

GENETIC TESTING

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Overview

Genetic testing refers to the laboratory analysis of DNA. Compared to other types of laboratory testing, genetic testing is unique in that it can provide a diagnosis and/or a prediction of the likelihood of developing a particular disease before symptoms even appear; it can also reveal if a person is carrying a specific gene that could be passed on to his or her children. While genetic testing holds great potential, it also has many limitations:

1. Genetic tests may predict the chances of developing a particular disease. Such results may leave a person wondering what to do with the results, particularly if there are treatments available that may change the course of the disease.
2. While genetic tests may reveal if a mutation exists, it does not guarantee that the disease will develop, nor can it predict how severely the disease will manifest in the person carrying the mutation, e.g., some individuals with cystic fibrosis have mild symptoms, while others develop debilitating lung disease and pancreatitis.
3. Many genetic tests cannot detect all mutations that can cause disease, and thus, while a positive result can be informative, a negative result is “not always conclusive” or “may be inconclusive.”
4. Many diseases are the result of an interaction between genes and environment, and the way these interactions cause disease is not clearly understood.
5. There are many legal and social issues that must be considered.

Because of these limitations, it is essential that individuals are thoroughly informed before undergoing any type of genetic testing. Results of genetic testing can have implications not only for an individual, but for an individual's family as well. Genetic counseling is advised to communicate the limitations of genetic testing and to also counsel patients about the results.

Massachusetts law Chapter 111, Section 70G, requires prior written consent before genetic testing. The consent form must be signed by the person who is the subject of the test or, if that person lacks capacity to consent, signed by the person authorized to consent for such person. Prior written consent must include:

1. A statement of the purpose of the test;
2. A statement that prior to signing the consent form, the consenting person discussed with the medical practitioner ordering the test the reliability of positive or negative test results and the level of certainty that a positive test result for that disease or condition serves as a predictor of such disease;
3. A statement that the consenting person was informed about the availability and importance of genetic counseling and provided with written information identifying a genetic counselor or medical geneticist from whom the consenting person might obtain such counseling;
4. A general description of each specific disease or condition tested for; and
5. The person or persons to whom the test results may be disclosed.

FCHP does not cover direct-to-consumer genetic testing, including, but not limited to, “home-testing kits” or genetic tests ordered by patients over the telephone or Internet. The American College of Medical Genetics recommends that genetic testing should only be provided by a qualified health care professional who is responsible for both ordering and interpreting the genetic tests as well as pretest and post-test counseling of individuals and families regarding the medical significance of the test results and the need for follow-up, if any.

Definitions

First-degree relative – a blood relative with whom an individual shares approximately 50% of his or her genes, including parents, full siblings and children

Second-degree relative – a blood relative with whom an individual shares approximately 25% of his/her genes, including grandparents, grandchildren, aunts, uncles, nephews, nieces and half-siblings

Guidelines for Genetic Testing

Genetic testing requires preauthorization

All of the Guidelines for Genetic Testing and the disease specific criteria below must be met to satisfy coverage requirements for genetic testing:

1. The test is to be used for the diagnosis or determination of risk for a suspected disease for a plan member who is either:
 - symptomatic (e.g., exhibiting signs and symptoms of a disease), or;
 - presymptomatic, but at an increased risk of disease, as determined by current scientific literature which may be due to family history, ethnicity, or gender.
2. The results of the test will be clinically useful to the medical management of the patient (e.g., initiate a new course of therapy, alter an existing therapy, or determine level of surveillance).
3. There is a sufficient amount of evidence in the scientific literature to support the validity and predictive accuracy of the test.
4. The patient/family has consulted with a genetic practitioner (as defined above) to discuss their questions and concerns about the test and how the results will be used.
5. Prior written consent has been obtained.
6. All testing must be at a contracted facility when available.
7. Repeat genetic testing is not covered.

Due to the rapidly evolving field of genetic tests, this policy is not inclusive of all known genetic tests. The above Guidelines for Genetic Testing apply to all genetic testing whether or not disease specific criteria are listed below. Coverage for other genetic tests are managed on an individual basis. Refer to the Infertility/Assisted Reproductive Technology Policy for coverage of preimplantation genetic testing.

