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Overview
Predictive genetic testing is performed in people known to be at increased risk of developing an inherited non-cancer condition based on their family history. For some conditions, a positive genetic test predicts with certainty that the person will eventually develop signs and symptoms of a condition. For other conditions, a positive genetic test result indicates an increased risk (susceptibility) for a condition. A negative result may rule out a condition, or lower the risk significantly. Having test results may improve medical management through improved screening, preventive measures, prophylactic medication, and other means.

• This policy does not include testing of a symptomatic individual. Please refer to Diagnostic Genetic Testing of a Symptomatic Patient for that purpose.
• Predictive testing for hereditary cancer syndromes is addressed separately under Genetic Testing for Cancer Susceptibility and Hereditary Cancer Syndromes.
Coverage guidelines

General coverage guidelines
Individuals may be considered for diagnostic genetic testing when ALL of the following conditions are met:

- The individual is known to be at-risk for developing inherited condition because a parent, sibling, or child is affected by or known to be a carrier of a genetic disease.
- Technical and clinical validity: The test must be accurate, sensitive and specific, based on sufficient, quality scientific evidence to support the claims of the test.
- Clinical utility: Healthcare providers can use the test results to provide significantly better medical care for the individual.
- Reasonable use: The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social or ethical challenges.

Limits:
- Testing will be considered only for the number of genes or tests necessary to establish carrier status. A tiered approach to testing, with reflex to more detailed testing and/or different genes, will be required when clinically possible.
- Predictive genetic testing will be allowed once per lifetime per condition. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.
- Predictive testing will be considered only for adult individuals (age 18 and over). Exceptions may be considered if there are medical management and/or significant psychosocial benefits to testing prior to adulthood.¹²

Special circumstances

Testing for known familial mutations
The genetic mutation(s) associated with a genetic disease can often be defined in an affected family member, allowing for testing of at-risk relatives for those specific mutations. Testing for known familial mutations may be considered when ALL of the following conditions are met:

- The mutations in the family have been clearly defined by previous genetic testing and information about those mutations can be provided to the testing lab.
- Technical and clinical validity: The test must be accurate, sensitive and specific to the familial mutations.
- Clinical utility: Healthcare providers can use the test results to provide significantly better medical care for the individual.
- Reasonable use: The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social or ethical challenges.

¹²
Policy Guidelines:
Predictive Genetic Testing or Risk Assessment for Diseases Other Than Cancer

Limits:
- Testing will be considered only for the known familial mutations when clinically possible.
- Predictive genetic testing will be allowed once per lifetime per condition.
- Predictive testing will be considered only for adult individuals (age 18 and over). Exceptions may be considered if there are medical management and/or significant psychosocial benefits to testing prior to adulthood.1,2

References:

Test-specific examples

APOE testing for Alzheimer’s disease
Alzheimer’s disease (AD) is considered a polygenic, multifactorial condition, characterized by adult-onset, progressive dementia.1 Clinical neuropathological findings (which are the gold standard for diagnosis) including beta-amyloid plaques and intraneuronal neurofibrillary tangles.2 Other features can include: confusion, poor judgment, agitation, withdrawal, hallucinations, speech issues, seizures and increased muscle tone.1

Variants in the apolipoprotein E (apoE) gene have been associated with an increased risk for AD.3 APOE has three common subtypes: APOE 2, APOE 3, and APOE 4. APOE 4 occurs in about 40 percent of all people who develop late-onset AD and is present in about 25 to 30 percent of the population.3 While there appears to be an increased risk of AD if APOE 4 is present, many people with AD do not have an APOE4 allele.

The presence of APOE4 cannot fully predict if a person with develop AD, and there is no treatment or other intervention strategy validated at this time to reduce the risk of developing AD, delay the onset of AD, or otherwise treat AD. Therefore, testing has limited clinical utility at this time. Consensus-based guidelines from the American College of Medical Genetics and National Society of Genetic Counselors2, the National Institute of Aging/Alzheimer’s Association Working Group3, and the European Federation of Neurological Societies5, do not endorse APOE4 predictive testing for AD.

Testing is not indicated for any individual for predicting Alzheimer’s disease.

References:
Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a genetic condition associated with unexplained thickening of the heart wall surrounding the left ventricle (called left ventricular hypertrophy or LVH).\(^1\)\(^2\) A clinical diagnosis is suggested by a non-dilated left ventricle with a wall thickness of 13-15 mm or more.\(^3\)\(^4\) Signs and symptoms are variable ranging from a lifelong asymptomatic course to progressive heart failure and sudden cardiac death.\(^1\)\(^2\)

HCM affects about 1 in 500 people, and is the most common cause of sudden cardiac death among young people under 35 - especially athletes.\(^4\) Familial HCM is autosomal dominant, therefore, first degree relatives (parents/siblings/children) of affected individuals have a 50% chance of also having the mutation.\(^2\) Extensive cardiac screening is recommended by guidelines from the American College of Cardiology and the European Society of Cardiology\(^4\) and the Heart Failure Society of America\(^5\) for individuals at-risk for HCM based on family history.

