Test Specific Guidelines

Bloom Syndrome Genetic Testing

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Introduction

Bloom syndrome testing is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
BLM Deletion/Duplication Analysis	81479
BLM Known Familial Mutation Analysis	81403
BLM Sequencing	81479
BLM Targeted Mutation Analysis	81209
Sister Chromatid Exchange	88245

What Is Bloom Syndrome?

Definition

Bloom syndrome is an autosomal recessive disorder resulting from biallelic pathogenic mutations in the BLM gene which encodes the BLM DNA helicase. Pathogenic mutations in BLM lead to genomic instability where the chromosomes contain gaps and breaks that impair normal cell activities.[1,2]

Prevalence

Fewer than 300 cases of Bloom syndrome have been reported since the disease was first described over 50 years ago. Approximately one third are of Ashkenazi Jewish descent due to founder alleles.[1,3-5]

Symptoms

Affected individuals are usually smaller than average and may have a variety of symptoms.[1-3]

- **Pre- and post-natal growth deficiency**

- Short statureLong, narrow face, small lower jaw, and prominent nose and ears
- Sensitivity to sunlight: Exposure to sunlight causes a characteristic butterfly-shaped rash on the face
- Chronic lung problems, insulin resistance, and immune deficiencies
- Gastroesophageal reflux
- Decreased fertility in males
- Skin lesions that develop over time
- Cancer predisposition (including, but not limited to, gastrointestinal, genital and urinary tract, lymphoma, acute lymphoblastic leukemia, acute myeloid leukemia (AML), sarcoma, Wilms tumor, medulloblastoma, retinoblastoma)
- Learning disabilities

Cause

Bloom syndrome is caused by biallelic mutations in the BLM gene.[1,2,4-6]

The BLM gene encodes the BLM DNA helicase, a member of the RECQ family and is essential to maintaining the stability of chromosomes during DNA replication and cell division.[1,4-6]

Pathogenic mutations in the BLM gene lead to mistakes during cellular replication.[4-6]

Individuals with Bloom syndrome have multiple breaks, gaps, and genetic rearrangements in their chromosomes, leading to a unique combination of signs and symptoms. Cells from individuals with Bloom syndrome with absent BLM activity demonstrate a 10 times higher rate of sister chromatid exchange.[1,4,5]

Inheritance

Bloom syndrome 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 Bloom syndrome is established in an individual with characteristic clinical features and/or biallelic pathogenic mutations in BLM. Increased frequency of sister-chromatid exchange and exclusion of RMI1, RMI2, and TOP3A-related disorders may be helpful in establishing the diagnosis in those with characteristic clinical features who do not have biallelic pathogenic mutations in BLM.[4,5]

Targeted mutation testing analyzes for the pathogenic BLM mutation most often found in Ashkenazi Jewish individuals, called blm^{Ash}.[5] The detection rate of this mutation in Ashkenazi Jewish individuals is greater than 93%.[5]

Next generation sequencing analyzes for mutations across the entire gene, and can identify at least 87% of disease-causing mutations in individuals with non-Jewish ancestry and greater than 99% of disease-causing mutations in Ashkenazi Jewish individuals.[5] It is typically used only for diagnosis of an affected individual or carrier testing of a non-Ashkenazi Jewish individual when the partner is a known carrier.

Deletion/duplication testing may be performed when there is a high suspicion for disease but targeted mutation analysis and next generation sequencing did not identify biallelic mutations.[5]

Treatment

There is no cure for Bloom syndrome. Treatment involves continuous monitoring by multiple physicians and specialists.[2,5,6] Treatment and surveillance may include the following:[5]

- Skin protection
- Nutrition and developmental services and therapies as needed
- Insulin resistance and hyperglycemia are treated as in type 2 diabetes
- Modification of chemotherapy as needed with cautious use of ionizing radiation or alkylating agents
- Gamma globulin infusions in individuals with recurrent infections
- Surveillance includes:
    - Abdominal ultrasound: completed every 3 months until 8 years
    - Whole body MRI: beginning at 12-13 years and completed every 1-2 years
    - Colonoscopy: beginning at 10-12 years and completed annually
    - Fecal immunochemical testing: beginning at 10-12 years and completed every 6 months
    - Breast MRI: beginning at 18 years in women and completed annually

- **Fasting blood glucose, hemoglobin A1C, serum TSH with reflex to T4, and lipid profile: beginning at 10 years and completed annually**

Survival

Lifespan is limited. No individuals have been reported to survive past 50 years. The most common cause of death is from cancer.[6,7]

Test Information

Introduction

Testing for Bloom syndrome may include sister chromatid exchange, known familial mutation analysis, targeted mutation analysis, next generation sequencing, and/or deletion/duplication analysis.

Sister Chromatid Exchange

Sister chromatid exchange (SCE) testing involves exposing an individual's cells to bromodeoxyuridine (BrdU), a compound that helps identify which cells contain chromosomes with unusually large numbers of rearrangements, or "exchanges." Individuals with Bloom syndrome will have a substantially higher number of these exchanges compared with unaffected individuals.[4,8] Increased SCE may be helpful in situations where BLM mutation analysis is inconclusive but SCE analysis alone is not sufficient to confirm a diagnosis of Bloom syndrome because increased SCEs are observed in other disorders (such as RMI1, RMI2, and TOP3A).[5]

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 patient 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.

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.

Guidelines and Evidence

Introduction

This section includes relevant guidelines and evidence pertaining to Bloom syndrome testing.

Diagnostic Testing Strategy

A 2019 expert-authored review suggested the following diagnostic testing strategy:[5]

"The diagnosis of Bloom Syndrome (Bsyn) is established in a proband with identification of biallelic pathogenic variants in BLM on molecular genetic testing."

Carrier Testing Strategy

The American College of Medical Genetics and Genomics (ACMG, 2008)[9] and the American College of Obstetrics and Gynecologists (ACOG, 2017)[10] supported offering carrier testing for Bloom syndrome to individuals of Ashkenazi Jewish descent for the common blm^{Ash} mutation.

- **Guidelines support the testing of individuals of Ashkenazi Jewish descent, even when their partner is non-Ashkenazi Jewish. In this situation, testing would start with the individual who is Jewish and if blm^{Ash} mutation is detected, sequencing of BLM in the non-Ashkenazi Jewish partner would**

follow.[9] If the woman is pregnant, testing may need to be conducted on both partners simultaneously in order to receive results in a timely fashion.[10]

- If one or both partners are found to be carriers of Bloom syndrome, genetic counseling should be provided and prenatal testing offered, if appropriate.

Prenatal Testing Strategy

A 2019 expert-authored review stated:[5]

- **"Once the BLM pathogenic variants have been identified in an affected family member, prenatal diagnosis (by amniocentesis or chorionic villus sampling (CVS) and preimplantation genetic diagnosis are possible."**

Criteria

Introduction

Requests for Bloom syndrome testing are reviewed using these criteria.

Sister Chromatid Exchange (Chromosome Analysis for Breakage Syndromes)

- **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 sister chromatid exchange analysis performed, and**
  - **No previous BLM full sequencing, or BLM sequencing performed and only one mutation identified, and**
  - **No known BLM mutation in biologic relative, and**
  - **If Ashkenazi Jewish, targeted mutation analysis performed and no mutation detected or one mutation detected, AND**
- **Diagnostic Testing for Symptomatic Individuals:**
  - **Unexplained severe intrauterine growth deficiency (less than 10th percentile) that persists throughout infancy and childhood, or**
  - **An individual with moderate-to-severe growth deficiency who develops erythematous skin lesions in the "butterfly area" of the face after sun exposure, or**
  - **An individual with moderate-to-severe growth deficiency who develops a malignancy OR**
- **Prenatal Testing for At-Risk Pregnancies:**
  - **Known increased risk due to affected first-degree relative, AND**

- **Rendering laboratory is a qualified provider of service per the Health Plan policy.**

BLM 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 of BLM that would detect the familial mutation, AND**
- **Carrier Screening:**
  - **Known family mutation in BLM identified in 1st, 2nd, or 3rd degree biologic relative(s), OR**
- **Prenatal Testing for At-Risk Pregnancies:**
  - **BLM mutation identified in both biologic parents, AND**
- **Rendering laboratory is a qualified provider of service per the Health Plan policy.**

BLM Targeted 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 BLM genetic testing, including Ashkenazi Jewish screening panels containing targeted mutation analysis for blm^{Ash}, AND**
- **Carrier Screening:**
  - **Ashkenazi Jewish descent, and**
  - **Have the potential and intention to reproduce, AND**
- **Rendering laboratory is a qualified provider of service per the Health Plan policy.**

BLM 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 BLM full sequencing, and
- No known BLM mutation in biologic relative, and
- If Ashkenazi Jewish, targeted mutation analysis performed and no mutation detected or one mutation detected, AND

- Diagnostic Testing for Symptomatic Individuals:
  - Unexplained severe intrauterine growth deficiency (less than 10th percentile) that persists throughout infancy and childhood, or
  - An individual with moderate-to-severe growth deficiency who develops erythematous skin lesions in the "butterfly area" of the face after sun exposure, or
  - An individual with moderate-to-severe growth deficiency who develops a malignancy, OR
- Testing for Individuals with Family History or Partners of Carriers:
  - 1st, 2nd, or 3rd degree biologic relative with Bloom syndrome clinical diagnosis, family mutation unknown, and testing unavailable, or
  - Partner is monoallelic or biallelic for BLM mutation, and
  - Have the potential and intention to reproduce, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

BLM Deletion/Duplication Analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - Previous BLM full sequencing, and no mutations or only one mutation detected, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Unexplained severe intrauterine growth deficiency (less than 10th percentile) that persists throughout infancy and childhood, or
  - An individual with moderate-to-severe growth deficiency who develops erythematous skin lesions in the "butterfly area" of the face after sun exposure, or
  - An individual with moderate-to-severe growth deficiency who develops a malignancy, OR

- **Testing for Individuals with Family History or Partners of Carriers:**
  - **1st, 2nd, or 3rd degree biologic relative with Bloom syndrome clinical diagnosis, family mutation unknown, and testing unavailable, or**
  - **Partner is monoallelic or biallelic for BLM mutation, and**
  - **Have the potential and intention to reproduce, AND**
- **Rendering laboratory is a qualified provider of service per the Health Plan policy.**

References

Introduction

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