Polymerase Gamma (POLG) Related Disorders Genetic Testing

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Introduction

Polymerase gamma (POLG) related disorders genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
POLG deletion/duplication analysis	81479
POLG full gene sequencing	81406
POLG known familial mutation analysis	81403

Criteria

Introduction

Requests for genetic testing for polymerase gamma (POLG)-related disorders, including Alpers-Huttenlocher syndrome (AHS), childhood myocerebrohepatopathy spectrum (MCHS), myoclonic epilepsy myopathy sensory ataxia (MEMSA), ataxia neuropathy spectrum (ANS), autosomal dominant progressive external ophthalmoplegia (adPEO), or autosomal recessive progressive external ophthalmoplegia (arPEO), are reviewed using the following criteria.

Known POLG Family Mutation Testing

- Genetic Counseling:

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  - Pre- and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Diagnostic Testing for Symptomatic Individuals
  - No previous genetic testing of POLG that would detect the familial mutation, and
  - If adPEO is suspected:
    - Clinical examination is consistent with a diagnosis of adPEO, and
    - POLG mutation identified in 1st degree biological relative, OR
  - If AHS, MCHS, MEMSA, ANS, or arPEO is suspected:
    - Clinical examination is consistent with a diagnosis of AHS, MCHS, MEMSA, ANS, or arPEO, and
    - Two POLG mutations identified in a sibling, or
    - One POLG mutation identified in both parents

POLG Full Gene Sequencing

- Genetic Counseling:
  - Pre- and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous POLG sequencing, and
  - No known POLG mutation in the family, AND
- Diagnostic Testing for Symptomatic Individuals:
  - If adPEO is suspected:
    - Clinical examination is consistent with a diagnosis of adPEO, and
    - Genetic testing is needed to confirm the diagnosis, OR
  - If AHS, MCHS, MEMSA, ANS, or arPEO is suspected:
    - Clinical examination is consistent with a diagnosis of AHS, MCHS, MEMSA, ANS, or arPEO, and
    - Genetic testing is needed to confirm the diagnosis, OR
  - If evaluating the risk for valproate-induced hepatic toxicity:
    - The member has epilepsy, and
    - There is suspicion for a POLG-related disorder based on the presence of at least one of the following:
      - unexplained encephalopathy, or
      - refractory epilepsy, or

- status epilepticus at presentation, or
- developmental delays, or
- psychomotor regression, or
- axonal sensorimotor neuropathy, or
- myopathy and/or hypotonia, or
- progressive spastic paraparesis, or
- renal tubular acidosis, or
- sensorineural hearing loss, or
- cyclic vomiting, or
- pancreatitis, or
- movement disorder (incl extrapyramidal movement disorders such as parkinsonism & chorea, & cerebellar ataxia), or
- ophthalmoplegia and/or ptosis, or
- cortical blindness and/or cataracts, or
- complicated migraine with occipital aura, and

▪ The member is currently on Depakene (valproate) or Depakote ER (divalproex sodium) therapy, or the use of one of these medications is being proposed.

POLG Deletion/Duplication Analysis

- Genetic Counseling:
  - Pre- and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Criteria for POLG Full Gene Sequencing is met, AND
- If adPEO is suspected:
  - No mutations found on POLG Full Gene Sequencing, OR
- If AHS, MCHS, MEMSA, ANS, or arPEO is suspected:
  - No mutations or only one mutation found on POLG Full Gene Sequencing, OR
- If evaluating the risk for valproate-induced hepatic toxicity:
  - No mutations or only one mutation found on POLG Full Gene Sequencing

What are POLG-related disorders?

"POLG-related disorders" is a term used to describe medical conditions caused by mutations in the POLG gene. This is a wide spectrum of conditions that may involve multiple organ systems and have variable severity and age at onset.[1,2]

Prevalence

Although Alpers-Huttenlocher syndrome (AHS) is clinically reported to occur in 1/51,000 individuals, disease frequency calculated based on prevalence of the most common POLG mutations may be as high as 1/10,000.[1]

Symptoms

There are 6 main phenotypes attributed to POLG mutations. Onset of the POLG-related disorders can range from infancy to late adulthood. Younger individuals typically present with seizures and lactic acidosis.[3] Later in life, the most common presenting symptoms are myopathy, chronic progressive external ophthalmoplegia (CPEO), and sensory ataxia.[3] Liver failure may also occur, particularly with exposure to the antiepileptic drug, valproic acid.[1,4,5] Most affected individuals have some features ascribed to each phenotype, but rarely have all.