Genetic testing can influence cardiac screening, help determine whether lifestyle changes are needed, and offer prognostic risks for sudden death. Testing is not useful in predicting age-of-onset, severity, type of symptoms or rate of progression in asymptomatic individuals with a mutation.\(^2\) Once a mutation is identified in a family member, the family mutation can be specifically identified with >99% accuracy in asymptomatic family members, or those with equivocal symptoms.\(^2\)

Predictive genetic testing for HCM may be considered when an individual has a first-degree relative (parent, sibling, child) affected with HCM, that relative has had genetic testing, and the family mutation is known.

Since symptoms can appear in childhood, testing of children who are at-risk of having a mutation may be appropriate, but requires careful consideration of the ethics of testing a minor.\(^2\) A common scenario is testing at risk, pre-symptomatic adolescents to determine sports participation limitations and appropriate screening programs.

References:

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**NOTCH3 testing for CADASIL**

CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) is an adult onset disorder of cerebrovascular disease that progresses to dementia.\(^1\) It is caused by mutations in the NOTCH3 gene.\(^1\)

Because CADASIL is autosomal dominant, first-degree relatives (parents, siblings, children) of affected individuals have a 50% chance of also having the mutation.\(^1\) The chance for an at-risk relative who is NOTCH3 mutation-positive to develop symptoms is likely close to 100%.\(^1\) However, it is impossible to predict the severity of disease, because symptoms can vary considerably even within families.\(^1\)\(^-\)\(^3\)

Genetic testing is available for asymptomatic relatives at risk of having inherited a known familial NOTCH3 gene mutation. Testing involves targeted DNA sequence analysis of the NOTCH3 gene where the known familial mutation is located.\(^1\) The detection rate in asymptomatic individuals is high when the familial mutation is known.\(^1\)\(^,\(^2\)

Test results can affect clinical management. Evidence has demonstrated that individuals who test positive for a CADASIL mutation should:

- Avoid anticoagulants and angiography, due to reports of provoked stroke\(^1\)\(^,\(^2\)
- Avoid smoking, which has been associated with an earlier age of onset of stroke in this population\(^5\)
- Control blood pressure, glucose levels, and high cholesterol, as these factors increase the risk for ischemic stroke\(^2\)

Predictive genetic testing may be considered when an individual has a first-degree relative (parent, sibling, child) affected with CADASIL, that relative has had genetic testing, and the family mutation is known. Predictive genetic testing for CADASIL should be carried out according to published guidelines for other late-onset neurologic conditions for which no specific disease treatment is available, including appropriate genetic counseling.\(^1\)\(^,\(^4\)\) The potential psychosocial impact of test results on the individual and the family should be considered, and the possibility of discrimination in regards to insurance coverage, employment, and education should be reviewed.\(^1\)
Policy Guidelines:
Predictive Genetic Testing or Risk Assessment for Diseases Other Than Cancer

References:

SOD1 testing for amyotrophic lateral sclerosis (ALS; Lou Gehrig’s disease)
Amyotrophic lateral sclerosis (ALS) is a neurological disease caused by the progressive degradation of motor neurons (nerve cells that control voluntary muscle movement).\(^1\) ALS initially presents as muscle weakness, twitching, cramping, or slurred speech.\(^1\) Symptoms then worsen and include muscle atrophy and difficulty swallowing\(^1\), with death usually related to failure of the respiratory muscles.

The majority of ALS cases are sporadic, but some familial forms have been identified. About 20% of familial ALS cases are caused by mutations in the SOD1 gene.\(^1\) The SOD1 gene encodes superoxide dismutase, an enzyme whose function remains unclear.\(^1,2\)

SOD1-related ALS is usually inherited in an autosomal dominant fashion. First-degree relatives (parents, siblings, children) of affected individuals have a 50% chance of also having the mutation.\(^1,3\) Predictive testing for SOD1 mutations is endorsed by consensus-based guidelines from the European Federation of Neurological Societies (EFNS), which state: "Pre-symptomatic genetic testing should only be performed in first degree adult blood-relatives of patients with a known SOD1 gene mutation. Testing should only be performed on a strictly volunteer basis."

Identifying a SOD1 mutation in a pre-symptomatic individual can impact future management and overall prognosis of ALS, but is considered controversial because of reduced penetrance (not everyone with a mutation will necessarily develop symptoms), lack of overall intervention or prevention strategies, and inability to predict the age of onset.\(^1,2\)

Predictive genetic testing may be considered when an individual has a first-degree relative (parent, sibling, child) affected with SOD1-related ALS, that relative has had SOD1 genetic testing, and the family mutation is known. The EFNS guidelines outline a presymptomatic testing protocol similar to those for other late-onset neurologic conditions for which no specific disease treatment is available, including appropriate genetic counseling.\(^4\) The potential psychosocial impact of test results on the individual and the family should be considered, and the possibility of discrimination in regards to insurance coverage, employment, and education should be reviewed.\(^1,4\)
References:


