Introduction

Bloom syndrome 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.

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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.\(^1\)\(^2\)

Symptoms

Affected individuals are usually smaller than average and suffer from a variety of symptoms.\(^1\)\(^3\)

- Pre- and post-natal growth deficiency
- Short stature
- Long, 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
Bloom Syndrome

• 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

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

Prognosis

There is no cure for Bloom syndrome. Treatment involves continuous monitoring by multiple physicians and specialists.2,4,5

Cause

Bloom syndrome is caused by biallelic mutations in the BLM gene.1,2,4,5

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.1,4,5

Pathogenic mutations in the BLM gene lead to mistakes during cellular replication.4,5

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 patients with Bloom syndrome with absent BLM activity demonstrate a 10 times higher rate of sister chromatid exchange.1,4,5

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.5

Inheritance

Bloom syndrome is an autosomal recessive disorder, meaning that an affected individual inherits BLM gene mutations from each parent.2,5
Individuals who inherit only one mutation are called carriers. Heterozygous carriers are asymptomatic.

Two carriers of Bloom syndrome have a 1 in 4 (25%) chance for each pregnancy to be affected with Bloom syndrome and a 1 in 2 (50%) chance for each pregnancy to be an unaffected carrier.

**Test information**

**Introduction**

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

**Sister Chromatid Exchange (SCE)**

SCE method 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. 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).

**BLM Known Familial Mutation Analysis**

Once a pathogenic mutation has been identified in an affected person, relatives and at-risk pregnancies can be tested.

**BLM Targeted Mutation Analysis**

This test looks for the pathogenic BLM mutation most often found in Ashkenazi Jewish individuals, called blm\textsuperscript{Ash}. The detection rate of this mutation in Ashkenazi Jewish individuals is greater than 93%.

**BLM Sequencing**

This test looks 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. 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.
BLM Deletion/Duplication Analysis

This test looks for deletions and duplication in the gene that would not be detected by sequencing analysis.\(^5\) It is typically performed in reflex to sequencing analysis when there is a high suspicion for disease.\(^5\)

Guidelines and evidence

Introduction

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

Diagnostic testing strategy

A 2019 expert-authored review suggests 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 (ACMG, 2008)\(^7\) and the American College of Obstetrics and Gynecologists (ACOG, 2009 and 2017)\(^8,9\) support offering carrier testing for Bloom syndrome to individuals of Ashkenazi Jewish descent for the common blm\(^{\text{Ash}}\) 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\(^{\text{Ash}}\) mutation is detected, sequencing of BLM in the non-Ashkenazi Jewish partner would follow.\(^7\) If the woman is pregnant, testing may need to be conducted on both partners simultaneously in order to receive results in a timely fashion.\(^8\)

• 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 states:\(^5\)

• “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 retardation that persists throughout infancy and childhood (less than 5th percentile), or
  - An unusually small individual (less than 5th percentile) who develops erythematous skin lesions in the “butterfly area” of the face after sun exposure, or
  - An unusually small individual (less than 5th percentile) 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, AND
• Carrier Screening:
  o Known family mutation in BLM identified in 1\textsuperscript{st}, 2\textsuperscript{nd}, or 3\textsuperscript{rd} degree biologic relative(s), OR

• Prenatal Testing for At-Risk Pregnancies:
  o BLM mutation identified in both biologic parents, AND

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

\textbf{BLM Targeted Mutation Analysis}

• Genetic Counseling:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

• Previous Genetic Testing:
  o No previous BLM genetic testing, including Ashkenazi Jewish screening panels containing targeted mutation analysis for blm\textsuperscript{Ash}, AND

• Carrier Screening:
  o Ashkenazi Jewish descent, and
  o Have the potential and intention to reproduce, AND

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

\textbf{BLM Sequencing}

• Genetic Counseling:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

• Previous Genetic Testing:
  o No previous BLM full sequencing, and
  o No known BLM mutation in biologic relative, and
  o If Ashkenazi Jewish, targeted mutation analysis performed and no mutation detected or one mutation detected, AND

• Diagnostic Testing for Symptomatic Individuals:
  o Unexplained severe intrauterine growth retardation that persists throughout infancy and childhood (less than 5\textsuperscript{th} percentile), or
• An unusually small individual (less than 5th percentile) who develops erythematous skin lesions in the “butterfly area” of the face after sun exposure, or
  
• An unusually small individual (less than 5th percentile) who develops a malignancy, OR

• Testing for Individuals with Family History or Partners of Carriers:
  
  o 1st, 2nd, or 3rd degree biologic relative with Bloom syndrome clinical diagnosis, family mutation unknown, and testing unavailable, or
  
  o Partner is monoallelic or biallelic for BLM mutation, and
  
  o 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:
  
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

• Previous Genetic Testing:
  
  o Previous BLM full sequencing, and no mutations or only one mutation detected, AND

• Diagnostic Testing for Symptomatic Individuals:
  
  o Unexplained severe intrauterine growth retardation that persists throughout infancy and childhood (less than 5th percentile), or
  
  o An unusually small individual (less than 5th percentile) who develops erythematous skin lesions in the “butterfly area” of the face after sun exposure, or
  
  o An unusually small individual (less than 5th percentile) who develops a malignancy, OR

• Testing for Individuals with Family History or Partners of Carriers:
  
  o 1st, 2nd, or 3rd degree biologic relative with Bloom syndrome clinical diagnosis, family mutation unknown, and testing unavailable, or
  
  o Partner is monoallelic or biallelic for BLM mutation, and
  
  o Have the potential and intention to reproduce, AND

• Rendering laboratory is a qualified provider of service per the Health Plan policy.
References

Introduction
These references are cited in this guideline.