- Alpers- Huttenlocher syndrome (AHS):[6,7]
  - Most common symptoms
    - seizures (commonly refractory)
    - severe and progressive encephalopathy
    - liver disease and/or liver failure
  - Other possible symptoms
    - migraine with visual auras
    - stroke or stroke-like episodes
    - cortical blindness
    - hypotonia
    - ataxia
    - episodic psychomotor regression
    - extrapyramidal movements and/or myoclonus
    - peripheral neuropathy and/or areflexia
    - progressive spastic paraparesis
    - renal tubular acidosis
    - hearing loss
    - cyclic vomiting
    - pancreatitis
  - Development is often normal until disease onset, which is typically before 4 years of age. However, congenital static encephalopathy and juvenile-onset have also been described.[2] Disease progression varies, however life expectancy is shortened with individuals typically passing away between 3 months to over a decade from symptom onset. When seizure etiology is unknown, valproic acid must be used with extreme caution, as it can precipitate liver dysfunction and/or failure in AHS.[4,5]

- Childhood myocerebrohepatopathy spectrum (MCHS):[8]
  - Most common / presenting symptoms:
    - failure to thrive
    - lactic acidosis
    - developmental delay
    - encephalopathy
    - dementia
    - myopathy
    - hypotonia
  - Other possible symptoms:
    - liver failure
    - renal tubular acidosis
    - pancreatitis
    - cyclic vomiting
    - hearing loss
  - MCHS is a rapidly progressive disease with a fatal outcome that usually presents between the first few months of life and 3 years. MCHS has a similar presentation to AHS, however severe myopathy, specific liver pathology, and nonspecific brain MRI brain findings (diffuse atrophy) help differentiate MCHS from AHS. In addition, seizures are less prominent and more easily controlled in MCHS compared to AHS.
- Myoclonic epilepsy myopathy sensory ataxia (MEMSA):[9]
  - Common symptoms:
    - epilepsy
    - myopathy (proximal, distal, or including exercise intolerance)
    - ataxia
    - ophthalmoplegia
  - MEMSA has also been known as spinocerebellar ataxia with epilepsy (SCAE). Disease onset typically occurs in adolescence and presents with cerebellar and sensory ataxia. Epilepsy usually follows, with refractory seizures leading to a progressive encephalopathy.
- Ataxia neuropathy spectrum (ANS):[10]
  - Common symptoms:
    - migraine headaches
    - ataxia
    - neuropathy (sensory, motor, or mixed)
    - encephalopathy with seizures
  - Other possible symptoms:
    - myoclonus

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        - blindness
        - hearing loss
        - liver dysfunction and/or failure
        - stroke-like episodes
        - psychiatric diagnoses (commonly depression)
    - Disease onset ranges between adolescence and adulthood. Migraine headaches may be the first presenting symptom and precede the other symptoms by many years. Clinical myopathy is very rare. The encephalopathy present in most, but not all, affected individuals is often milder than AHS and more slowly progressive. ANS was previously referred to as mitochondrial recessive ataxia syndrome (MIRAS) and sensory ataxia neuropathy dysarthria and ophthalmoplegia (SANDO).
- Autosomal recessive progressive external ophthalmoplegia (arPEO):[11]
    - Common symptoms:
        - ptosis
        - ophthalmoparesis
    - Onset is typically in adulthood and is isolated to progressive weakness of the extraocular muscles, without associated systemic involvement. Of note, apparently isolated arPEO can present with additional symptoms later in life causing the individual to be reclassified as having another POLG-related disorder.
- Autosomal dominant progressive external ophthalmoplegia (adPEO):[1,10]
    - Common symptoms:
        - ptosis
        - ophthalmoparesis
        - strabismus
        - generalized myopathy (early fatigue and exercise intolerance)
        - sensorineural hearing loss (of varying degree)
        - axonal neuropathy
        - ataxia
        - depression
        - Parkinsonism
        - hypogonadism
        - cataracts
    - Previously, adPEO was called Chronic Progressive External Ophthalmoplegia plus (CPEO+). Onset is typically in adulthood with all individuals presenting with progressive weakness of the extraocular muscles and at least one other symptom listed above. Less commonly, cardiomyopathy and gastrointestinal dysmotility are reported.

