its results will influence diagnosis or management of the patient or family members at risk for hereditary cancer (57). The American College of Obstetricians and Gynecologists Committee Opinion on breast and ovarian cancer screening, written in 2000, recommends offering *BRCA* mutation testing to families in which multiple family members have had breast or ovarian cancer or in which a *BRCA* mutation has been found (58).

APPENDIX

Members of the U.S. Preventive Services Task Force are Alfred O. Berg, MD, MPH, *Chair* (University of Washington, Seattle, Washington); Janet D. Allan, PhD, RN, CS, *Vice-Chair* (University of Maryland, Baltimore, Baltimore, Maryland); Ned Calonge, MD, MPH (Colorado Department of Public Health and Environment, Denver, Colorado); Paul S. Frame, MD (Tri-County Family Medicine, Cohocton, and University of Rochester, Rochester, New York); Leon Gordis, MD, MPH, DrPH (Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland); Kimberly D. Gregory, MD, MPH (Cedars-Sinai Medical Center, Los Angeles, California); Russell Harris, MD, MPH (University of North Carolina School of Medicine, Chapel Hill, North Carolina); Mark S. Johnson, MD, MPH (University of Medicine and Dentistry of New Jersey–New Jersey Medical School, Newark, New Jersey); Jonathan D. Klein, MD, MPH (University of Rochester School of Medicine, Rochester, New York); Carol Loveland-Cherry, PhD, RN (University of Michigan School of Nursing, Ann Arbor, Michigan); Virginia A. Moyer, MD, MPH (University of Texas Health Science Center, Houston, Texas); Judith K. Ockene, PhD (University of Massachusetts Medical School, Worcester, Massachusetts); Diana B. Petitti, MD, MPH (Kaiser Permanente Southern California, Pasadena, California); Albert L. Siu, MD, MSPH (Mount Sinai Medical Center, New York, New York); Steven M. Teutsch, MD, MPH (Merck & Co., Inc., West Point, Pennsylvania); and Barbara P. Yawn, MD, MSc (Olmstead Research Center, Rochester, Minnesota).

This list includes members of the Task Force at the time these recommendations were finalized. For a list of current Task Force members, go to www.ahrq.gov/clinic/uspstfab.htm.

Appendix Table 1. **U.S. Preventive Services Task Force Recommendations and Ratings***

Grade	Recommendation
A	The USPSTF strongly recommends that clinicians provide [the service] to eligible patients. *The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.*
B	The USPSTF recommends that clinicians provide [the service] to eligible patients. *The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.*
C	The USPSTF makes no recommendation for or against routine provision of [the service]. *The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.*
D	The USPSTF recommends against routinely providing [the service] to asymptomatic patients. *The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.*
I	The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. *Evidence that [the service] is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.*

* The U.S. Preventive Services Task Force (USPSTF) grades its recommendations according to one of five classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms).

Appendix Table 2. **U.S. Preventive Services Task Force Grades for Strength of Overall Evidence***

Grade	Definition
Good	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes
Fair	Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes
Poor	Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes

* The U.S. Preventive Services Task Force (USPSTF) grades the quality of the overall evidence for a service on a three-point scale (good, fair, poor).

From the U.S. Preventive Services Task Force, Agency for Healthcare Research and Quality, Rockville, Maryland.

Requests for Single Reprints: Reprints are available from the USPSTF Web site (www.preventiveservices.ahrq.gov) and in print through the Agency for Healthcare Research and Quality Publications Clearinghouse (800-358-9295).

References

1. **Nelson HD, Huffman LH, Fu R, Harris EL, Walker M, Bougatsos C.** Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility. Systematic Evidence Synthesis No. 37 (Prepared by the Oregon Evidence-based Practice Center under contract no. 290-02-0024). 2005. Available at www.ahrq.gov/clinic/uspstfix.htm.

2. **Yang Q, Khoury MJ, Rodriguez C, Calle EE, Tatham LM, Flanders WD.** Family history score as a predictor of breast cancer mortality: prospective data from the Cancer Prevention Study II, United States, 1982-1991. Am J Epidemiol. 1998;147:652-9. [PMID: 9554604]

3. **Colditz GA, Willett WC, Hunter DJ, Stampfer MJ, Manson JE, Hennekens CH, et al.** Family history, age, and risk of breast cancer. Prospective data from the Nurses' Health Study. JAMA. 1993;270:338-43. [PMID: 8123079]

4. **Slattery ML, Kerber RA.** A comprehensive evaluation of family history and breast cancer risk. The Utah Population Database. JAMA. 1993;270:1563-8. [PMID: 8371466]

5. **Johnson N, Lancaster T, Fuller A, Hodgson SV.** The prevalence of a family history of cancer in general practice. Fam Pract. 1995;12:287-9. [PMID: 8536831]

6. **Pharoah PD, Day NE, Duffy S, Easton DF, Ponder BA.** Family history and the risk of breast cancer: a systematic review and meta-analysis. Int J Cancer. 1997;71:800-9. [PMID: 9180149]

7. **Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, et al.** A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science. 1994;266:66-71. [PMID: 7545954]

8. **Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, et al.** Identification of the breast cancer susceptibility gene BRCA2. Nature. 1995;378:789-92. [PMID: 8524414]

9. **Frank TS, Deffenbaugh AM, Reid JE, Hulick M, Ward BE, Lingenfelter B, et al.** Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10, 000 individuals. J Clin Oncol. 2002;20:1480-90. [PMID: 11896095]

10. **Srivastava A, McKinnon W, Wood ME.** Risk of breast and ovarian cancer in women with strong family histories. Oncology (Williston Park). 2001;15:889-902; discussion 902, 905-7, 911-13. [PMID: 11499690]

11. **Shattuck-Eidens D, Oliphant A, McClure M, McBride C, Gupte J, Rubano T, et al.** BRCA1 sequence analysis in women at high risk for susceptibility mutations. Risk factor analysis and implications for genetic testing. JAMA. 1997; 278:1242-50. [PMID: 9333265]

12. **Couch FJ, DeShano ML, Blackwood MA, Calzone K, Stopfer J, Campeau L, et al.** BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer. N Engl J Med. 1997;336:1409-15. [PMID: 9145677]

13. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Anglian Breast Cancer Study Group. Br J Cancer. 2000;83:1301-8. [PMID: 11044354]

14. **Antoniou AC, Pharoah PD, McMullan G, Day NE, Stratton MR, Peto J, et al.** A comprehensive model for familial breast cancer incorporating BRCA1, BRCA2 and other genes. Br J Cancer. 2002;86:76-83. [PMID: 11857015]

15. **Peto J, Collins N, Barfoot R, Seal S, Warren W, Rahman N, et al.** Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer. J Natl Cancer Inst. 1999;91:943-9. [PMID: 10359546]

16. **Antoniou AC, Gayther SA, Stratton JF, Ponder BA, Easton DF.** Risk models for familial ovarian and breast cancer. Genet Epidemiol. 2000;18:173-90. [PMID: 10642429]

17. Myriad Genetic Laboratories, Inc. Accessed at www.myriadtests.com/home.htm on 30 April 2004.

18. **Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, et al.** Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet. 2003;72:1117-30. [PMID: 12677558]

19. **Brose MS, Rebbeck TR, Calzone KA, Stopfer JE, Nathanson KL, Weber BL.** Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. J Natl Cancer Inst. 2002;94:1365-72. [PMID: 12237282]

20. **Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, et al.** Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. Am J Hum Genet. 1998;62:676-89. [PMID: 9497246]

21. **Hopper JL, Southey MC, Dite GS, Jolley DJ, Giles GG, McCredie MR, et al.** Population-based estimate of the average age-specific cumulative risk of breast cancer for a defined set of protein-truncating mutations in BRCA1 and BRCA2. Australian Breast Cancer Family Study. Cancer Epidemiol Biomarkers Prev. 1999;8:741-7. [PMID: 10498392]

22. **Risch HA, McLaughlin JR, Cole DE, Rosen B, Bradley L, Kwan E, et al.** Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. Am J Hum Genet. 2001;68: 700-10. [PMID: 11179017]

23. **King MC, Marks JH, Mandell JB.** Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science. 2003;302:643-6. [PMID: 14576434]

24. **Moslehi R, Chu W, Karlan B, Fishman D, Risch H, Fields A, et al.** BRCA1 and BRCA2 mutation analysis of 208 Ashkenazi Jewish women with ovarian cancer. Am J Hum Genet. 2000;66:1259-72. [PMID: 10739756]

25. **Satagopan JM, Boyd J, Kauff ND, Robson M, Scheuer L, Narod S, et al.** Ovarian cancer risk in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. Clin Cancer Res. 2002;8:3776-81. [PMID: 12473589]

26. **Satagopan JM, Offit K, Foulkes W, Robson ME, Wacholder S, Eng CM, et al.** The lifetime risks of breast cancer in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. Cancer Epidemiol Biomarkers Prev. 2001;10:467-73. [PMID: 11352856]

27. **Struewing JP, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, et al.** The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med. 1997;336:1401-8. [PMID: 9145676]

28. **Warner E, Foulkes W, Goodwin P, Meschino W, Blondal J, Paterson C, et al.** Prevalence and penetrance of BRCA1 and BRCA2 gene mutations in unselected Ashkenazi Jewish women with breast cancer. J Natl Cancer Inst. 1999; 91:1241-7. [PMID: 10413426]

29. **Fodor FH, Weston A, Bleiweiss IJ, McCurdy LD, Walsh MM, Tartter PI, et al.** Frequency and carrier risk associated with common BRCA1 and BRCA2 mutations in Ashkenazi Jewish breast cancer patients. Am J Hum Genet. 1998; 63:45-51. [PMID: 9634504]

30. **Domchek SM, Eisen A, Calzone K, Stopfer J, Blackwood A, Weber BL.** Application of breast cancer risk prediction models in clinical practice. J Clin Oncol. 2003;21:593-601. [PMID: 12586794]

31. **Gilpin CA, Carson N, Hunter AG.** A preliminary validation of a family history assessment form to select women at risk for breast or ovarian cancer for referral to a genetics center. Clin Genet. 2000;58:299-308. [PMID: 11076055]

32. **Evans DG, Eccles DM, Rahman N, Young K, Bulman M, Amir E, et al.** A new scoring system for the chances of identifying a BRCA1/2 mutation outperforms existing models including BRCAPRO. J Med Genet. 2004;41:474-80. [PMID: 15173236]

33. **Emery J, Walton R, Coulson A, Glasspool D, Ziebland S, Fox J.** Computer support for recording and interpreting family histories of breast and ovarian cancer in primary care (RAGs): qualitative evaluation with simulated patients. BMJ. 1999;319:32-6. [PMID: 10390458]

