Leber Hereditary Optic Neuropathy (LHON) Genetic Testing Policy

Procedure(s) addressed by this policy:	Procedure Code(s)
LHON Known Familial Mutation Analysis	81403
MT-ND4, MT-ND6 Targeted Mutation Analysis	81401
Whole Mitochondrial Genome	81460

What Is Leber Hereditary Optic Neuropathy?

- Leber Hereditary Optic Neuropathy (LHON) is a mitochondrial disorder that mainly affects the eye. It is characterized by bilateral painless subacute vision loss that begins in the second and third decades of life. It usually has onset between 15-30 years of age, and leads to rapid, progressive blindness. Visual acuity usually deteriorates to 20/200 or worse.[1,2,3]
- The primary cell type that is lost in LHON is the retinal ganglion cell, which is highly susceptible to disrupted ATP production and oxidative stress.[4]
- A diagnosis of LHON can be made clinically. "The pathologic hallmark of LHON is the selective degeneration of the retinal ganglion cell layer and optic nerve."[1]
- LHON has three phases:[1]
    - **Presymptomatic/subacute phase**: Mild abnormalities in the fundus may be present. Additionally, color vision, contrast, and electroretinogram may be mildly affected.
    - **Acute phase**: Onset features blurred or clouded central vision usually starting in one eye, followed by other eye within weeks to months. Onset involves both eyes simultaneously in about 25% of cases. The vision loss gets progressively worse with the blurred central field enlarging (called a scotoma). Evaluation of fundus in 80% of affected patients will show disk swelling, edema of the peripapillary nerve fiber layer, retinal telangiectasia, and increased vascular tortuosity without corresponding leakage on fluorescein angiography.
    - **Atrophic phase**: Optic atrophy and worsening central scotoma will progress to severe impairment over the course of six weeks. Once the atrophic phase begins, visual acuity rarely recovers. Most individuals become legally blind.
- Within 1 year, 97% of those affected have involvement of the second eye, such that a patient presenting with a unilateral optic neuropathy for longer than 1 year is highly unlikely to suffer from LHON-related vision loss.[4]
- Other neurologic features may include: tremor, peripheral neuropathy, myopathy and/or movement disorders. Additionally, women may develop a multiple sclerosis-like progressive disease.[1]

- Unaffected LHON point mutation carriers can display subclinical signs of disease on fundus examination, including peripapillary microangiopathy, zones of mild disc pseudoedema, and telangiectasia.
- Some clinicians treat children presymptomatically with antioxidants when their genetic status is known.
- People who have a pathogenic variant consistent with LHON should avoid smoking, and secondary smoke. Restriction of alcohol consumption and exposure to mitotoxic agents is also advisable.[1]
- Idebenone has been approved in Europe for stabilizing the visual loss of the remaining better eye in LHON.[5]
- The prevalence of LHON in most populations is unknown. In Caucasian populations estimates range from 1 in 31,000 to 1 in 50,000. Men are about 4-5 times more likely to develop LHON than women.[1,2]
- LHON is caused by point mutations in the mitochondrial genome which is separate from nuclear DNA.
- Several mtDNA mutations have been reported to cause LHON. However, 90% of affected individuals have one of three common mitochondrial mutations: m.3460G>A (13%), m.11778G>A (70%) and m.14484T>C (14%).[4]
- A 2016 expert-authored review stated the following regarding genotype-phenotype correlations:[1]
    - The mtDNA mutation m.14484T>C is associated with a partial recovery rate of 37%–58%, while the m.11778G>A mutation has the lowest partial recovery rate of 4%. Patients with the m.3460G>A mutation have an intermediate prognosis, with an approximate 20% partial recovery rate.[1]
    - "m.3460G>A is associated with the worst impairment in visual function. m.11778G>A has an intermediate phenotype. Although published reports would appear to indicate otherwise, the m.3460G>A pathogenic variant is generally accepted among experts as having the worst visual recovery rate."[1]
- "The clinical penetrance of primary mtDNA LHON mutations is also thought to be influenced by the specific mitochondrial genetic background on which they occur. These mtDNA haplogroups are defined by a number of common genetic polymorphisms that have clustered together during human evolution and population migrations. The haplogroup J background, which is found in about 10% of people of European extraction, increases the clinical penetrance in LHON pedigrees harboring the m.11778G>A and m.14484T>C mutations. On the other hand, carriers of the m.3460G>A mutation are more likely to become visually affected on a haplogroup K background."[6]
- Earlier age of onset (younger than 20 years), a subacute time course of vision loss, and larger optic discs are all associated with a better visual prognosis.
- Mitochondrial DNA is maternally transmitted. Pathogenic variants in the mtDNA may be de novo or maternally inherited. A male who carries a mtDNA mutation cannot pass it on to his children.[1,7]