Cause

POLG-related disorders are caused by mutations in the POLG gene. POLG codes for a subunit of DNA polymerase protein that replicates and repairs mitochondrial DNA (mtDNA). Disease-causing mutations can affect polymerase activity, processing, DNA binding, or subunit association.[1]

Inheritance

POLG-related disorders can be inherited in an autosomal recessive or autosomal dominant pattern.

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Autosomal recessive inheritance

In autosomal recessive inheritance, individuals have 2 copies of the gene and an individual typically inherits a gene mutation from both parents. Usually only siblings are at risk for also being affected. Males and females are equally affected. Individuals who inherit only one mutation are called carriers. Carriers do not typically show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children. If both parents are carriers of a mutation, the risk for each pregnancy to be affected is 1 in 4, or 25%.

AHS, MCHS, MEMSA, ANS, and arPEO are inherited in an autosomal recessive inheritance pattern, while adPEO is inherited in an autosomal dominant pattern. There is not always a clear genotype-phenotype relationship for all POLG variants and associated disorder/inheritance, which can make correlation to clinical presentation difficult for individuals with single variants identified. A case of arPEO caused by digenic inheritance of POLG and TWNK mutations has been reported.[1]

Diagnosis

As no clinical diagnostic criteria exist, genetic testing of POLG is required to confirm clinical suspicion of a disorder in this spectrum.

Management

Management is supportive and based on presenting symptoms, and typically involves referral for speech therapy, physical therapy, and occupational therapy. Respiratory and nutritional support are provided as needed.

Any medications metabolized by hepatic enzymes should be carefully dosed to avoid liver toxicity. Certain antiepileptic drugs should be avoided due to the risk for precipitating or accelerating liver disease.[1]

Occurrence of dehydration, fever, anorexia and infection can create physical stress and hasten medical deterioration. These events should be avoided as much as possible.

Survival

The range of survival is broad and is largely dependent on the presenting phenotype, age at onset, and the occurrence of secondary complications.

Test information

Introduction

Testing for POLG-related disorders may include known familial mutation analysis, next generation sequencing, and/or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Sequence analysis for this group of disorders is typically limited to full sequencing of the POLG gene only, although POLG may appear on multigene panels for mitochondrial-related disorders.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Given that clinical diagnostic criteria do not exist, genetic testing of POLG is required in order to confirm the diagnosis of a POLG-related disorder.[1]

- For individuals with suspected adPEO, identification of one POLG mutation is required to confirm the diagnosis.
- For individuals presenting with clinical features consistent with one of the five other phenotypes, identification of two (biallelic) mutations is required to confirm the diagnosis.

While biochemical analyses of an affected tissue may be informative, they are not sensitive or specific enough to definitively diagnose a POLG-related disorder. Muscle biopsy can be completely normal in children and adults with a POLG-related disorder and in clinically unaffected tissue.[12]

Guidelines and evidence

European Federation of Neurological Sciences/European Neurological Society

The European Federation of Neurological Sciences/European Neurological Society (EFNS/ENS, 2014) consensus guidelines on the diagnosis and management of chronic ataxias in adulthood recommended POLG testing in the following evaluation of individuals with autosomal recessive cerebellar ataxia:[13]

- "Step 1: mutation analysis of the FRDA gene for Friedreich's ataxia (although one can refrain from this in the case of severe cerebellar atrophy), and biochemical testing that includes cholestanol, vitamin E, cholesterol, albumin, creatine kinase (CK) and a-fetoprotein. Also consider doing nerve conduction studies/EMG (presence versus absence of peripheral neuropathy, axonal versus demyelinating) and referral to an ophthalmologist (retinitis pigmentosa, cataract, cherry red spot etc.) (Table S2) (good practice point)."
- "Step 2: mutation analysis of the SACS, POLG, Aprataxin (APTX) and SPG7 genes (taking into account specific phenotypes, as given in Table S2), and biochemical testing for white cell enzymes, phytanic acid and long chain fatty acids (good practice point)."
- "Step 3: referral to a specialized centre, e.g. for skin or muscle biopsy targeted at diagnoses such as Niemann - Pick type C, recessive ataxia with coenzyme Q deficiency [aarF domain containing kinase 3 (ADCK3)/autosomal recessive

spinocerebellar ataxia 9 (SCAR9)] and mitochondrial disorders, or for extended genetic screening using gene panel diagnostics (good practice point)."

