Gaucher Disease Genetic Testing

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Introduction

Gaucher disease 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
GBA Gene Analysis, Common Mutations	81251
GBA Known Familial Mutation Analysis	81403
GBA Sequencing	81479

Criteria

Introduction

Requests for Gaucher disease testing are reviewed using these criteria.

Carrier Testing

GBA Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing that would detect the familial mutation, AND
- Carrier Screening:
  - GBA mutation(s) identified in 1st, 2nd, or 3rd degree biologic relative(s), OR
- Prenatal Testing for At-Risk Pregnancies:
  - GBA mutation(s) identified in both biologic parents, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

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GBA Common Mutation Analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous GBA genetic testing, including Ashkenazi Jewish screening panels containing targeted mutation analysis for Gaucher disease, AND
- Carrier Screening:
  - Ashkenazi Jewish descent, regardless of disease status and results of glucocerebrosidase assay, and
  - Intention to reproduce, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Diagnostic and Expanded Carrier Testing

GBA Sequencing

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous GBA full sequencing analysis, and
  - If performed, testing for 4 common mutations is negative, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Glucocerebrosidase enzyme activity in peripheral blood leukocytes is 0-15% of normal activity, and
  - Characteristic bone changes including osteopenia, focal lytic or sclerotic bone lesions or osteonecrosis, or
  - Hepatosplenomegaly and hematologic changes including anemia or thrombocytopenia, or
  - Primary neurologic disease which could include one or more of the following: cognitive impairment, bulbar signs, pyramidal signs, oculomotor apraxia, or seizures (progressive myoclonic epilepsy), OR
- Diagnostic Testing for Asymptomatic Carriers:
  - One mutation detected by targeted mutation analysis, and

- Glucocerebrosidase enzyme activity in peripheral blood leukocytes is 0-15% of normal activity, OR

- Testing for Individuals with Family History or Partners of Carriers:
  - 1st, 2nd, or 3rd degree biologic relative with clinical diagnosis of Gaucher disease, familial mutation unknown, and testing unavailable, or
  - Partner is monoallelic or biallelic for GBA mutation, and has the potential and intention to reproduce with this partner, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

What is Gaucher Disease?

Definition

Gaucher disease is a genetic disorder of lipid metabolism that affects multiple organs and tissues.[1]

Incidence

Gaucher disease is relatively common in Ashkenazi Jewish populations, with Gaucher disease type 1 affecting about 1 in 855 people.[2] Gaucher disease is much less common in the general population, affecting about 1 in 57,000 to 1 in 100,000 people.[2] Other populations with an enrichment for this disease include Spanish, Portuguese, Swedish, Jenin Arab, Greek, and Albanian. "The prevalence of neuropathic GD [Gaucher disease] varies across ethnic groups but appears to be higher among those who are not of European origin."[2]

Symptoms

There are several types of Gaucher disease, each with varying signs and symptoms:[1,2]

- Type 1: This is the most common type of Gaucher Disease. Unlike other types, type 1 does not affect the central nervous system (CNS). Symptoms include enlargement of the liver and spleen (hepatosplenomegaly), cytopenias, coagulation abnormalities, lung disease, immunologic abnormalities, and bone abnormalities.
- Type 2/Type 3: These types are more rare, usually more severe, and affect the brain and CNS. Common symptoms include seizures, hyperextension of the spine, and lockjaw, in addition to the symptoms listed above for type 1.
- Perinatal lethal: The most severe form of Gaucher disease has symptoms that begin during pregnancy or in early infancy. Prenatal symptoms include non-immune hydrops fetalis. Early infantile symptoms include swelling, dry/scaly skin (ichthyosis), and serious neurological problems.
- Cardiovascular: This type has heart manifestations. Symptoms include the hardening of heart valves as well as eye abnormalities, bone disease, and enlarged

spleen. This form has only been reported in individuals who are homozygous for a specific variant (c.1342G>C, p.Asp448His).

- Some general genotype/phenotype correlations have been observed. However, "[s]ignificant overlap in clinical manifestations found between individuals with various genotypes precludes specific counseling about prognosis in individual cases. … Discordance in phenotype has been reported even among monozygotic twins."[2] Subtypes of Gaucher disease are identified through clinical symptoms and, with the exception of the cardiovascular type, do not correlate well with the various mutations that cause Gaucher disease.[2]

Cause

Gaucher disease is caused by mutations in the GBA gene.[1-3] The GBA gene produces the enzyme beta-glucosylceramidase, also called acid beta-glucocerebrosidase. This enzyme helps break down fatty substances in cells. Mutations in GBA lead to a buildup of these fatty substances to toxic levels. This buildup damages tissues and organs, leading to symptoms of Gaucher disease.[1-3]

Inheritance

Gaucher disease is an autosomal recessive disorder.

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%.

Diagnosis

A diagnosis of Gaucher disease requires 0-15% normal glucocerebrosidase enzyme activity, or detection of biallelic pathogenic variants in the GBA gene.[2] Clinical findings alone are insufficient for a definitive diagnosis of Gaucher disease.[2]

If Gaucher disease is suspected in a symptomatic person, glucocerebrosidase enzyme testing should be performed first. People affected with Gaucher disease have 0-15% the normal level of glucocerebrosidase compared to healthy individuals. Measuring glucocerebrosidase levels is a reliable way to confirm a suspected case of Gaucher disease.[2,4] Individuals with type 1 Gaucher disease typically will have 10-15% enzyme level function while individuals with Type 2 or Type 3 will have much lower levels. However, the types cannot be reliably distinguished from one another.[2] Enzyme levels within the normal range rule out Gaucher disease.[2] Enzyme testing is not appropriate to identify unaffected carriers.[2]

Genetic testing can be used to identify the disease-causing mutations in an affected person diagnosed by enzyme analysis.[1,2] Identifying the causative GBA mutations can confirm a diagnosis and impact recurrence risks and family planning. Some mutations can give prognostic information, such as whether or not CNS involvement is expected. High variability exists among phenotypes, even within families.[2]

- Clinically-available testing panels assess four or more of most common mutations in the GBA gene.
    - Four mutations (N370S, L444P, 84GG, IVS2+1) account for approximately 90% of mutations in the Ashkenazi Jewish population and approximately 50%-60% of mutations in the non-Ashkenazi Jewish population.[1,2]
    - Some laboratories include other mutations in their panels.
    - GBA common mutation analysis is widely available as part of carrier screening panels. These panels are often ethnicity based, but can also be pan-ethnic screens, including a variety of conditions affecting multiple ethnic groups. GBA common mutation testing is offered as part of an “Ashkenazi Jewish Panel” that includes several other genetic diseases that are more common in this population.[2,5-7]
        - For information on Ashkenazi Jewish carrier screening, please refer to the guideline *Ashkenazi Jewish Carrier Screening,* as this testing is not addressed here.
- Next generation sequencing of the entire coding region of the GBA gene will detect mutations that the GBA mutation panel would not.[1,2]
    - The detection rate of sequencing is approximately 99%.[2]
    - This test is indicated in people with Gaucher disease who have one or no mutations identified by mutation panel testing.
    - This test is also indicated for reproductive partners of individuals who have 1 or more GBA mutations.

Management

There is no cure for Gaucher disease. The main therapeutic options are enzyme replacement therapy (ERT) and substrate reduction therapy (SRT). "Individuals with type 1 GD report improved health-related quality of life after 24-48 months of ERT. … Individuals with type 2 GD and pyramidal tract signs are not likely to respond to ERT or SRT, perhaps because the underlying neuropathology is cell death rather than lysosomal storage of GL1."[2] ERT can be used for individuals with Type 3 disease, but will not improve any symptoms involving the CNS as treatment does not cross the blood-brain barrier.[2] "SRT used in combination with ERT for type 3 GD with progressive neurologic disease does not appear to alter ultimate prognosis."[2]

Survival

Many individuals with Type 1 disease can expect a normal lifespan. Type 2 is more severe than type 3, and affected individuals usually do not survive past childhood. Individuals with Type 3 have more slowly progressing symptoms and can survive into adulthood. Infants affected with the perinatal lethal type usually survive only a few days after birth.[1,2]

Test information

Introduction

Testing for Gaucher disease may include known familial mutation analysis, targeted mutation analysis, or next generation sequencing.

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.

Targeted Mutation Analysis

Targeted mutation analysis uses hybridization, single nucleotide extension, select exon sequencing, or similar methodologies to assess a set of disease-causing mutations. This analysis identifies common and/or recurring mutations. Targeted mutation panels or select exon sequencing may have differing clinical sensitivities dependent upon ethnicity, phenotypic presentation, or other case-specific characteristics.

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.

Guidelines and evidence

Introduction

This section includes relevant guidelines and evidence pertaining to Gaucher disease testing. Professional guidelines generally supported Gaucher disease carrier screening for those at increased risk.[5-7]

American College of Medical Genetics and Genomics

Consensus guidelines from the American College of Medical Genetics and Genomics (ACMG, 2008) recommended routine carrier screening for a group of disorders that includes Gaucher disease when at least one member of the couple is Ashkenazi Jewish and that couple is pregnant or planning pregnancy.[6]

ACMG (2021) released an educational practice resource on carrier screening.[7] This consensus statement asserted that general population carrier screening should be ethnicity and family history agnostic. To accomplish this, screening all individuals in the prenatal/preconception period for autosomal recessive and X-linked conditions with a carrier frequency of >1/200 was suggested. ACMG generated a list of 113 genes, which included the GBA gene, meeting the criteria.

American College of Obstetricians and Gynecologists

Consensus guidelines from the American College of Obstetricians and Gynecologists (ACOG, 2020) stated:[5]

- "Some experts have advocated for a more comprehensive screening panel for those of Ashkenazi descent, including tests for several diseases that are less common [than the four conditions mentioned above] (carrier rates 1 in 15 to 1 in 168)." A list of autosomal recessive conditions for which screening could be considered, inclusive of Gaucher disease, was provided in this guideline.

International Working Group of Gaucher Disease

The Diagnostic Working Group of the International Working Group of Gaucher Disease (IWGGD, 2022) published guidelines for implementation and interpretation of testing for the diagnosis of Gaucher Disease type 1.[8] The guideline addressed biochemical and genetic testing. In this guideline, the GBA gene is denoted as GBA1 and BGLU refers to enzyme activity assayed by the use of an artificial substrate. They stated the following specific to genetic testing of GBA:

- The following had a level of evidence of II and IV ("retrospective cohort studies or case series with consistent results") and "Grade B (Recommendation)":
    - "Molecular analysis of the GBA1 gene should always be performed when biomarker results or phenotype are at odds with the enzymology and is highly recommended in subjects with BGLU activity below normal reference intervals in

cells to further support/confirm the diagnosis of GD and provide genetic counseling. ..."

- "Genetic testing could be done as a primary test (before testing enzymatic activity). However, results should be interpreted with caution since GBA1 testing is challenging … Therefore, confirmation of diagnosis through the assessment of enzymatic activity in patient's cells is mandatory."
- "Genetic testing is the most reliable method to detect heterozygous carriers and it should be made available to family members at risk of being a carrier."
- "In all cases, molecular testing should be accompanied by a pre and post-test genetic counseling delivered by a counsellor experienced in GD to ensure informed choices."
- "Sequencing analysis of GBA1 exons and intron exon boundaries should be performed as the primary molecular test. It should be performed using specific long template amplification of the GBA gene (avoiding the amplification of the pseudogene) followed by Sanger sequencing or NGS specifically designed to avoid reads misalignments."
- "GBA1 could be included in gene panels analyzed by NGS. This technology allows the detection of point mutations, although false positive results have been reported. Therefore, point mutations detected by NGS methods should always be confirmed by Sanger sequencing. Standard workflows are not suitable for the detection of large deletions or recombinant alleles."
- "Segregation of alleles by identifying variants in parents, should be determined."
- "The presence of homozygous pathogenetic variants not confirmed in parents, as well as the absence of pathogenetic variants (in one or both allele) after sequencing should always be questioned and additional investigations should be performed. ..."
- "Variants should be classified following the ACMG criteria and in case of identification of VUS, pathogenicity should be investigated by functional analysis."

- The following had a level of evidence of V ("case reports") and "Grade D (Option)":
  - "In the absence of pathogenetic variants in the GBA1 gene in subjects with a clinical phenotype compatible with GD, increased chitotriosidase activity, increased levels of GlcSph [glucosylsphingosine] and normal or low BGLU activity in cells, a Sap C [Saposin C] deficiency should be suspected and the PSAP gene analyzed."

Selected Relevant Publications

A 2023 expert-authored review recommended the following testing strategy for diagnosis of an affected person.[2] These recommendations were supported by the ACMG Work Group on Diagnostic Confirmation of Lysosomal Storage Diseases.[9]

- "The diagnosis of GD relies on demonstration of deficient glucocerebrosidase (glucosylceramidase) enzyme activity in peripheral blood leukocytes or other nucleated cells or by the identification of biallelic pathogenic variants in GBA."[2]
- "Sequence analysis of GBA is performed first and followed by gene-targeted deletion/duplication analysis if only one or not pathogenic variant is found. Targeted analysis for pathogenic variants can be performed first, particularly in individuals of Ashkenazi Jewish ancestry. ... Molecular genetic testing can be used to identify carriers among at-risk family members once the pathogenic variants have been identified in the family."[2]

References

Introduction

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