34. **Emery J, Walton R, Murphy M, Austoker J, Yudkin P, Chapman C, et al.** Computer support for interpreting family histories of breast and ovarian cancer in primary care: comparative study with simulated cases. BMJ. 2000;321:28-32. [PMID: 10875832]

35. **Warner E, Plewes DB, Hill KA, Causer PA, Zubovits JT, Jong RA, et al.** Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. JAMA. 2004;292:1317-25. [PMID: 15367553]

36. **Burke W, Petersen G, Lynch P, Botkin J, Daly M, Garber J, et al.** Recommendations for follow-up care of individuals with an inherited predisposition to cancer. I. Hereditary nonpolyposis colon cancer. Cancer Genetics Studies Consortium. JAMA. 1997;277:915-9. [PMID: 9062331]

37. **Bourne TH, Campbell S, Reynolds KM, Whitehead MI, Hampson J, Royston P, et al.** Screening for early familial ovarian cancer with transvaginal ultrasonography and colour blood flow imaging. BMJ. 1993;306:1025-9. [PMID: 8490496]

38. **Cuzick J, Forbes J, Edwards R, Baum M, Cawthorn S, Coates A, et al.** First results from the International Breast Cancer Intervention Study (IBIS-I): a ran-

domised prevention trial. Lancet. 2002;360:817-24. [PMID: 12243915]
39. **Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, et al.** Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst. 1998;90:1371-88. [PMID: 9747868]
40. **King MC, Wieand S, Hale K, Lee M, Walsh T, Owens 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;286:2251-6. [PMID: 11710890]
41. **Klaren HM, van't Veer LJ, van Leeuwen FE, Rookus MA.** Potential for bias in studies on efficacy of prophylactic surgery for BRCA1 and BRCA2 mutation. J Natl Cancer Inst. 2003;95:941-7. [PMID: 12837830]
42. **Hartmann LC, Schaid DJ, Woods JE, Crotty TP, Myers JL, Arnold PG, et al.** Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. N Engl J Med. 1999;340:77-84. [PMID: 9887158]
43. **Rebbeck TR, Friebel T, Lynch HT, Neuhausen SL, van 't Veer L, Garber JE, et al.** Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol. 2004; 22:1055-62. [PMID: 14981104]
44. **Meijers-Heijboer H, van Geel B, van Putten WL, Henzen-Logmans SC, Seynaeve C, Menke-Pluymers MB, et al.** Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med. 2001;345:159-64. [PMID: 11463009]
45. **Hartmann LC, Sellers TA, Schaid DJ, Frank TS, Soderberg CL, Sitta DL, et al.** Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene mutation carriers. J Natl Cancer Inst. 2001;93:1633-7. [PMID: 11698567]
46. **Struewing JP, Watson P, Easton DF, Ponder BA, Lynch HT, Tucker MA.** Prophylactic oophorectomy in inherited breast/ovarian cancer families. J Natl Cancer Inst Monogr. 1995:33-5. [PMID: 8573450]
47. **Rebbeck TR, Levin AM, Eisen A, Snyder C, Watson P, Cannon-Albright L, et al.** Breast cancer risk after bilateral prophylactic oophorectomy in BRCA1 mutation carriers. J Natl Cancer Inst. 1999;91:1475-9. [PMID: 10469748]
48. **Rebbeck TR.** Prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers. Eur J Cancer. 2002;38 Suppl 6:S15-7. [PMID: 12409058]
49. **Kauff ND, Satagopan JM, Robson ME, Scheuer L, Hensley M, Hudis CA, et al.** Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med. 2002;346:1609-15. [PMID: 12023992]
50. **Kauff ND, Satagopan JM, Robson ME, Scheuer L, Hensley M, Hudis CA, et al.** Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med. 2002;346:1609-15. [PMID: 12023992]
51. **Meiser B, Halliday JL.** What is the impact of genetic counselling in women at increased risk of developing hereditary breast cancer? A meta-analytic review. Soc Sci Med. 2002;54:1463-70. [PMID: 12061481]
52. **Unger MA, Nathanson KL, Calzone K, Antin-Ozerkis D, Shih HA, Martin AM, et al.** Screening for genomic rearrangements in families with breast and ovarian cancer identifies BRCA1 mutations previously missed by conformation-sensitive gel electrophoresis or sequencing. Am J Hum Genet. 2000;67:841-50. [PMID: 10978226]
53. **Frank TS, Deffenbaugh AM, Reid JE, Hulick M, Ward BE, Lingenfelter B, et al.** Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10, 000 individuals. J Clin Oncol. 2002;20:1480-90. [PMID: 11896095]
54. **American College of Medical Genetics Foundation.** Genetic Susceptibility to Breast and Ovarian Cancer: Assessment, Counseling and Testing Guidelines. June 1998. Accessed at www.health.state.ny.us/nysdoh/cancer/obcancer/contents.htm on 4 March 2005.
55. **American College of Medical Genetics.** Statement on Population Screening for BRCA-1 Mutation in Ashkenazi Jewish Women. 1996. Accessed at www.acmg.net/resources/policies/pol-002.asp on 25 March 2005.
56. **National Comprehensive Cancer Network.** Clinical Practice Guidelines in Oncology. Genetic/Familial High Risk Assessment: Breast and Ovarian Cancer. 2005. Accessed at www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf on 4 March 2005.
57. American Society of Clinical Oncology Policy Statement Update: Genetic Testing for Cancer Susceptibility. 11 April 2003. J Clin Oncol. Accessed at www.asco.org/asco/downloads/GeneticTesting.pdf on 4 March 2005.
58. ACOG committee opinion. Breast-ovarian cancer screening. Number 239, August 2000. American College of Obstetricians and Gynecologists. Committee on genetics. Int J Gynaecol Obstet. 2001;75:339-40. [PMID: 11794298]

HEREDITARY BREAST AND/OR OVARIAN CANCER SYNDROME TESTING CRITERIA[a,b,c]

- Individual from a family with a known deleterious BRCA1/BRCA2 mutation
- Personal history of breast cancer[d] + one or more of the following:
  - Diagnosed age ≤ 45 y
  - Diagnosed age ≤ 50 y with ≥ 1 close blood relative[e] with breast cancer ≤ 50 y and/or ≥ 1 close blood relative[e] with epithelial ovarian/fallopian tube/primary peritoneal cancer at any age
  - Two breast primaries[f] when first breast cancer diagnosis occurred prior to age 50 y
  - Diagnosed age < 60 y with a triple negative breast cancer
  - Diagnosed age < 50 y with a limited family history[c]
  - Diagnosed at any age, with ≥ 2 close blood relatives[e] with breast and/or epithelial ovarian/ fallopian tube/ primary peritoneal cancer at any age
  - Close male blood relative[e] with breast cancer
  - Personal history of epithelial ovarian[g]/fallopian tube/primary peritoneal cancer
  - For an individual of ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish) no additional family history may be required[h]
- Personal history of epithelial ovarian[g]/fallopian tube/ primary peritoneal cancer
- Personal history of male breast cancer
- Personal history of breast and/or ovarian cancer at any age with ≥ 2 close blood relatives[e] with pancreatic cancer at any age
- Personal history of pancreatic cancer at any age with ≥ 2 close blood relatives[e] with breast and/or ovarian and/or pancreatic cancer at any age
- Family history only:[i]
  - First- or second-degree blood relative meeting any of the above criteria
  - Third-degree blood relative with breast cancer and/or ovarian[g]/fallopian tube/ primary peritoneal cancer with ≥ 2 close blood relatives[e] with breast cancer (at least one with breast cancer ≤ 50 y) and/or ovarian cancer

HBOC criteria met → See Follow-up (HBOC-2)

HBOC criteria not met → See NCCN Breast Cancer Screening and Diagnosis Guidelines

[a] One or more of these criteria is suggestive of hereditary breast/ovarian cancer syndrome that warrants further professional evaluation. The maternal and paternal sides should be considered independently. Other malignancies reported in some HBOC families include prostate and melanoma.

[b] Patients who have received an allogeneic bone marrow transplant should not have molecular genetic testing via blood or buccal samples due to contamination by donor DNA. DNA should be extracted from a fibroblast culture.

[c] Individuals with limited family history, such as fewer than 2 first- or second-degree female relatives or female relatives surviving beyond 45 years in either lineage, may have an underestimated probability of a familial mutation.

[d] For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.

[e] Close blood relatives include first-, second-, and third-degree relatives. (See BR/OV-3)

[f] Two breast primaries including bilateral disease or cases where there are two or more clearly separate ipsilateral primary tumors.

[g] Ovarian cancer is a component tumor of hereditary non-polyposis colorectal cancer/ Lynch syndrome, be attentive for clinical evidence of this syndrome. See NCCN Colorectal Cancer Screening Guidelines.

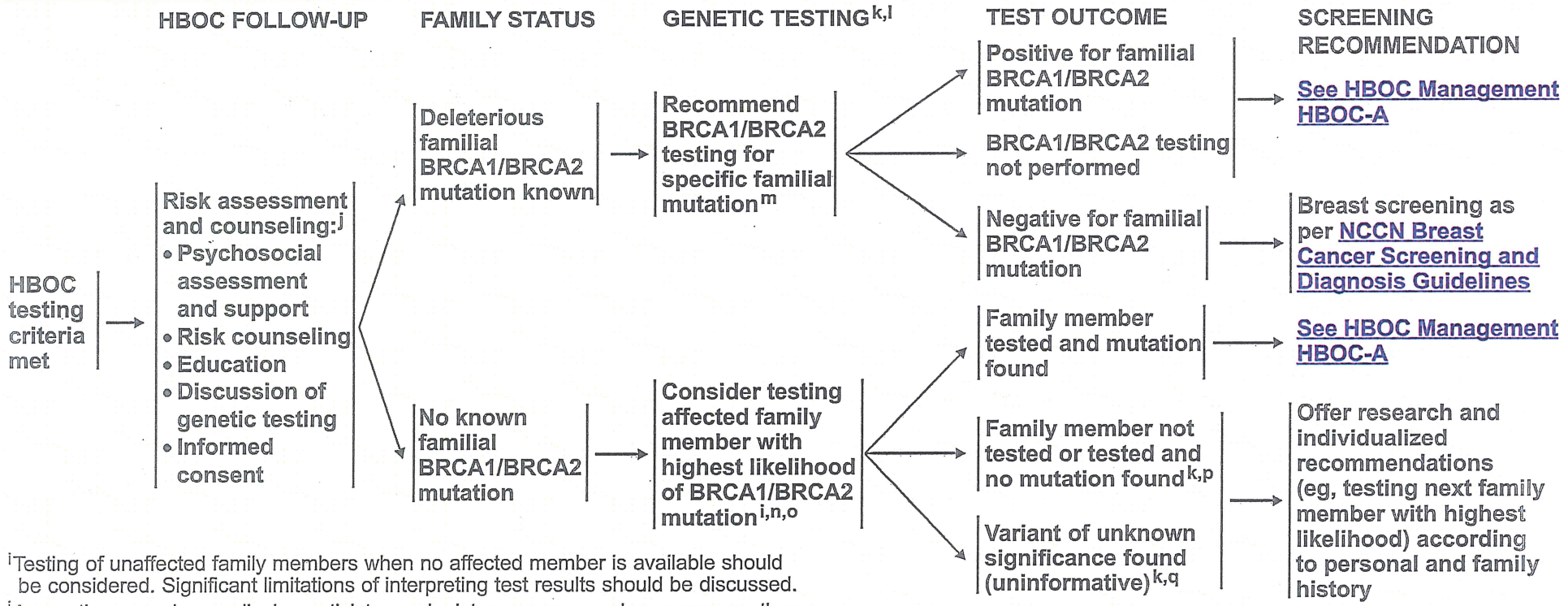
[h] Testing for Ashkenazi Jewish founder-specific mutation(s), should be performed first. Full sequencing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or other HBOC criteria is met. Founder mutations exist in other populations.