Breast and Ovarian Cancer

Currently, sequence analysis is the only commercially available method of mutation detection in an affected individual when the familial mutation is unknown. However, a negative result does not necessarily indicate that the individual does not carry an inherited mutation. It is possible that a mutation exists, but current testing methods have not identified it. Once a BRCA1 or BRCA2 mutation is detected in a family, it is reasonable to test other family members who wish to learn whether or not they have inherited the mutation and the associated cancer risks. Three specific mutations account for approximately 90% of the BRCA1 and BRCA2 mutations in at risk individuals of Ashkenazi Jewish descent; namely: 185delAG, 538insC, and 617delT. If the individual is of Ashkenazi Jewish descent, testing for these three common mutations, called multi-site analysis, should be done first. If results are negative, consider sequence analysis.

Covered Services

Genetic testing requires preauthorization

FCHP covers BracAnalysis® (full sequencing of BRCA1 and BRCA2 genes) when the familial mutation is unknown, single-site BracAnalysis® when the familial mutation is known, or multi-site 3 BRACAnalysis® when the individual is a member of an ethnic group with a known higher frequency of BRCA1 and BRCA2 mutations, such as of Ashkenazi Jewish descent, and both the Guidelines for Genetic Testing and the Criteria for BRCA1 and/or BRCA2 Testing are met.

Criteria for BRCA1 and/or BRCA2 Testing

Criteria for BRCA1 and BRCA2 testing were adapted from the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Version 1.2006.

One of the following criteria may indicate a susceptibility to inherited breast or ovarian cancer:

1. Family member¹ (includes first or second-degree relatives) with known BRCA1 or BRCA2 mutation
2. Female with breast cancer (for the purposes of these criteria, invasive and ductal carcinoma in situ breast cancers should be included) AND one of the following:
 - a. Diagnosed at age 40 or younger
 - b. Diagnosed at age 50 or younger and one or more family members diagnosed with breast cancer at age 50 or younger
 - c. Diagnosed at age 50 or younger and one or more family members diagnosed with ovarian cancer
 - d. Two or more primary breast tumor sites (including bilateral disease or cases involving two or more clearly separate ipsilateral tumors) and one or more family members diagnosed with breast cancer at age 50 or younger
 - e. Two or more primary breast tumor sites (including bilateral disease or cases involving two or more clearly separate ipsilateral tumors) and one or more family members diagnosed with ovarian cancer
 - f. Diagnosed at any age with two or more family members with ovarian cancer
 - g. Diagnosed at any age with two or more family members with breast cancer, especially if one or more is diagnosed before age 50 or has two primary breast tumor sites
 - h. Male family member with breast cancer
 - i. Personal history of ovarian cancer
 - j. Of certain ethnic groups with known higher frequency of BRCA1 and BRCA2 mutations, such as of Ashkenazi Jewish descent, and one or more family members diagnosed with breast or ovarian cancer
3. Female with ovarian Cancer AND one of the following:
 - a. One or more family members diagnosed with ovarian cancer
 - b. One or more female family members diagnosed with breast cancer at age 50 or younger
 - c. One or more female family members diagnosed with two or more primary breast tumor sites
 - d. One or more male family members with breast cancer
 - e. Of certain ethnic groups with known higher frequency of BRCA1 and BRCA2 mutations, such as of Ashkenazi Jewish descent
4. Male with breast cancer AND one of the following:
 - a. One or more male family members with breast cancer
 - b. One or more female family members with breast cancer or ovarian cancer
 - c. Of certain ethnic groups with known higher frequency of BRCA1 and BRCA2 mutations, such as of Ashkenazi Jewish descent

¹ Unless otherwise indicated, family members include first and second degree relatives.

Exclusions

1. Genetic testing for BRCA1 or BRCA2 is not covered for individuals under the age of 18, because there are no recommended preventive interventions for those known to have BRCA1 or BRCA2 mutations and breast and ovarian cancer rarely manifest in this group.
2. BRCA mutations have been investigated as a cause for certain other cancers, such as pancreatic, prostate and colon cancer. The peer-reviewed published scientific literature does not support BRCA testing for the assessment of risk of cancers other than breast or ovarian cancer.

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Hereditary Non-Polyposis Colon Cancer (HNPCC)

HNPCC, also known as Lynch Syndrome, is an autosomal dominant disorder caused by a germ-line mutation of one of the five mismatch repair genes (MLH1, MSH2, MSH6, PMS1, or PMS2). Individuals with HNPCC have an 80% lifetime risk of developing colon cancer and are at increased risk for developing several other extracolonic cancers as well.