    - About 60% of people with LHON have an identifiable maternal family history of disease. In the remaining 40%, the family history may be incomplete or the affected individual could have a new (de novo) mutation but this is rare.[1,2]
    - Not all people with an LHON disease-causing mtDNA mutation will develop symptoms. Only about 50% of males and 10% of females who have a known disease-causing LHON mutation will develop blindness.[2] There must be other genetic and environmental factors that explain the variable appearance of symptoms and the gender differences.[1,2]
- Diseases like LHON that are attributed to mtDNA mutations have unique patterns of inheritance and penetrance governed by the principles of maternal inheritance, heteroplasmy, replicative segregation, and the critical threshold. Heteroplasmy and replicative segregation contribute to the heterogeneity of mitochondrial disease phenotypes, even among related individuals. Critical threshold is reached when the wild-type mtDNA cannot compensate for the mutant mtDNA in a cell or tissue. This accounts for targeted tissue involvement and age dependent onset. Even more variability is present because tissue-specific segregation of mutant mtDNA is stochastic during embryogenesis.[4] Heteroplasmy is present in 10%-15% of individuals with a LHON-causing mtDNA variant; the majority of individuals with a LHON-causing mtDNA variant are homoplasmic.[1]

Test Information

- An ophthalmological evaluation can confirm the diagnosis of LHON:[1,2]
    - Eye testing may include fundus exam, visual field testing, and imaging. Other testing, including angiography and electrophysiology, are sometimes warranted. This testing may reveal characteristic findings of LHON or rule out other causes of acute vision loss.
    - In cases where a diagnosis can't be confirmed by eye findings alone, molecular genetic testing may be useful.
- The LHON Three mtDNA Mutation Panel involves targeted testing of three common mutations in mtDNA (m.3460G>A, m.11778G>A and m.14484T>C).[1,2,3] These three mutations account for about 90% of mtDNA mutations found in people with LHON.[1]
- The three LHON mutations are also included on a number of more general mitochondrial targeted mutation panels (in conjunction with genes for MELAS, MERFF and Leigh syndrome).
- Full sequencing of the entire mitochondrial genome can be done to identify the remaining 10% of mtDNA mutations in individuals affected with LHON. Since the mitochondrial genome is highly polymorphic, this is not routinely offered unless clinical suspicion is very high and paternal transmission has been ruled out.[1] If the status of heteroplasmy is of concern, next generation testing with high read depth may be preferable.[6] Typically, Sanger sequence analysis will miss heteroplasmy below 20%. With suitable depth of coverage, NGS can detect heteroplasmy down to ~1%.[8,9]
- A number of large panels sequence the mitochondrial genome in conjunction with nuclear-encoded mitochondrial genes for a broad approach to testing.
- DNA testing can be performed on a blood specimen. Muscle biopsy is generally not necessary, but some labs accept blood, saliva and muscle samples.[7]