[i] Testing of unaffected family members when no affected member is available should be considered. Significant limitations of interpreting test results should be discussed.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines™ Version 1.2011
Hereditary Breast and/or Ovarian Cancer Syndrome

NCCN Guidelines Index
Genetics Table of Contents
Discussion



[i] Testing of unaffected family members when no affected member is available should be considered. Significant limitations of interpreting test results should be discussed.

[j] A genetic counselor, medical geneticist, oncologist, surgeon, oncology nurse or other health professional with expertise and experience in cancer genetics should be involved early in counseling patients who potentially meet criteria for an inherited syndrome. Genetic counseling is highly recommended when genetic testing is offered and after results are disclosed.

[k] Certain mutations (ie, large rearrangements) are not detectable by the primary sequencing assay and supplementary testing may be necessary.

[l] Genetic testing for familial BRCA1/2 in children < 18 y is generally not recommended.

[m] If of Ashkenazi Jewish descent, in addition to the specific familial mutation, test for all three founder mutations.

[n] If more than one affected, first consider: youngest age at diagnosis, bilateral disease, multiple primaries, ovarian cancer, most closely related to the proband/patient/consultand. If no living family member with breast or ovarian cancer, consider testing first- or second- degree family members affected with cancers thought to be related to BRCA1/BRCA2 eg, prostate, pancreas, or melanoma.

[o] For both affected and unaffected individuals of Ashkenazi Jewish descent with no known familial mutation, first test for the three common mutations. Then, if negative for the three mutations, consider full sequence testing if ancestry also includes non-Ashkenazi Jewish relatives or other HBOC criteria is met. If all affected family members are deceased, consider testing of paraffin-derived DNA from deceased relatives, if DNA is obtainable. For both affected and unaffected individuals who are non-Ashkenazi Jewish and who have no known familial mutation, full sequence testing is the approach, if testing is done.

[p] If individual affected with breast cancer is < 30 y especially if there is a family history of sarcoma, brain tumor, or adrenocortical carcinoma, consider p53 gene testing.

[q] Testing for variant of unknown significance should not be used for clinical purposes. Consider referral to research studies that aim to define functional impact of variant.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Connecticut

Potential Cases of Lynch Syndrome
2008-2009

Cancer site	Number of diagnosed cancers Connecticut
Colon or rectum (≤ 50 yrs of age)	383
Colon or rectum (All ages)	3,517
Endometrium (All ages)	1,411
Multiple primary sites*	2,471

Source: Connecticut Tumor Registry

* Primary sites include colon, rectum, endometrium, ovary, pancreas, small intestine, stomach, hepatobiliary tract, and renal pelvis/ureter. The most recent cancer diagnosis was in 2008-2009.

This table contains the number of cancers diagnosed during 2008-2009 in Connecticut patients who could be predisposed to Lynch syndrome (hereditary nonpolyposis colorectal cancer or HNPCC).

WHY THESE DATA ARE IMPORTANT FOR YOU TO KNOW

Lynch syndrome is an inherited genetic disorder caused by mutations in DNA mismatch repair genes. It is the most common cause of hereditary colorectal and endometrial cancers, and may also predispose people to several other cancers (*see footnote to Table*).

An individual with Lynch syndrome has an increased risk of certain cancers.

- Up to 80% risk of colorectal cancer (compared to 5-6% in the general population)
- Up to 60% risk of endometrial cancer (compared to 2-3% in the general population)
- 16% risk of a second primary colorectal cancer within 10 years of first diagnosis

Patients with either of the following diagnoses might be predisposed by Lynch syndrome mutations to colorectal cancer and other cancers.

- Early onset colorectal cancer (diagnosed at or before 50 years of age)
- Two or more of any combination of certain primary cancers of the digestive, urinary, and female reproductive systems (*see footnote to Table*)

Patients with either of the above diagnoses should be considered for formal risk assessment and genetic counseling and/or testing.

- Refer patients to a health care provider who is suitably trained in cancer genetics.
- Individuals diagnosed with Lynch syndrome may have a higher risk for developing future cancers and may benefit from closer monitoring or special medical management.
- Family members of these individuals also may be affected.

This report was developed by the Connecticut Department of Public Health's Genomics Office in partnership with the Connecticut Tumor Registry, and was funded through a Healthy People 2020 Action Project grant.

Connecticut Department of Public Health
410 Capitol Avenue, Hartford, CT 06106
(860) 509-8070

January 2012

Lynch Syndrome

Fact Sheet for Connecticut Healthcare Professionals

What is Lynch syndrome?

Lynch syndrome, formerly known as hereditary non-polyposis colorectal cancer (HNPCC) syndrome, is a hereditary cancer predisposition condition caused by mutations in the *MLH1, MSH2, MSH6*, and *PMS2*. All of these genes are involved in the repair of mistakes made when DNA is copied (DNA replication) in preparation for cell division. Mutations in any of these genes prevent the proper repair of DNA replication mistakes. As the abnormal cells continue to divide, the accumulated mistakes can lead to uncontrolled cell growth and possibly cancer. In addition, deletions affecting the epithelial cell adhesion molecule (*EPCAM*) gene can also cause Lynch syndrome by epigenetic inactivation of the respective *MSH2* allele.

Facts about Lynch syndrome

- Approximately 1 in 35 (2%-3%) of colon cancer patients has Lynch syndrome.
- People with Lynch syndrome have a 52%-80% chance of developing colon cancer in their lifetimes compared to 5%-6% for people in the general population.
- Women with Lynch syndrome have a 30%-60% chance of developing endometrial cancer in their lifetimes compared to a 2%-3% chance for women in the general population.
- Individuals with Lynch syndrome also have a slightly increased risk of developing stomach, ovarian, hepatobiliary, small intestine, and urinary tract cancers.
- The average age of onset of colon cancer in Lynch syndrome patients is between 42 and 61 years compared to 71 years in the general population.

Are there any screening tests for Lynch syndrome in a colorectal cancer patient?

There are several screening tests for Lynch syndrome, including microsatellite instability (MSI) testing and immunohistochemistry (IHC) testing. Either or both of these tests can be performed on a tumor from a person suspected of having Lynch syndrome. Such screening often is recommended prior to genetic testing.

Who is most likely to have a *MLH1, MSH2* (including *EPCAM*), *MSH6*, or *PMS2* mutation?

The likelihood is highest in families with a history of colorectal cancer and other Lynch syndrome-associated cancers (e.g., endometrial, stomach, small intestine, renal pelvis/ureter, ovarian, pancreatic, biliary tract, and brain, as well as sebaceous gland adenomas and keratocanthomas); young age of onset; and synchronous or metachronous colorectal cancer. However, not every person in such families carries a harmful *MLH1, MSH2* (or *EPCAM*), *MSH6*, or *PMS2* mutation, and not every cancer in such families is linked to a harmful mutation in one of these genes but instead may be the result of a sporadic mutation. Furthermore, not every person who has Lynch syndrome will develop colorectal or endometrial cancer.

Specific indications for genetic counseling and testing vary among professional organizations. Guidelines are not a substitute for clinical judgment. Not all clinical scenarios can be anticipated, such as when there is a limited family structure or family medical history.

Developed by the Connecticut Department of Public Health's Genomics Office in partnership with the Connecticut Tumor Registry, and funded through a Healthy People 2020 Action Project grant.

Connecticut Department of Public Health
410 Capitol Avenue, Hartford, CT 06106
(860) 509-8070 *www.ct.gov/dph*

Why is genetic counseling important?
Genetic counseling helps people better understand their risk for hereditary cancer in order to make informed decisions about genetic testing and follow-up care.

What does genetic counseling entail?
Genetic counseling is a process that encompasses the following services:

- Reviewing an individual's personal and detailed family medical history.
- Assessing and explaining risk for hereditary cancers and the chance of finding a mutation through genetic testing.
- Discussing the benefits, limitations, and other possible consequences of genetic testing.
- Outlining medical implications of a positive or a negative test result.
- Determining which family member is most appropriate to begin the genetic testing process in a family.
- Interpreting genetic test results and explaining what they mean for individuals and their relatives.
- Providing referrals to experts for follow-up screening and risk management.
- Providing referrals to support resources and research opportunities (including research on genetic testing, screening, treatment, etc.).
- Discussing risks and medical management options with a patient's other health care provider(s).
- Addressing common concerns about the privacy and confidentiality of personal genetic information.

What are some of the benefits of genetic testing for Lynch syndrome?

- A positive test result can bring relief from uncertainty and allow people to make informed decisions about their futures. They can take steps to reduce their cancer risk through increased surveillance or other medical and lifestyle choices.
- A positive test result may help to explain why individuals or family members had cancer in the past, and, should they choose to share test results, may provide their family members with useful information.
- Those who have a positive test result may be able to participate in medical research that could, in the long run, help reduce deaths from colorectal cancer.
- A negative test result may provide a sense of relief and preclude the need for special preventive checkups, tests, or surgeries.

What are the disadvantages of genetic testing?
Test results may affect a person's emotions, family relationships, finances, privacy, and medical choices.

- A positive result may make a person feel anxious, angry, or depressed. Medical treatments, such as surgery to try to prevent the cancer, could have serious, long-term implications and uncertain effectiveness.
- A negative result may make a person feel guilty because they escaped a disease that affected a loved one. They may also get a false sense of security that they have no chance of getting cancer, when, in fact, their cancer risk is the same as that of the general population.
- Because genetic testing can reveal information about more than one family member, the emotions caused by the results can create tension within families. The results also can affect personal choices, such as marriage and childbearing.
- Privacy and confidentiality of genetic test results are additional potential concerns. There is no guarantee that a person's test results will remain private.
- Genetic testing can be expensive, depending on the extent of testing. Although many insurance plans cover the cost of the testing for individuals at high risk, coverage is unlikely for those not considered to be at high risk.