A history revealing the following risk factors suggests an individual may be *at-risk* for HNPCC:

- Colon cancer at age 50 years or less
- Autosomal dominant pattern of inheritance
- Colon cancer in a first or second-degree family member, right-sided colon cancer predominance
- Multiple primary cancers (colon, endometrial, ovarian, duodenal/small bowel, stomach ureteral/renal pelvis, sebaceous adenomas or sebaceous carcinomas)

A characteristic of HNPCC tumors is microsatellite instability (MSI). Detection of MSI-high in a tumor sample increases the probability of detecting a germ-line mutation in one of the mismatch repair genes. Individuals whose tumors show MSI-low or microsatellite stable are unlikely to carry a germ-line mutation and genetic testing is not recommended. Immunohistochemistry (IHC) testing uses antibodies to measure expression of mismatch repair proteins in a tumor. Loss of expression of a specific protein produced by one of the mismatch repair genes may be an indicator of a germ-line mutation. IHC testing pinpoints the gene that is implicated and facilitates

the search for the underlying mutation. Currently, commercial laboratory testing is only available for the MLH1, MSH2, and MSH6 genes. A negative test result does not necessarily mean that the individual does not carry an inherited mutation; it is possible that a mutation exists, but current testing methods have not identified it.

Once a mutation is detected in a family, it is reasonable to test other family members who wish to learn whether or not they have inherited the mutation and the associated cancer risks. The penetrance of HNPCC is high, and a carrier of a mismatch repair gene mutation should follow strict surveillance.

Covered Services

Genetic testing requires preauthorization

FCHP covers microsatellite instability (MSI) testing and/or immunohistochemistry (IHC) of a tumor sample when the familial mutation is unknown, full sequence analysis of the MLH1, MSH2 and MSH6 genes when the familial mutation is unknown, and targeted mutation analysis of the appropriate gene (MLH1, MSH2 or MSH6) when the familial mutation is known, and both the Guidelines for Genetic Testing and the Criteria for HNPCC Testing are met.

Criteria for HNPCC Testing

Criteria for HNPCC testing were adapted from the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Version 1.2006.

One of the following criteria may indicate an inherited susceptibility to HNPCC:

1. Individual *at-risk* for HNPCC, familial mismatch repair mutation known, genetic testing is indicated
2. Individual *at-risk* for HNPCC, familial mismatch repair mutation unknown, and tumor sample available, proceed to Revised Bethesda Guidelines:

Revised Bethesda Guidelines

If one or more of these Guidelines are met, the tumor sample should be tested for microsatellite instability and/or immunohistochemistry; if one or more of these Guidelines are not met, genetic testing is not indicated

- Colorectal cancer diagnosed in an individual who is less than 50 years of age, or
- Presence of synchronous, or metachronous HNPCC-associated tumors (i.e., colorectal, endometrial, stomach, ovarian, pancreas, ureteral renal pelvis, biliary tract or brain), regardless of age, or
- Colorectal cancer with the MSI-high histology (i.e., presence of tumor infiltrating lymphocytes, Crohn's like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern), or
- Colorectal cancer diagnosed in an individual with one or more first-degree relatives with an HNPCC-related cancer, with one of the cancers being diagnosed under 50 years of age, or
- Colorectal cancer diagnosed in an individual with two or more first or second-degree relatives with HNPCC-related cancers, regardless of age
 - a. If tumor sample MSI-high or IHC abnormal, genetic testing is indicated
 - b. If tumor sample MSI-low or microsatellite stable (MSS) proceed to Amsterdam Criteria II:

Amsterdam Criteria II

If all of the following Criteria are met, genetic testing is indicated; if all of the following Criteria are not met, genetic testing is not indicated

- At least three relatives of the *at-risk* individual have a cancer associated with HNPCC (colorectal, endometrial, small bowel, or ureteral renal pelvis) and
 - One must be a first-degree relative of the other two, and
 - At least two successive generations must be affected, and
 - At least one of the relatives with cancer associated with HNPCC should be diagnosed before the age of 50 years, and
 - Familial adenomatous polyposis (FAP) should be excluded in the colorectal cancer cases, and
 - Tumors should be verified whenever possible
3. Individual *at-risk* for HNPCC, familial mismatch repair mutation unknown, and tumor sample not available, proceed to Amsterdam Criteria II:

Amsterdam Criteria II

If all of the following Criteria are met, genetic testing is indicated; if all of the following Criteria are not met, genetic testing is not indicated

- At least three relatives of the *at-risk* individual have a cancer associated with HNPCC (colorectal, endometrial, small bowel, or ureteral renal pelvis) and
- One must be a first-degree relative of the other two, and
- At least two successive generations must be affected, and
- At least one of the relatives with cancer associated with HNPCC should be diagnosed before the age of 50 years, and
- Familial adenomatous polyposis should be excluded in the colorectal cancer cases, and
- Tumors should be verified whenever possible

Exclusions

1. HNPCC testing for individuals under the age of 18. When there is a known familial mutation, surveillance should begin between the ages of 20 and 25 or 10 years younger than the youngest age at diagnosis in the family. The average age at diagnosis of colon cancer is 44 years.