Guidelines and Evidence

- No evidence-based U.S. testing guidelines identified for LHON.
- Although not specific to genetic testing for LHON, the **Mitochondrial Medicine Society (2015)**[10] developed consensus recommendations for the diagnosis and management of mitochondrial disease. Testing strategies, including strategies for genetic testing, were discussed.
    - Recommendations for DNA testing include the following:
        - "Massively parallel sequencing/NGS of the mtDNA genome is the preferred methodology when testing mtDNA and should be performed in cases of suspected mitochondrial disease instead of testing for a limited number of pathogenic point mutations.
        - Patients with a strong likelihood of mitochondrial disease because of a mtDNA mutation and negative testing in blood, should have mtDNA assessed in another tissue to avoid the possibility of missing tissue-specific mutations or low levels of heteroplasmy in blood; tissue-based testing also helps assess the risk of other organ involvement and heterogeneity in family members and to guide genetic counseling.
        - Heteroplasmy analysis in urine can selectively be more informative and accurate than testing in blood alone, especially in cases of MELAS due to the common m.3243A>G mutation.
        - When considering nuclear gene testing in patients with likely primary mitochondrial disease, NGS methodologies providing complete coverage of known mitochondrial disease gene is preferred. Single-gene testing should usually be avoided because mutations in different genes can produce the same phenotype. If no mutation is identified via known NGS panels, then whole exome sequencing should be considered."
- The **European Federation of Neurological Sciences (2009)** [11] provided molecular diagnostic consensus-based guidelines based on literature reviews: "If the phenotype suggests syndromic mitochondrial disease due to mtDNA point mutations (MELAS, MERRF, NARP, LHON) DNA-microarrays using allele-specific oligonucleotide hybridisation, real-time-PCR or single-gene sequencing are indicated."
- The **Clinical Molecular Genetics Society (CMGS) of the United Kingdom (2008)**[7] practice-based guidelines for the molecular diagnosis of mitochondrial disease state that: "Investigation for the G3460A, G11778A and T14484C mutations are indicated for all LHON referrals."
- A 2016 expert-authored review suggests the following testing strategy for those with a known or suspected diagnosis of LHON:[1]
    - "Three common mtDNA pathogenic variants account for 90%-95% of LHON. Targeted analysis for one of these three variants should be performed first."
    - "A multi-gene panel that includes the mitochondrial genes that encode subunits of NADH dehydrogenase, *MT-ND1*, *MT-ND2*, *MT-ND4*, *MT-ND4L*, *MT-ND5*, and *MT-ND6*, which are known to cause LHON and other genes of interest may also be considered."

- "Complete mtDNA sequencing may be considered if use of targeted testing and/or a multi-gene panel did not identify a pathogenic variant, clinical suspicion remains high, and there is no evidence of paternal transmission."
- For those seeking predictive testing (e.g. they are not currently affected), this review states:
  - "Testing of at-risk asymptomatic adults for LHON is possible ... Such testing is not useful in predicting age of onset, severity, or rate of progression of visual loss in asymptomatic individuals."
  - "Testing of asymptomatic individuals younger than age 18 years who are at risk for adult-onset disorders for which no treatment exists is not considered appropriate."

Criteria

LHON Known Familial Mutation Testing

- Genetic Counseling:
  - Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing in the individual for LHON*, and
  - LHON pathogenic variant identified in first degree biological maternal relative, AND
- Predictive Testing for Asymptomatic Individual:
  - 18 years of age or older, or
  - Under the age of 18 years, and
    - Presymptomatic treatment with antioxidants is being considered, OR
- Diagnostic Testing for Symptomatic Individual:
  - Ophthalmology examination is suggestive, but not confirmatory, of a diagnosis of LHON, OR
- Prenatal Testing for At-Risk Pregnancies:
  - LHON causing mutation identified in a previous child or in the mother.

LHON Targeted Mutation Analysis

- Genetic Counseling:
  - Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous genetic testing in the individual for LHON*, and
  - No known LHON pathogenic variants in the family, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Ophthalmology examination is suggestive, but not confirmatory, of a diagnosis of LHON, and
    - Genetic testing is needed to confirm the diagnosis, or

    - An individual has a clinical diagnosis of LHON and genetic testing is needed for one of the following purposes:
        - To offer testing to family members, or
        - For prenatal diagnostic purposes, AND
- No evidence of paternal transmission.

Whole mtDNA Sequencing

- Genetic Counseling:
    - Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Criteria for LHON Targeted Mutation Analysis is met, AND
- No pathogenic variants identified in the Targeted Mutation Analysis, if performed, AND
- Member has not had previous whole mtDNA sequencing performed*, AND
- No evidence of paternal transmission.

*Genetic testing has rapidly advanced over the last 20 years. Exceptions may be considered if an individual has previously had negative genetic testing, but technical advances in testing demonstrate significant advantages that would support a medical need to re-test.

References

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