Evidence-based Practice Guidelines Supporting Genetic Susceptibility Testing for Lynch Syndrome

Individuals who meet the following criteria should be suspected as having Lynch syndrome (LS). Referral to genetic counseling and testing should be considered. Criteria have been adapted from the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group recommendations,[1] the Amsterdam II criteria,[2] and the revised Bethesda guidelines.[3]

Individual is diagnosed WITH colorectal cancer[1] [and preliminary tumor tissue analysis indicates that individual has pathology with suspicious immunohistochemistry and/or microsatellite instability].

Individuals WITHOUT a personal history of a Lynch syndrome-related cancer* with at least three close relatives† with a LS-related cancer*, and ALL of the following criteria are met:[2]

- At least one relative with a LS-related cancer* was diagnosed before age 50 years; and
- At least two successive generations are affected; and
- One must be a 1st-degree relative of the other two; and
- Familial Adenomatous Polyposis should be excluded in the colorectal cancer cases (if any).

Individuals WITHOUT a personal history of a Lynch syndrome-related cancer and AT LEAST ONE of the following criteria is met**:[3]

- A 1st-degree relative with a combination of colorectal cancer and another LS-related cancer** has at least one of the cancers diagnosed before age 50 years.
- Two or more close relatives† are diagnosed with a combination of colorectal cancer and another LS-related cancer**, regardless of their age at diagnosis.

---

*Lynch syndrome-related cancers include colorectal, endometrial, small intestine, renal pelvis/ureter.

** Same as above with addition of stomach, ovarian, pancreatic, hepatobiliary, brain (predominantly glioblastoma as seen in Turcot syndrome), and sebaceous gland adenomas and keratoacanthomas as seen in Muir-Torre syndrome.

† Close relative = 1st or 2nd degree blood relative

1st-degree relative includes parent, sibling, or child

2nd-degree relative includes aunt, uncle, niece, nephew, grandparent, grandchild, or half-sibling

REFERENCES

1. Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP working group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. *Genet Med* 2009;11:35-41.

2. Vasen H F, Watson P, Mecklin J P, Lynch H T. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. *Gastroenterology* 1999;116:1453–1456.

3. Umar A, Boland C R, Terdiman J P, Syngal S, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst* 2004; 96:261–268.

Developed by the Connecticut Department of Public Health's Genomics Office in partnership with the Connecticut Tumor Registry, and funded through a Healthy People 2020 Action Project grant.

Connecticut Department of Public Health
410 Capitol Avenue, Hartford, CT 06106
(860) 509-8070 *www.ct.gov/dph*

Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives

*Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group**

Disclaimer: *This recommendation statement is a product of the independent EGAPP Working Group. Although the Centers for Disease Control and Prevention (CDC) provides support to the EGAPP Working Group, including staff support in the preparation of this document, recommendations made by the EGAPP Working Group should not be construed as official positions of the CDC or the U.S. Department of Health and Human Services.*

Summary of Recommendations: The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group found sufficient evidence to recommend offering genetic testing for Lynch syndrome to individuals with newly diagnosed colorectal cancer to reduce morbidity and mortality in relatives. We found insufficient evidence to recommend a specific genetic testing strategy among the several examined.

Rationale: Genetic testing to detect Lynch syndrome in individuals with newly diagnosed colorectal cancer (CRC) is proposed as a strategy to reduce CRC morbidity and mortality in their relatives (see Clinical Considerations section for definition of Lynch syndrome). The EGAPP Working Group (EWG) constructed a chain of evidence that linked genetic testing for Lynch syndrome in patients with newly diagnosed CRC with improved health outcomes in their relatives. We found that assessing patients who have newly diagnosed CRC with a series of genetic tests could lead to the identification of Lynch syndrome. Relatives of patients with Lynch syndrome could then be offered genetic testing, and, where indicated, colorectal, and possibly endometrial, cancer surveillance, with the expectation of improved health outcome. The EWG concluded that there is moderate certainty that such a testing strategy would provide moderate population benefit. **Analytic Validity:** The EWG found adequate evidence to conclude that the analytic sensitivity and specificity for preliminary and diagnostic tests were high. **Clinical Validity:** After accounting for the specific technologies and numbers of markers used, the EWG found at least adequate evidence to describe the clinical sensitivity and specificity for three preliminary tests, and for four selected testing strategies. These measures of clinical validity varied with each test and each strategy (see Clinical Considerations section). **Clinical Utility:** The EWG found adequate evidence for testing uptake rates, adherence to recommended surveillance activities, number of relatives approachable, harms associated with additional follow-up, and effectiveness of routine colonoscopy. This chain of evidence supported the use of genetic testing strategies to reduce morbidity/mortality in relatives with Lynch syndrome. Several genetic testing strategies were potentially effective, but none was clearly superior. The evidence for or against effectiveness of identifying mismatch repair (MMR) gene mutations in reducing endometrial cancer morbidity or mortality was inadequate. **Contextual Issues:** CRC is a common disease responsible for an estimated 52,000 deaths in the United States in 2007. In about 3% of newly diagnosed CRC, the underlying cause is a mutation in a MMR gene (Lynch syndrome) that can be reliably identified with existing laboratory tests. Relatives inheriting the mutation have a high (about 45% by age 70) risk of developing CRC. Evidence suggests these relatives will often accept testing and increased surveillance. ***Genet Med*** **2009:11(1):35–41.**

Key Words: *colorectal cancer, Lynch syndrome, HNPCC*

*EGAPP Working Group: Chair: Alfred O. Berg, MD, MPH (University of Washington), Members: Katrina Armstrong, MD, MSCE (University of Pennsylvania School of Medicine); Jeffrey Botkin, MD, MPH (University of Utah); Ned Calonge, MD, MPH (Colorado Department of Public Health and Environment); James Haddow, MD (The Warren Alpert Medical School of Brown University); Maxine Hayes, MD, MPH (Washington State Department of Health); Celia Kaye, MD, PhD (University of Colorado School of Medicine); Kathryn A. Phillips, PhD (University of California, San Francisco); Margaret Piper, PhD, MPH (Blue Cross/Blue Shield Association Technology Evaluation Center); Carolyn Sue Richards, PhD, FACMG (Oregon Health & Science University); Joan A. Scott, MS, CGC (Johns Hopkins University); Ora L. Strickland, PhD, DSc (Hon.), RN, FAAN (Emory University); Steven Teutsch, MD, MPH (Merck & Co.).

E-mail: egappinfo@egappreviews.org.

Disclosure: Steven Teutsch is an employee, option and stock holder in Merck & Co., Inc.

Submitted for publication August 13, 2008.

Accepted for publication September 29, 2008.

DOI: 10.1097/GIM.0b013e31818fa2ff

CLINICAL CONSIDERATIONS

Definitions

- Lynch syndrome is defined as a hereditary predisposition to CRC and certain other malignancies (e.g., endometrial and gastric cancer) as a result of a germline mismatch repair (MMR) gene mutation. Lynch syndrome includes both individuals with an existing cancer and those who have not yet developed cancer.
- The associated MMR gene mutations are inherited in an autosomal dominant manner.
- Analytic validity refers to a test's ability to accurately and reliably measure the genetic characteristic (e.g., genotype, mutation, polymorphism) of interest.

- Clinical validity defines how well test results correlate with the intermediate or final outcomes of interest. This is usually reported as a clinical sensitivity/specificity.

Patient population under consideration

These recommendations apply to all individuals with a new diagnosis of CRC. An estimated 2–4% can be identified as having Lynch syndrome.

Preliminary (screening) tests

Microsatellite instability (MSI) testing or immunohistochemical (IHC) testing (with or without *BRAF* mutation testing) of the tumor tissue are examples of preliminary testing strategies that could be used to select patients for subsequent diagnostic testing. Diagnostic testing involves MMR gene mutation (and deletion/duplication) testing of the proband, usually using a blood sample. Lynch syndrome is most commonly caused by mutations in the two MMR genes *MLH1* and *MSH2*; less commonly by mutations in *MSH6* and *PMS2*.

Clinical performance (sensitivity/specificity) to identify Lynch syndrome:

- 80–91% sensitivity of MSI testing among those with *MLH1* or *MSH2* mutations, depending on MSI panel composition; associated specificity is 90%.
- 55–77% sensitivity of MSI testing among those with *MSH6* (or *PMS2*) mutations, depending on panel composition; associated specificity is 90%.
- 83% sensitivity of IHC testing, regardless of MMR gene involved; associated specificity of 89%.
- Virtually 100% of individuals with Lynch syndrome do not carry the *BRAF* mutation, whereas 68% of those without Lynch syndrome do. *BRAF* mutation testing is usually restricted to CRC cases with absent staining for *MLH1*.
- An estimated 84% of the individuals with Lynch syndrome can be identified with current methods for DNA sequencing and deletion analysis. The 16% not detectable are associated with *PMS2* mutations. Testing of this gene has only recently become commercially available, and its use was not included in this review. This rate is only achievable if all newly diagnosed CRC cases are tested.

Treatment/follow-up of probands and relatives

Evidence does not exist to make specific recommendations for changes in CRC treatment in probands. The EWG recommends that probands be informed of the advantages of contacting blood relatives to offer counseling and targeted testing to diagnose Lynch syndrome. Among relatives diagnosed with Lynch syndrome (MMR positive), more frequent colonoscopies are indicated and should begin at an earlier age than recommended for average risk individuals. Increased surveillance results in reduced rates of colon cancer and death from all causes. Among women with Lynch syndrome (both probands and relatives), additional surveillance for early identification of endometrial cancer may be considered, but there is less evidence to support it.

Other considerations

- The general debate on the issue of consent is acknowledged. However, because of the potential impact on the patient's relatives, the EWG recommends that individuals with newly diagnosed CRC should be routinely offered counseling and educational materials aimed at informing them and their relatives of the potential benefits and harms associated with genetic testing to identify Lynch syndrome.
- Protocols for sample collection, laboratory testing, and reporting of results need to be instituted, as well as for contacting, educating, testing, and following relatives with Lynch syndrome.

Other approaches

Family history is an important risk factor for CRC in the general population. Among individuals with newly diagnosed CRC, however, family history is less useful as the first step in identifying Lynch syndrome than strategies involving the analysis of tumor samples (e.g., MSI, IHC). The application of Amsterdam and Bethesda criteria has resulted in variable and generally poor performance in identifying Lynch syndrome. Therefore, the EWG does not recommend the use of family history to exclude individuals with newly diagnosed cancer from the offer of genetic testing.

Economic considerations

Costs per Lynch syndrome case detected depend on the testing strategy selected; higher costs are associated with higher sensitivity. Total program costs are highest when no preliminary tests are employed (e.g., all individuals with newly diagnosed CRC are offered DNA sequencing).