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APC-Associated Polyposis

APC-associated polyposis conditions include familial adenomatous polyposis (FAP) and attenuated FAP (AFAP). FAP is an autosomal dominant germ-line mutation, in which hundreds to thousands of polyps develop beginning at age 16 years, on average. By age 35, 95% of individuals with FAP will have polyps, and if untreated, the lifetime risk of developing colon cancer approaches 100% by age 50.

A history revealing the following risk factors suggests an individual may be *at-risk* for FAP:

- Presence of 100s to 1,000s of adenomas
- Early age of onset of adenomas; average age 16 years (range 7-36). 95% of individuals will develop polyps by age 35
- Autosomal dominant pattern of inheritance
- Associated findings, such as Congenital Hypertrophy of Retinal Pigment Epithelium (CHRPE), osteomas, supernumerary teeth, odontomas, etc.
- Extracolonic malignancies, such as medulloblastoma, hepatoblastoma, pancreatic and gastric cancers, etc.

AFAP is variant form of FAP caused by a mutation in the same APC gene. AFAP is differentiated from FAP by the number of polyps and the age at which the polyps develop. AFAP is typically associated with fewer polyps, the average being 20-30, occasionally may be as few as 10. The majority of polyps are located in the proximal colon, which can make it difficult to distinguish from hereditary non-polyposis colon cancer. The average age of onset of polyps is 44 years, which is much later than that associated with FAP, and the average age of colon cancer is age 50-55 years—10-15 years later than in those with FAP, but earlier than in those with sporadic colon cancer.

A history revealing the following risk factors suggests an individual may be *at-risk* for AFAP:

- Usually fewer than 100 polyps, average 20-30
- Predominantly located in the proximal colon
- Average age of onset of polyps is age 44 years

It is important to note that not all individuals with FAP or AFAP will have a family history of colorectal cancer or polyps. Although the majority of APC mutations are inherited, 20% to 30% may be caused by *de novo* mutations, meaning that the APC mutation may be present in an individual even if it is absent in both parents. Also, not all families with FAP carry known APC mutations. If a mutation responsible for FAP within a family is not found, it is important to remember the limitations of gene testing. Interpreting a test in which “no mutation is found” is not the same as a “negative” test.

Covered Services

Genetic testing requires preauthorization

FCHP covers full sequence analysis of the APC gene when the familial mutation is unknown, and targeted mutation analysis of the APC gene when the familial mutation is known, and both the Guidelines for Genetic Testing and the Criteria for FAP/AFAP Testing are met.

Note: Although genetic testing is not generally recommended for individuals under age 18, APC gene sequencing and targeted mutation analysis is recommended for plan members age 10 and over, because of the early age of onset of adenomas associated with FAP.

Criteria for FAP/AFAP Testing

Criteria for FAP/AFAP testing were adapted from the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Version 1.2006.

1. Individual *at-risk* for FAP (personal history > 100 polyps)
2. Individual *at risk* for AFAP (personal history < 100 polyps, average 20)
3. Presymptomatic individual with family member with FAP, mutation known
4. Presymptomatic individual with family member with AFAP, mutation known

Exclusions

1. Genetic testing for the I1307K mutation because there is insufficient evidence in the published peer-reviewed literature to determine the affect of testing on health outcomes.

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MYH-Associated Polyposis (MAP)

MAP is a biallelic germ-line mutation in the base excision repair gene mutY homologue (MYH). Individuals with MAP have inherited mutations in both copies of their MYH genes (one from each parent). MAP has a phenotype that is very similar to familial adenomatous polyposis, and should figure in the differential diagnosis of an individual with multiple colorectal adenomas in the absence of an identifiable APC mutation. On the basis of studies of FAP registries, 7%-8% of individuals with an FAP phenotype and without a detectable APC mutation carry a biallelic mutation in the MYH gene. One characteristic that distinguishes MAP from FAP, however, is that MAP is typically autosomal recessive. Due to the autosomal recessive pattern of inheritance, individuals with MAP may have no apparent family history. The rate of penetrance for MAP has not been established, but the published, peer-reviewed literature suggests that the care of individuals with MYH mutations should be similar to that of individuals with FAP or AFAP.