Mitochondrial Medicine Society

Although not specific to genetic testing for POLG, the Mitochondrial Medicine Society (MMS, 2015)[14] developed consensus recommendations for the diagnosis and management of mitochondrial disease. Testing strategies, including strategies for genetic testing, were discussed. Recommendations for testing included:

- "When considering nuclear gene testing in patients with likely primary mitochondrial disease, NGS methodologies providing complete coverage of known mitochondrial disease genes 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."

US Food and Drug Administration

The Food and Drug Administration (FDA) stated that Depakene (valproic acid) capsules and oral solution (2020), Depakote ER (divalproex sodium) extended-release tablets (2023), Depakote (divalproex sodium) delayed-release tablets (2020), and Depakote Sprinkles Capsules (2023) are contraindicated for individuals known to have mitochondrial disorders caused by POLG mutations and children under two years of age who are clinically suspected of having a mitochondrial disorder:[15-18]

- "Valproate-induced acute liver failure and liver-related deaths have been reported in patients with hereditary neurometabolic syndromes caused by mutations in the gene for mitochondrial DNA polymerase γ (POLG) (e.g., Alpers-Huttenlocher Syndrome) at a higher rate than those without these syndromes. Most of the reported cases of liver failure in patients with these syndromes have been identified in children and adolescents."[15]
- "POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to: unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy, cerebellar ataxia, ophthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders. The A467T and W748S mutations are present in approximately 2/3 of patients with autosomal recessive POLG-related disorders."[16]
- "There is an increased risk of valproate-induced acute liver failure and resultant deaths in patients with hereditary neurometabolic syndromes caused by DNA mutations of the mitochondrial DNA Polymerase γ (POLG) gene (e.g. Alpers Huttenlocher Syndrome). Depakote Sprinkle Capsules is contraindicated in patients

known to have mitochondrial disorders caused by POLG mutations and children under two years of age who are clinically suspected of having a mitochondrial disorder. … In patients over two years of age who are clinically suspected of having a hereditary mitochondrial disease, Depakote Sprinkle Capsules should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with Depakote Sprinkle Capsules for the development of acute liver injury with regular clinical assessments and serum liver testing. POLG mutation screening should be performed in accordance with current clinical practice."[17]

Selected Relevant Publications

An expert-authored review (updated 2024) suggested the following testing strategy for those with a known or suspected diagnosis of a POLG-related disorder:[1]

- "POLG-related disorders comprise a continuum of overlapping phenotypes that were clinically defined before the molecular basis was known. POLG-related disorders can therefore be considered an overlapping spectrum of disease presenting from early childhood to late adulthood. The age of onset broadly correlates with the clinical phenotype."
- "Establishing the diagnosis of a POLG-related disorder relies on clinical findings and the identification of biallelic POLG pathogenic variants on molecular genetic testing for all phenotypes except autosomal dominant progressive external ophthalmoplegia (adPEO), for which identification of a heterozygous POLG pathogenic variant on molecular genetic testing is diagnostic."
- "Sequence analysis of POLG is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect intragenic and whole-gene deletions or duplications."
- "In individuals with a suspected autosomal recessive POLG-related disorder but in whom only one POLG pathogenic variant has been identified by single-gene testing, identification of a second in trans pathogenic variant in POLG, use of RNA sequencing of POLG, or identification of pathogenic variants in other genes known to be associated with the phenotype may be revealing."
- "Sequence analysis of TWNK (formerly C10orf2 or PEO1) may be considered in persons with a suspected autosomal recessive POLG-related disorder but in whom only one POLG pathogenic variant was identified by single-gene testing, to investigate the possibility of digenic inheritance."
- "A multigene panel that includes POLG, TWNK (formerly C10orf2 or PEO1), and other genes of interest ... may be considered to identify the genetic cause of the

condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype."

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for POLG testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

References

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