BACKGROUND AND CLINICAL CONTEXT FOR THE RECOMMENDATION

CRC is the second leading cause of cancer-related death in the United States in both men and women, with an estimated 52,000 deaths in 2007.[1] About 1 in 30 CRC patients (2–4%) have Lynch syndrome.[2] When other relatives are found to carry a deleterious MMR gene mutation, they are also classified as having Lynch syndrome, because they are predisposed to developing these cancers, as well. The EWG avoids the term hereditary nonpolyposis colorectal cancer (HNPCC) because it now adds confusion to the understanding of this disorder. HNPCC has been applied to families meeting only limited family history criteria and to individuals with CRC having MSI-high test results, but no vertical transmission of a MMR gene mutation.[3,4]

The four MMR genes of major interest are *MLH1*, *MSH2*, *MSH6*, and *PMS2*. Mutations in *MLH1* and *MSH2* together account for the majority of Lynch syndrome cases diagnosed; mutations in *MSH6* and *PMS2* are less common. The risk of CRC in individuals with Lynch syndrome is high for both a second primary CRC in the patient (estimated at 16% within 10 years), and a new cancer in a first- or second-degree family member with Lynch syndrome (about 45% for men and 35% for women by age 70).[5] Changing management of both patients and relatives with the MMR gene mutation has the potential for reducing CRC-related morbidity and mortality. To better understand the utility of DNA testing strategies in reducing morbidity and mortality from Lynch syndrome, EGAPP commissioned an evidence-based review to address an overarching question regarding the following specific clinical scenario:

Does risk assessment and MMR gene mutation testing in individuals with newly diagnosed CRC lead to improved outcomes for the patient or relatives, or is it useful in medical, personal, or public health decision making?

REVIEW OF SCIENTIFIC EVIDENCE

This statement summarizes the supporting scientific evidence used by the EWG to make recommendations regarding the use of testing strategies to identify Lynch syndrome (presence of a MMR gene mutation) among newly diagnosed cases of CRC.

Methods

EGAPP is a project developed by the National Office of Public Health Genomics at the Centers for Disease Control and Prevention to support a rigorous, evidence-based process for evaluating genetic tests and other genomic applications that are in transition from research to clinical and public health practice in the United States [6] A key goal of the EWG is to develop conclusions and recommendations regarding clinical genomic applications, and to establish clear linkage to the supporting scientific evidence.[7] The EWG members are nonfederal multidisciplinary experts convened to establish methods and processes, set priorities for review topics, participate in technical expert panels for commissioned evidence reviews, and develop and publish recommendations.

EGAPP commissioned an evidence review through the Agency for Healthcare Research and Quality (AHRQ); the Tufts New England Medical Center Evidence-based Practice Center conducted the review.[8] The review focused on the accuracy of diagnostic strategies for HNPCC, and the implications of testing to individuals with CRC and their families. It was anticipated that data might not be available to directly answer the overarching question. The EWG, therefore, constructed an analytic framework and key questions to address different components of evaluation (e.g., analytic and clinical validity, intermediate outcomes of interest, and clinical utility) for the purpose of providing relevant indirect evidence of efficacy. Established methods were followed in conducting this review.[9] A Technical Expert Panel that included three EWG members was available to provide expert guidance during the course of the review. The final report, "*Hereditary Nonpolyposis Colorectal Cancer: Accuracy of Diagnostic Strategies and Implications to Patients with Colorectal Cancer and Their Families*," is available online.[8]

In addition, a technical contractor with experience in evidence review collaborated with EGAPP staff and consultants to conduct a supplementary targeted evidence review[5] based on EGAPP methodology.[10] This supplementary review was initiated because Lynch syndrome emerged as being of more specific interest than the less well-defined clinical constellation of HNPCC, and because EWG members requested additional information to address questions dealing with impact of testing strategies on relatives.

EWG members reviewed the AHRQ evidence report, the supplementary targeted review, and key primary publications in detail, and examined other sources of information to address specific gaps in the evidence. The writers of the supplementary report and these EGAPP panel members further collaborated in constructing simple economic models to assist in analyzing the limited evidence available on clinical utility and in estimating how various testing strategies might function in practice. The final EGAPP recommendation statement regarding the use of testing strategies aimed at reducing morbidity and mortality from Lynch syndrome was formulated based on magnitude of effect, certainty of evidence, and consideration of contextual factors (e.g., severity of disorder, family considerations, and costs).

Technology

Strategies for risk assessment are defined in this review as a test or a specific series of tests offered to individuals with newly diagnosed CRC to identify those at sufficient risk for Lynch syndrome to be candidates for MMR gene testing. Based on the AHRQ evidence report, it was decided not to use the family history as an initial screening test (e.g., Amsterdam II or Bethesda criteria) because of the difficulty and costs of obtaining reliable family history and the overall poor sensitivity and specificity of this approach as a first step in identifying risk for Lynch syndrome in this clinical scenario. Possible preliminary tests include either MSI of tumor tissue that can identify the loss of MMR gene function, or IHC testing that identifies the absence of MMR gene protein in tumor tissue. Direct testing of the patient's DNA can then be performed by sequencing to identify deleterious mutations in MMR genes, and multiplex ligation-dependent probe amplification (MLPA) to detect deletions in MMR gene exons. Testing for the *BRAF* V600E mutation is also being evaluated for use in patients whose IHC study indicates absence of the MLH1 protein. *BRAF* mutation testing is associated with methylation abnormalities of the *MLH1* promoter region which are not found in association with *MLH1* mutations. Individuals found with the *BRAF* mutation are unlikely to have Lynch syndrome and, therefore, can avoid the need for expensive MMR gene testing.

Analytic validity

Analytic validity refers to a test's ability to accurately and reliably measure the analyte or genotype of interest, and includes measures of analytic sensitivity and specificity, assay robustness, and quality control. Three preliminary tests (MSI, IHC, and *BRAF*) are relevant for Lynch syndrome, as well as diagnostic testing for mutations in specific MMR genes via sequencing, and for MMR gene deletions by MLPA. Although a comprehensive review of these tests was not performed, general information regarding these tests is summarized below.

- DNA sequencing is considered a gold standard, but the actual analytic performance is difficult to estimate. A recently instituted European external proficiency testing program is focused on sequencing methodology rather than sequencing a specific gene.[11] It is not yet known whether this approach will serve as an adequate measure of analytic validity.
- MSI testing is offered in many laboratories in the United States, and a high proportion will participate in the College of American Pathologists (CAP) external proficiency testing program (Molecular Pathology, MSI).[12] Based on those program results, the analytic performance was high, but deficiencies were identified. Participant summary reports suggest that general adherence to best practices (e.g., documenting a high proportion of tumor cells, using three or more mononucleotide repeats) may be associated with higher analytic validity.
- IHC testing for MMR gene proteins is not currently subjected to CAP external proficiency testing, but IHC testing for other proteins (HER2, CD117, ER, CD-20, or EGFR) is offered as part of the CAP Immunohistochemistry Survey.[13]
- *BRAF* mutation testing is less available than these other tests. Given that this test is aimed at identifying a single mutation, analytic validity is likely to be high; similar to that found through CAP proficiency testing for other single mutation tests such as the gene associated with

hemochromatosis.[14] *BRAF* mutation testing has very high clinical validity, as few reported MMR gene mutation carriers have also been found to carry this mutation; this provides indirect evidence of high analytic validity.

Clinical validity

The clinical validity of a genetic test defines how well test results correlate with the intermediate or final outcomes of interest. In this clinical scenario, the evidence for clinical validity is dispersed among studies examining MSI, IHC, *BRAF* and MMR gene testing, singly and in various combinations. MMR gene testing for one of the mutations of interest is the standard for defining Lynch syndrome. Thus, the EWG examined evidence comparing performance of MSI, IHC, and *BRAF* as preliminary tests to identify individuals who should be offered diagnostic MMR gene testing.

Microsatellite instability testing

To determine clinical sensitivity of MSI testing, the ideal study would be to enroll individuals consecutively diagnosed with CRC from a typical population and perform MMR gene mutation testing on all, followed by MSI testing on those identified with Lynch syndrome. No such studies were found. Of 11 studies meeting inclusion criteria (examining a total of 150 patients with Lynch syndrome), only one was population based, but it was restricted to younger probands.[5] The review was further complicated in that studies did not use the same markers (or the same number of markers) in the MSI panel, with some using as few as two and others as many as 11. A high proportion of mutations in the *MLH1* and *MSH2* genes can be associated with MSI-high results; about 89% if three or more mononucleotide markers are used. Sensitivity for *MSH6* is probably lower, estimated at 77%, even with a comprehensive panel. Current practice in clinical laboratories may result in lower performance than in research laboratories. Six studies provide information regarding clinical specificity, leading to an estimate of approximately 90.2% (false positive rate of 9.8%). Two used only one mononucleotide marker (*BAT26*) to define MSI status and, as might be expected, both showed higher specificities (lower false positive rates) than the consensus.

Immunohistochemical testing

The optimal study design to determine clinical sensitivity of IHC testing would be similar to that for MSI; none were identified. Nine studies met inclusion criteria (examining a total of 149 patients with Lynch syndrome).[5] Sensitivity for *MLH1, MSH2*, and *MSH6* are each estimated at 83%, based on seven studies for *MLH1* and *MSH2*, and five studies for *MSH6*. Two studies were informative with respect to specificity, leading to an estimate of approximately 90% (false positive rate of 10%).

BRAF V600E mutation testing

About 90% of the mutations in the *BRAF* gene in CRC tumors are accounted for by a transversion (1799 T>A), identified as V600E. The *BRAF* mutation is often present when the promoter region of the *MLH1* gene is methylated (methylation is the most common cause of absent MLH1 staining). When the *BRAF* V600E mutation is present, a deleterious MMR gene mutation has not yet been reported. These characteristics can be useful in determining which patients with absent MLH1 staining should be offered *MLH1* gene sequencing. Among the three studies with useable results, no *BRAF* mutations were found among 42 Lynch syndrome patients with absent MLH1 staining, whereas 68% of sporadic cancers (e.g., MLH1 absent staining, but no detectable MMR gene mutation) had the *BRAF* mutation.[5] This reduces the number of patients needing MMR gene sequencing without reducing clinical sensitivity. Indirect evidence and gray data support this finding.