A history revealing the following risk factors suggests an individual may be *at-risk* for MAP:

- Usually fewer than 100 adenomas, although may present with up to 1,000 adenomas, negative APC mutation
- Autosomal recessive pattern of inheritance
- Average age of onset of adenomas has not been established, typically consistent with AFAP

Covered Services

Genetic testing requires preauthorization

FCHP covers full sequence analysis of the MYH gene when the familial mutation is unknown, and targeted mutation analysis of the MYH gene when the familial mutation is known, and both the Guidelines for Genetic Testing and the Criteria for MYH Testing are met.

Criteria for MYH Testing

Criteria for MYH testing were adapted from the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Version 1.2006.

1. Individual *at-risk* for MAP (personal history of polyposis) consistent with recessive inheritance, with negative APC mutation testing*
2. Individual *at-risk* for MAP, no personal history of polyposis, family history of sibling with MAP, mutation known

* When polyposis is present in a single person with negative family history, consider and test for *de novo* APC mutation; if negative, follow with MYH testing. When family history is positive only for a sibling (recessive inheritance), test for MYH first. In a polyposis family with clear autosomal dominant inheritance, and in the absence of an APC mutation, MYH testing is unlikely to be informative.

Exclusions

1. MYH testing when there is a family history of autosomal dominant inheritance in the absence of an identified APC mutation.

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Cystic Fibrosis

Cystic fibrosis (CF) occurs when an individual inherits biallelic mutations of the cystic fibrosis transmembrane regulator (CFTR) gene. The CFTR gene was identified as the cause of CF in 1989, and since then, more than 1,000 mutations have been identified. 1 in 25 Caucasians in the U.S. are carriers of a CFTR mutation, and one particular mutation, delF508, occurs in 72% of these carriers.

Classic CF is a chronic, progressive disorder, which usually manifests in early childhood and is associated with pulmonary disease and pancreatic insufficiency. Virtually all males with classic CF have congenital bilateral absence of the vas deferens (CBAVD). Diagnosing CF is essential to providing appropriate therapeutic interventions.

The diagnosis of CF may be established in individuals with one or more characteristic phenotypic features of CF, plus evidence of an abnormality in the CFTR gene based upon the presence of two disease-causing mutations in the CFTR gene or two abnormal quantitative pilocarpine iontophoresis sweat chloride values (>60 mEq/L).

Some individuals with CF have a non-classic or atypical phenotype which is often difficult to diagnose because the laboratory evidence and genetic testing may be inconclusive.

Covered Services

Genetic testing requires preauthorization

FCHP covers genetic testing for CFTR mutations, using the American College of Medical Genetics recommended 25-mutation panel, when the both the Guidelines for Genetic Testing and the criteria for CF testing/screening are met:

Criteria for diagnostic testing

1. An individual who has one or more characteristic phenotypic features of CF, but normal sweat chloride values
2. An infant who has a meconium ileus or other symptoms indicative of CF, but who is too young to undergo a sweat chloride test
3. An individual who does not have characteristic phenotypic features of CF, but who has both
 - a. A sibling with CF or a family member with a known CFTR mutation, and
 - b. Abnormal sweat chloride values
4. A male with CBAVD

Criteria for carrier screening

1. An individual of reproductive age, potential and intention with one of the following:
 - a. A family history of CF, or
 - b. A family member with a known CFTR mutation, or
 - c. A reproductive partner with CF, or
 - d. A reproductive partner with a family history of CF, or
 - e. A male reproductive partner with CBAVD

Criteria for prenatal (fetal) testing

1. A fetus when both parents have any combination of a diagnosis of CF, or is a known carrier of a CFTR mutation, or has a family history of CF
2. A fetus when both parents are CFTR mutation carriers and an echogenic bowel is identified on ultrasound²

Exclusions

1. Newborn screening.
2. CFTR gene sequence analysis or extended mutation panels.

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² Using genetic testing, approximately 75% of cases involving cystic fibrosis can be detected with noninvasive studies of the parents, and confirmation by amniocentesis is performed only in those cases in which both parents are carriers of known mutations. (Hogge WA et al.)

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Committee Review Date(s):

Benefits Committee: 05/02, 11/02

Technology Assessment Subcommittee: 05/23/06

Technology Assessment Committee: 03/02, 04/02, 11/02, 06/01/2006

Utilization Management Committee: 06/03

Pharmacy & Therapeutics Committee: 00/00

Approved by:

Signature on file

Dennis A. Batey, MD – Chief Medical Officer

06/01/2006

Date

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