Conclusions

The EWG found convincing evidence that the sensitivity of MSI testing is about 89% for mutations in *MLH1* and *MSH2*, with a lower sensitivity of about 77% for mutations in *MSH6* (and *PMS2*). Sensitivity is higher when three or more mononucleotide markers are included in the panel. Specificity is estimated to be 90.2%, with an adequate level of evidence. There is also convincing evidence that the sensitivity of IHC testing is 83%, regardless of the underlying MMR gene mutation. Specificity is more variable, with a central estimate of 88.8% and an adequate level of evidence. Inadequate evidence is available to determine the distribution of mutations in the MMR genes, but preliminary estimates are 32% *MLH1*, 39% *MSH2*, 14% *MSH6*, and 14% *PMS2*. Adequate evidence is available to estimate sensitivity (69%) and specificity (100%) for *BRAF* mutation testing among newly diagnosed CRC cases with absent IHC staining for MLH1.

Clinical utility

The clinical utility of a genetic test is the likelihood that using the test to guide management will significantly improve health-related outcomes. In this clinical scenario, the question is whether a multistep testing strategy leads to improved clinical outcomes in patients or their relatives. The EWG examined a chain of evidence[10] constructed from studies that individually assessed the components of clinical utility that might provide indirect evidence for clinical utility. At the highest level, these include whether testing leads to changes in clinical management for patients or relatives, and whether such changes in clinical management result in changes to outcomes, with attention to both benefits and harms. In each of these areas EGAPP found limited but promising evidence suggesting that testing can improve outcomes.

Clinical management

Evaluating clinical management involves answering the following two questions: (1) are management options for patients and relatives with an MMR mutation different from those without an MMR mutation; and (2) does knowledge of MMR mutation status change management decisions?

- Probands with Lynch syndrome—The EWG found a variety of surgical and medical management options for Lynch syndrome patients with CRC, but was unable to identify any comparative studies. Subtotal colectomy with ileorectal anastomosis is recommended as a reasonable alternative to segmental resection in these cases, but it has not been shown to be superior at follow-up. No alteration in chemotherapy is currently recommended for Lynch syndrome patients, although a small body of evidence suggests that MSI-high tumors are relatively resistant to 5-fluorouracil and more sensitive to irinotecan.[5] Further clinical trials will be necessary before clinical management recommendations are changed for Lynch syndrome patients with cancer.
- Family members with Lynch syndrome—Clinical management of first- and second-degree relatives of patients with

Lynch syndrome begins with counseling and genetic testing and then includes increased surveillance for relatives found to have Lynch syndrome. Seven studies on the question of counseling and testing showed that about half of the relatives received counseling, and 95% of these chose MMR gene mutation testing.[5] Among the seven studies that examined how testing affects surveillance among relatives with Lynch syndrome, uptake of colonoscopy was high beginning at age 20–25 years, ranging from 53% to 100%. Colonoscopy is recommended every 1–2 years for both patients and their relatives with Lynch syndrome, beginning at age 20–25 years.[15] Colonoscopy risks include nausea, abdominal pain, dizziness, bleeding (2–21/1000 procedures), perforation (0.3–3.0/1000 procedures), and death (0.0–0.2/1000 procedures).

- Risk-reducing colorectal resection in relatives is generally not recommended because of its inherent morbidity and rare mortality, but has been suggested as an option in special circumstances. No data are available regarding how often this option is presented and accepted. A decision analytic study[16] suggested that subtotal colectomy in patients under age 47 with Lynch syndrome increased life expectancy by 1–2.3 years. Indirect evidence from one study suggested that identification of MMR mutations was associated with better prognosis of CRC.
- Female probands and relatives with Lynch syndrome—In women with Lynch syndrome, transvaginal ultrasound and endometrial biopsy every 1–2 years, beginning at age 30–35 years, have been recommended by some, because of the associated risk for endometrial cancer. Two studies have shown that adherence to surveillance is higher in women found to carry a mutation.[17,18] Hysterectomy and bilateral salpingo-oophorectomy is also an option, although not recommended.[5]

Outcomes

Using the chain of evidence methodology,[10] the EWG found adequate evidence that an appropriate testing strategy could lead to acceptable changes in management that can improve clinical outcomes for patients and their relatives. Although there are no randomized trials exploring whether systematic colonic surveillance (e.g., colonoscopy) is effective in reducing Lynch syndrome–related morbidity and mortality, one long-term, nonrandomized controlled study from Finland followed 252 relatives at high risk of having Lynch syndrome.[19] Mutation testing became available during the course of the study, and all colon cancers that developed were found in relatives who carried a mutation. Using an intention to treat analysis, 10 incident CRC cases (8%) occurred among those having colonic surveillance, whereas 26 incident CRC cases (22%) occurred among relatives without such surveillance. This represents a 62% reduction in risk for CRC and a significant reduction in CRC-associated mortality among relatives of Lynch syndrome cases. Supporting evidence was also available from a cohort study of 2788 individuals from 146 Lynch syndrome families in the Netherlands (reduction in standardized mortality ratio between subjects with ($n = 897$) or without ($n = 1073$) colonic surveillance (6.5 vs. 23.9; $P < 0.001$).[20]

In a retrospective study, 61 of 315 women with MMR gene mutations selected risk reducing surgery for endometrial cancer.[21] After approximately 10 years, no endometrial cancers or ovarian cancers developed in the women with surgery, whereas a third of women who did not have surgery developed endometrial cancer, and 5.5% developed ovarian cancer.

Studies reporting psychosocial sequelae of mutation testing find that distress among mutation carriers is usually short term and that noncarriers experience significant relief.[5] Very few data are available with respect to concern about employment and insurance.

Preliminary cost descriptions

Existing economic analyses that included relatives with Lynch syndrome were reviewed and found to be inadequate (e.g., variability in assumptions and initial values, no consideration of impact on relatives, no assessment of IHC as the primary screening test or refined testing strategies that involve *BRAF* or methylation testing).[22–25] The EWG commissioned a basic economic analysis comparing selected strategies of combining MSI, IHC, *BRAF*, and MMR gene mutation testing for the identification of Lynch syndrome among individuals with CRC and their relatives.[5] Four selected sample testing strategies were included. The outcome of interest was the cost per Lynch syndrome case detected (proband, and proband and relatives), total program costs through identification of Lynch syndrome individuals, and the associated incremental costs. Although this cost consequences analysis did not allow the EWG to recommend a specific strategy, the results were used in context with the other findings to inform its recommendation.

Research gaps

Research gaps were identified in four areas. Further studies in these areas could contribute substantially to refining recommendations:

1. Analytical validity—The technology for MSI, IHC, and MMR mutation testing has changed significantly in the last few years and might be expected to continue to do so. Better quality data regarding analytical validity of testing and laboratory proficiency testing should be a high priority. More information on the analytic validity of tests used to refine these strategies (e.g., *BRAF* mutation testing, direct methylation testing) is needed.
2. Clinical validity—Several testing strategies are available, and some are in limited clinical use. Better quality studies comparing their clinical validity are needed in typical populations of individuals with CRC. For example, how would a strategy beginning with MSI testing only, followed by MMR mutation testing in positives, compare with strategies beginning with IHC only, or with both? How would the addition of *BRAF* or methylation testing change the overall clinical sensitivity and specificity? Are there circumstances under which collection of accurate family history information and use of Bethesda guidelines in a testing strategy might be effective in reducing the number of cases for which sequencing is warranted?
3. Clinical utility—CRC is common enough that a direct study that begins with genetic testing and follows through clinical outcomes should be possible in a multicenter protocol. Alternatively, higher quality studies of the individual components of clinical utility (e.g., changes in management, uptake of management recommendations, and long-term clinical outcomes) could be undertaken.
4. Cost-effectiveness analyses (CEA)—There are few CEAs for Lynch syndrome and they are limited in scope. Few have included the impact on relatives, none have examined IHC as the primary initial test, and they vary widely in their assumptions and initial values. In addition, none

have looked at refined testing strategies that involve *BRAF* or methylation testing. CEA studies could form the basis to recommend a specific testing strategy to identify Lynch syndrome, and such an analysis is currently underway in partnership with EGAPP.[26]

Recommendations of other groups

National Comprehensive Cancer Network (NCCN), Clinical Practice Guidelines in Oncology™ v.2.2008.[27]

Inherited colon cancer

- "HNPCC is the most common form of a genetically determined colon cancer predisposition . . . accounting for 2–3% of all colorectal cancer cases. Surveillance has been shown to reduce the risk of colorectal cancer and may be of benefit in the early diagnosis of endometrial cancer."

HNPCC molecular work-up and genetic testing

- "Mixed strategy (MSI testing for all colorectal cancer patients followed by *MSH2* and *MLH1* testing of MSI-high tumors) has been shown as the most cost-effective approach for HNPCC screening. However, conclusive data are not yet available that establishes which test is the most cost-effective screening mechanism in HNPCC"
- "Genetic screening for MSI is cost effective for patients with newly diagnosed colon cancer as well as for the siblings and children of mutation carriers."
- "When a mutation is found in the family, it offers an opportunity to provide predictive testing for at-risk relatives. Predictive testing can save people a lot of unnecessary procedures. It is important to consider genetic testing for at-risk family members when the family mutation is known."

American Society of Clinical Oncologists (ASCO) 2006,[30] Update of Recommendations for the Use of Tumor Markers in Gastrointestinal Cancer.

- *"2006 recommendation for use of microsatellite instability to determine prognosis*. Microsatellite instability (MSI) ascertained by polymerase chain reaction (PCR) is not recommended at this time to determine the prognosis of operable colorectal cancer nor to predict the effectiveness of FU (fluorouracil) adjuvant chemotherapy."

Contextual issues

Major contextual issues considered by the EWG included

- With limited benefit of genetic testing to the CRC patient, the EWG recommends that informed consent should be obtained before MSI or IHC testing.
- Results of several studies comparing psychosocial outcomes between MMR gene mutation carriers and noncarriers, and changes in outcomes over time, have provided no indication of adverse events relating to genetic testing. Furthermore, changes in distress seem to be short lived among mutation carriers, and there may be decreases in colon cancer worry, general anxiety, and depression among noncarriers who do not have Lynch syndrome. The EWG found no substantial evidence to show that identifying Lynch syndrome via routine genetic testing would lead to adverse psychosocial outcomes.
- Evidence shows relatively high levels of uptake for counseling among first-degree relatives contacted, subsequent MMR gene mutation testing, and adherence to increased surveillance among relatives found to have Lynch syndrome. The EWG concludes that the level of participation among relatives is sufficient to justify the resources needed to implement routine genetic testing strategies.

REFERENCES

1. Cancer Facts & Figures 2007. American Cancer Society. Available at: http://www.cancer.org/downloads/STT/CAFF2007PWSecured.pdf. Accessed June 5, 2008.
2. Hampel H, Frankel WL, Martin E, et al. Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). *N Engl J Med* 2005;352:1851–1860.
3. Jass JR. Hereditary non-polyposis colorectal cancer: the rise and fall of a confusing term. *World J Gastroenterol* 2006;12:4943–4950.
4. Lindor NM, Rabe K, Petersen GM, et al. Lower cancer incidence in Amsterdam-I criteria families without mismatch repair deficiency: familial colorectal cancer type X. *JAMA* 2005;293:1979–1985.
5. Palomaki GE, McClain MR, Melillo S, Hampel HL, Thibodeau SN. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. *Genet Med* 2009;11:42–65.
6. Centers for Disease Control: Evaluation of Genomic Applications in Practice and Prevention (EGAPP). Available at: http://www.cdc.gov/genomics/gtesting/EGAPP/about.htm. Accessed June 5, 2008.
7. Evaluation of Genomic Applications in Practice and Prevention (EGAPP): Implementation and Evaluation of a Model Approach. Available at: http://www.egappreviews. org/. Accessed June 5, 2008.
8. Hereditary nonpolyposis colorectal cancer: diagnostic strategies and their implications [structured abstract]. Rockville, MD: Agency for Healthcare Research and Quality, 2007. Available at: http://www.ahrq.gov/clinic/tp/hnpcctp.htm. Accessed June 5, 2008.
9. Evidence-based practice centers overview. Rockville, MD: Agency for Healthcare Research and Quality, 2007. Available at: http://www.ahrq.gov/clinic/epc/. Accessed June 5, 2008.
10. Teutsch SM, Bradley LA, Palomaki GE, et al. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative: Methods of the EGAPP Working Group. *Genet Med* 2009;11:3–14.
11. Patton SJ, Wallace AJ, Elles R. Benchmark for evaluating the quality of DNA sequencing: proposal from an international external quality assessment scheme. *Clin Chem* 2006;52:728–736.
12. College of American Pathologists. Enhance your molecular pathology analyses. Available at: http://www.cap.org/apps/cap.portal?_nfpb=true&cntvwrPtlt_actionOverride=%2Fportlets%2FcontentViewer%2Fshow&_windowLabel=cntvwrPtlt&cntvwrPtlt%7BactionForm.contentReference%7D=news_service%2F0501%2F0501_MPA.html&_state=maximized&_pageLabel=cntvwr. Accessed June 5, 2008.
13. College of American Pathologists. HER2 testing guidelines and resources. Available at: http:// www.cap.org/apps/cap.portal?_nfpb=true&cntvwrPtlt_actionOverride=%2Fportlets%2 FcontentViewer%2Fshow&_windowLabel=cntvwrPtlt&cntvwrPtlt%7BactionForm. contentReference%7D=committees%2Fcancer%2Fher2_index.html&_state=maximized&_pageLabel=cntvwr. Accessed June 5, 2008.
14. Palomaki GE, Haddow JE, Bradley LA, et al. Estimated analytic validity of HFE C282Y mutation testing in population screening: the potential value of confirmatory testing. *Genet Med* 2003;5:440–443.
15. Vasen HF, Moslein G, Alonso A, et al. Guidelines for the clinical management of Lynch syndrome (hereditary non-polyposis cancer). *J Med Genet* 2007;44:353–362.
16. de Vos tot Nederveen Cappel WH, Buskens E, van Duijvendijk P, et al. Decision analysis in the surgical treatment of colorectal cancer due to a mismatch repair gene defect. *Gut* 2003;52:1752–1755.
17. Collins V, Meiser B, Gaff C, St John DJ, Halliday J. Screening and preventive behaviors one year after predictive genetic testing for hereditary nonpolyposis colorectal carcinoma. *Cancer* 2005;104:273–281.
18. Wagner A, van Kessel I, Kriege MG, et al. Long term follow-up of HNPCC gene mutation carriers: compliance with screening and satisfaction with counseling and screening procedures. *Fam Cancer* 2005;4:295–300.
19. 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.
20. de Jong AE, Hendriks YM, Kleibeuker JH, et al. Decrease in mortality in Lynch syndrome families because of surveillance. *Gastroenterology* 2006;130:665–671.
21. 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.
22. Breheny N, Geelhoed E, Goldblatt J, Ee H, O'Leary P. Economic evaluation of the familial cancer programme in Western Australia: predictive genetic testing for familial adenomatous polyposis and hereditary non-polyposis colorectal carcinoma. *Community Genet* 2006;9:98–106.
23. Olsen KR, Bojesen SE, Gerdes AM, Lindorff-Larsen K, Bernstein IT. Cost-effectiveness of surveillance programs for families at high and mod-

erate risk of hereditary non-polyposis colorectal cancer. *Int J Technol Assess Health Care* 2007;23:89–95.
24. Syngal S, Weeks JC, Schrag D, Garber JE, Kuntz KM. Benefits of colonoscopic surveillance and prophylactic colectomy in patients with hereditary nonpolyposis colorectal cancer mutations. *Ann Intern Med* 1998;129:787–796.
25. Vasen HF, van Ballegooijen M, Buskens E, et al. A cost-effectiveness analysis of colorectal screening of hereditary nonpolyposis colorectal carcinoma gene carriers. *Cancer* 1998;82:1632–1637.
26. Mvundura M, Palomaki GE, McClain MR, Coates RJ, Grosse SD. Cost effectiveness of genetic testing for Lynch syndrome among newly diagnosed colorectal cancer patients and their first-degree relatives [abstract]. Presented at the 30th Annual Meeting of the Society for Medical Decision Making. October 19, 2008. Philadelphia, PA.
27. National Comprehensive Cancer Network (NCCN), Clinical Practice Guidelines in Oncology™ v. 2.2008. Available at: http://www.nccn.org/professionals/physician_ gls/PDF/colorectal_screening.pdf. Accessed December 8, 2008.
28. 2006 update of ASCO recommendations for the use of tumor markers in gastrointestinal cancer. *J Oncol Pract* 2006;2:314–316.

Cancer Genetic Counselors in Connecticut

Danbury Hospital/New Milford Hospital
24 Hospital Ave., Danbury, CT 06810
Phone: 203-739-4957
Fax: 203-739-1922
http://www.westernconnecticuthealthnetwork.org/

Shannon Morrill-Cornelius, MS, CGC

Hartford Hospital
Helen & Harry Gray Cancer Center
80 Seymour St., Hartford, CT 06102-5037
Phone: 860-545-6000
http://www.harthosp.org/cancer/default.aspx

Linda Steinmark, MS, CGC
Sara Rhode, MS, CGC

Norwalk Hospital
Whittingham Cancer Center
24 Stevens Street, Norwalk CT 06856
Phone: 203-852-2148
www.norwalkhospital.org

Susan Ingram, MS, CGC
Jessica Lipschutz, MS, CGC

Saint Francis/Mount Sinai Regional Cancer Center, Karvoski Genetics Program
114 Woodland St., Hartford, CT 06105-1299
Phone: 860-714-6483
http://www.stfranciscare.org/Content.aspx?id=12884902340

Linda Steinmark, MS, CGC
Sara Rhode, MS, CGC

Stamford Hospital, Bennett Cancer Center
30 Shelburne Rd., Stamford, CT 06904-9317
Phone: 203-276-7693
http://www.stamfordhospitalcancer.com/screening/screen_gen.aspx

Erin Ash, MS, CGC

The Hospital of Central Connecticut
The Katherine Ann King Rudolph Hereditary Cancer Genetics Program
100 Grand St., E121,
New Britain, CT 06050
Phone: 860-224-5900 x6630
http://thocc.org/services/cancer/genetics.aspx

Linda Steinmark, MS, CGC
Sara Rhode, MS, CGC

University of Connecticut
Hereditary Cancer Program
Division of Human Genetics
65 Kane Street, West Hartford, CT 06119
Phone: 860-523-6424
http://humangenetics.uchc.edu/hereditary/index.html

Robin Schwartz, MS, CGC
Jennifer Stroop, MS, CGC

Yale Cancer Genetic Counseling Program
Yale Cancer Center
55 Church St., Suite 402
New Haven, CT 06510
Outreach clinics: Greenwich, Griffin
Phone: 203-764-8400
Fax: 203-764-8401
www.yalecancercenter.org/genetics

Ellen T. Matloff, MS, CGC
Rachel E. Barnett, MS, CGC
Danielle Bonadies, MS, CGC
Karina L. Brierley, MS, CGC

Developed by the Connecticut Department of Public Health's Genomics Office in partnership with the Connecticut Tumor Registry, and funded through a Healthy People 2020 Action Project grant.

Connecticut Department of Public Health
410 Capitol Avenue, Hartford, CT 06106
(860) 509-8070 www.ct.gov/dph

Hereditary Breast and Ovarian Cancer Syndrome

Hereditary breast and ovarian cancer (HBOC) syndrome is a condition that greatly increases a person's chance of getting cancer. HBOC syndrome is *inherited*. This means it runs in families. It is caused by damaged genes that can be passed from parents to their children. Most cases of HBOC result from damage to genes called *BRCA1* and *BRCA2*.

Most breast and ovarian cancers are not related to HBOC syndrome. In fact, only about 5 of every 100 breast cancers and 10 of every 100 ovarian cancers are caused by the condition. A genetic test can tell if your cancer was caused by HBOC syndrome.

WHY IT IS IMPORTANT TO KNOW ABOUT HBOC SYNDROME

When people have HBOC syndrome, there is a 50/50 chance that their children, sisters, and brothers could also have it. Their parents and other blood relatives (grandparents, aunts, uncles, nieces, nephews) also are more likely than others to have the condition.

A person with HBOC syndrome has up to an 8 in 10 chance of getting breast cancer, compared to only 1 in 10 for the general population. For ovarian cancer, HBOC increases risk to as much as 6 in 10, compared to about 1 in 100 for the general population.

SIGNS THAT HBOC MAY RUN IN A FAMILY

Some signs that HBOC may run in a family are:

- Close blood relatives with breast or ovarian cancer
- Female blood relatives who got breast cancer before age 50
- A female relative who had both breast and ovarian cancer
- A male relative with breast cancer
- Eastern European (Ashkenazi) Jewish ancestry

GENETIC COUNSELING AND TESTING FOR HBOC SYNDROME

If HBOC is suspected, talk to a genetic counselor or another health care professional who has been trained to take a complete family health history and to discuss the pros and cons of genetic testing.

Genetic testing is a kind of blood test that looks for damaged genes. If test results are positive for damaged *BRCA1* or *BRCA2* genes, the affected person's family members can also be tested. Family members who test positive for HBOC syndrome can then get screened for breast cancer earlier and more often. They can also be watched carefully for signs of ovarian cancer. This could lead to finding cancer early and treating it successfully.

Family members who did not inherit HBOC syndrome still can get cancer, but their chances are much lower.

FOR MORE INFORMATION

First, talk with your doctor or other health care provider.

You can also find more information on breast cancer, cancer genetic testing, and genetic counseling services at the places shown below.

Centers for Disease Control and Prevention. Breast and Ovarian Cancer and Family Health History
http://1.usa.gov/vg2783

Genetics Home Reference. National Library of Medicine
www.ghr.nlm.nih.gov/condition/breast-cancer

National Cancer Institute. Understanding Cancer Series
http://1.usa.gov/vWPnil

Connecticut Department of Public Health. New England Cancer Genetic Counselors
http://1.usa.gov/tqzPZI

National Cancer Institute's Cancer Information Service
1-800-4CANCER
http://www.cancer.gov/aboutnci/cis/

Developed by the Connecticut Department of Public Health's Genomics Office in partnership with the Connecticut Tumor Registry, and funded through a Healthy People 2020 Action Project grant.

Connecticut Department of Public Health
410 Capitol Avenue, Hartford, CT 06106
(860) 509-8070 www.ct.gov/dph

Lynch Syndrome

Lynch syndrome is a condition that increases a person's chance of getting cancer, especially colorectal cancer (cancer of the large bowel or rectum), and especially at a young age (before age 50). For women, it also increases the chance of getting cancer of the endometrium (lining of the uterus or womb) and ovary.

About 3 out of every 100 colorectal cancers are caused by Lynch syndrome. A genetic test can tell if your cancer was caused by Lynch syndrome.

CAUSES OF LYNCH SYNDROME

Lynch syndrome is *inherited*. This means it runs in families. It is caused by damaged genes that can be passed from parents to their children.

When people have Lynch syndrome, the odds are about 50/50 that their children, sisters, and brothers could also have it. Their parents and other blood relatives (grandparents, aunts, uncles, nieces, nephews) also are more likely than others to have the condition.

GENETIC TESTING FOR LYNCH SYNDROME

Health care experts* recommend that every person with a new diagnosis of colorectal cancer should be offered counseling and information about genetic testing for Lynch syndrome.

Genetic testing is a kind of blood test that can confirm or rule out that a person has Lynch syndrome. It can tell if a person's colorectal cancer was caused by Lynch syndrome. If it was, family members also might benefit from genetic counseling and testing.

BENEFITS OF GENETIC TESTING TO FAMILY MEMBERS

Blood relatives can be tested to learn if they also have Lynch syndrome. If they have Lynch syndrome, they can get screened for colorectal cancer sooner (before age 50) and more often. The most common methods of screening for colorectal cancer are colonoscopy, sigmoidoscopy, and tests for blood in the stool.

OTHERS WHO MIGHT BENEFIT FROM COUNSELING AND TESTING

Other people who might benefit from genetic counseling are:

- People diagnosed with colorectal cancer in the past (especially before age 50)
- People with several family members who had colorectal cancer or cancer of the uterus (womb).

* Evaluation of Genomic Applications in Practice and Prevention Work Group

FOR MORE INFORMATION

First, talk with your doctor or other health care provider.

You can also find more information on colorectal cancer, Lynch syndrome, cancer genetic testing, and genetic counseling services at the places shown below.

Centers for Disease Control and Prevention. Genetic Testing for Lynch Syndrome
http://1.usa.gov/sJEgXS

Genetics Home Reference. National Library of Medicine
http://tiny.cc/1lqsw

National Cancer Institute. Understanding Cancer Series
http://1.usa.gov/vWPnil

Connecticut Department of Public Health. New England Cancer Genetic Counselors
http://1.usa.gov/tqzPZI

National Cancer Institute's Cancer Information Service
1-800-4CANCER
http://1.usa.gov/pG98K9

Developed by the Connecticut Department of Public Health's Genomics Office in partnership with the Connecticut Tumor Registry, and funded through a Healthy People 2020 Action Project grant.

Connecticut Department of Public Health
410 Capitol Avenue, Hartford, CT 06106
(860) 509-8070 www.ct.gov/dph

Additional Resources

Resources for Health Professionals

U.S. Centers for Disease Control and Prevention

- Hereditary Breast and Ovarian Cancer: BRCA and Your Patient
  CDC Expert Commentary on Medscape
  http://www.medscape.com/viewarticle/749018

National Cancer Institute

- Genetics of Breast and Ovarian Cancer (PDQ®)
  http://1.usa.gov/c3xkjs

- Genetics of Colorectal Cancer (PDQ®)
  http://1.usa.gov/bERdii

U.S. Department of Health and Human Services, Agency for Healthcare Research and Quality

- Hereditary Nonpolyposis Colorectal Cancer: Diagnostic Strategies and Their Implications (2007)
  http://1.usa.gov/xBVnKK

Evaluation of Genomic Applications in Practice and Prevention (EGAPP)

- EGAPP Working Group, Supplementary Evidence Review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome
  http://bit.ly/uJIIYZ

Developed by the Connecticut Department of Public Health's Genomics Office in partnership with the Connecticut Tumor Registry, and funded through a Healthy People 2020 Action Project grant.

Connecticut Department of Public Health
410 Capitol Avenue, Hartford, CT 06106
(860) 509-8070 www.ct.gov/dph

Resources for Consumers

U.S. Centers for Disease Control and Prevention

- Breast and Ovarian Cancer and Family Health History
  http://1.usa.gov/vg2783

- Genetic Testing for Lynch Syndrome
  http://1.usa.gov/sJEgXS

U.S. Surgeon General

- Family Health History Tool: "My Family Health Portrait"
  (available in multiple languages)
  https://familyhistory.hhs.gov/fhh-web/home.action

National Society of Genetic Counselors

- Considering the Services of a Genetic Counselor?
  http://bit.ly/zFyVvS

Connecticut Department of Public Health, Genomics Office

- Genetic Testing for Hereditary Breast & Ovarian Cancer:
  What You Should Know
  http://1.usa.gov/xADuUC

- Genetic Evaluation and Testing for Hereditary Colorectal Cancer:
  What You Should Know
  http://1.usa.gov/w8IYWK

- Your Family Health History Workbook: Knowing your past can
  influence your future
  http://1.usa.gov/w70Dt2

Michigan Department of Community Health, Genomics Program

- Cancer Genomics Terminology
  http://bit.ly/AmY9td

STANDARD 2.3
Risk Assessment and Genetic Counseling

Cancer risk assessment, genetic counseling, and testing services are provided to patients either on-site or by referral, by a qualified genetics professional.

DEFINITION AND REQUIREMENTS

Cancer risk assessment and genetic counseling are the processes to identify and counsel people at risk for familial or hereditary cancer syndromes The purposes of genetic counseling are to educate patients about their chance of developing cancers, help them obtain personal meaning from cancer genetic information, and empower them to make educated, informed decisions about genetic testing, cancer screening, and cancer prevention. Identifying patients at increased risk of developing cancer because of a family history of cancer or a known hereditary cancer syndrome can have dramatic effects on early detection and cancer outcome. For this reason, cancer risk assessment and genetic counseling are rapidly becoming standards of care for patients with personal and/or family history of cancer who are at high risk of having a hereditary syndrome.

The program provides cancer risk assessment and genetic counseling on-site or by referral to another facility or community-based organization.

Cancer risk assessment and genetic counseling are performed by a cancer genetics professional who has extensive experience and educational background in genetics, cancer genetics, counseling, and hereditary cancer syndromes to provide accurate risk assessment and empathetic genetic counseling to patients with cancer and their families.

Cancer risk assessment and the potential for referral may be discussed as part of the multidisciplinary cancer conference.

Genetics professionals include people with the following:

- An American Board of Genetic Counseling (ABGC) or American Board of Medical Genetics (ABMG) board-certified/board-eligible or (in some states) a licensed genetic counselor
- An American College of Medical Genetics physician board certified in medical genetics
- A Genetics Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APNG), credentialed through the Genetics Nursing Credentialing Commission (GNCC). Credentialing is obtained through successful completion of a professional portfolio review process.
- An advanced practice oncology nurse who is prepared at the graduate level (master or doctorate) with specialized education in cancer genetics and hereditary cancer predisposition syndromes*; certification by the Oncology Nursing Certification Corporation is preferred.
- A board-certified physician with experience in cancer genetics (defined as providing cancer risk assessment on a regular basis).

**Please note, specialized training in cancer genetics should be ongoing; educational seminars offered by commercial laboratories about how to perform genetic testing are not considered adequate training for cancer risk assessment and genetic counseling.*

The Cancer Committee defines the appropriate individuals who will provide risk assessment and counseling for major cancer disease sites (such as breast and colorectal). In addition, the programs not having immediate access to formal genetic counseling services should identify resources for referral.

Cancer risk assessment and genetic counseling involve pretest and posttest counseling. At a minimum, this counseling includes the following:

Pretest Counseling

- Collecting relevant information needed to assess a patient's personal and family medical history
  - » A 3- to 4-generation pedigree, including detailed medical information about the patient's first-, second-, and third-degree relatives should be obtained. Gathering information about paternal and maternal family history, ancestry/ethnicity, and consanguinity, as available, is necessary.
- Evaluating the patient's risk
  - » One aspect of risk assessment is discussing the absolute risk that the patient will develop a specific type of cancer or cancers based on the family history. The second aspect is the risk that the patient carries a heritable or germline mutation in a cancer susceptibility gene.
- Performing a psychosocial assessment
- Educating the patient about the suspected hereditary cancer syndrome, if appropriate
  - » The provider reviews and discusses with the patient the cancer risks associated with gene mutations, including basic concepts such as genes and inheritance patterns and more advanced concepts of penetrance and variable expressivity and the possibility of genetic heterogeneity.
- Obtaining informed consent for genetic testing (if genetic testing is recommended).

Posttest Counseling

- Disclosure of the results and posttest counseling include a discussion of the results, significance and impact of the test results, medical management options, informing other relatives, future contact, and available resources. The test results and interpretation will be communicated to the provider.

Guidelines and recommendations for cancer risk assessment and genetic counseling for hereditary cancer syndromes are available from the Agency for Healthcare Research and Quality (AHRQ) and the NCCN.

SPECIFICATIONS BY CATEGORY

All programs fulfill the standard as written.

DOCUMENTATION

The program completes the SAR.

During the on-site visit, the surveyor will discuss the process for providing cancer risk assessment and genetic counseling services either on-site or by referral.

MEASURING COMPLIANCE

Rating

(1) Compliance: The program fulfills the following criterion:

> Cancer risk assessment, genetic counseling, and testing services are provided to patients either on-site or by referral, by a qualified genetics professional.

(5) Noncompliance: The program does not fulfill the following criterion.

> Cancer risk assessment, genetic counseling, and testing services are provided to patients either on-site or by referral, by a qualified genetics professional.

Reprinted from:
American College of Surgeons Commission on Cancer. 2011. *Cancer Program Standards 2012: Ensuring Patient-Centered Care, v.1.0.* Pages 68-69: Standard 2.3. Risk Assessment and Genetic Counseling. Chicago: American College of Surgeons.
http://www.facs.org/cancer/coc/cocprogramstandards2012.pdf