Bloom Syndrome Testing

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 a genetic disorder in which an individual’s chromosomes contain large breaks, gaps, or rearrangements.¹

Symptoms

Affected individuals are usually smaller than average and suffer from a variety of symptoms.¹⁻²

- 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, diabetes, and immune deficiencies
- Gastroesophageal reflux
• Infertility
• Cancer predisposition
• Learning disabilities

Prevalence

Fewer than 300 cases of Bloom syndrome have been reported since the disease was first described over 50 years ago.\(^2,3\)

About 1 in 48,000 Ashkenazi Jewish individuals have Bloom syndrome, and 25% of all affected individuals have Ashkenazi Jewish ancestry.\(^2\)

Prognosis

There is no cure for Bloom syndrome. Treatment involves continuous monitoring by multiple physicians and specialists.\(^1,3\)

Cause

Bloom syndrome is caused by a genetic mutation in the BLM gene.\(^1,3,4\)
BLM is essential to maintaining the stability of chromosomes during DNA replication and cell division.\(^3,4\)
Mutations in BLM lead to mistakes during cellular replication.\(^3,4\)
Individuals with Bloom syndrome have multiple breaks, gaps, and genetic rearrangements in their chromosomes, leading to a unique combination of signs and symptoms.\(^3,4\)

Diagnosis

A diagnosis of Bloom syndrome is suspected when the patient presents with the characteristic suite of signs and symptoms. This diagnosis can be confirmed by genetic testing and may be needed to differentiate between other disorders with overlapping symptoms. There are several types of tests available for diagnostic purposes.

Inheritance

Bloom syndrome is an autosomal recessive disorder, meaning that an affected individual must inherit BLM gene mutations from each parent.\(^1,4\)
Individuals who inherit only one mutation are called carriers. Carriers do not show symptoms of Bloom syndrome, but have a 50% chance of passing on the mutation to their children.
Two carriers of Bloom syndrome have a 1 in 4 (25%) chance for each pregnancy to be affected with Bloom syndrome.
Test information

Introduction

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

Sister Chromatid Exchange

SCE is the standard analysis for diagnosis of Bloom syndrome. The 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. This test can be used for prenatal diagnosis of at-risk pregnancies on chorionic villi or amniocytes.

BLM Known Familial Mutation Analysis

Once a deleterious 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 BLM gene mutation most often found in Ashkenazi Jewish individuals, called $\text{blm}^{\text{Ash}}$. The detection rate of this mutation in Ashkenazi Jewish individuals is greater than 97%.

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. It is typically performed in reflex to sequencing analysis when there is a high suspicion for disease.
Guidelines and evidence

Introduction

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

Diagnostic testing strategy

A 2016 expert-authored review suggests the following diagnostic testing strategy:\(^4\)

“The diagnosis of Bloom Syndrome (Bsyn) is established in a proband with identification of biallelic pathogenic variants in BLM on molecular genetic testing or, if molecular genetic testing is inconclusive, with identification of increased frequency of sister-chromatid exchanges (SCEs) on specialized cytogenetic studies.”

Carrier testing strategy

The American College of Medical Genetics (ACMG, 2008)\(^6\) and the American College of Obstetrics and Gynecologists (ACOG, 2009)\(^7\) 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.\(^6\) If the woman is pregnant, testing may need to be conducted on both partners simultaneously in order to receive results in a timely fashion.\(^7\)
- 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 2016 expert-authored review states:\(^4\)

- “Prenatal diagnosis for pregnancies at increased risk is possible by sister-chromatid exchange (SCE) analysis of fetal cells obtained by amniocentesis usually performed at about 15 to 18 weeks’ gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks’ gestation.”
- “If the BLM pathogenic variants have been identified in an affected family member, prenatal testing for pregnancies at increased risk may be available from a clinical laboratory that offers either testing of this gene or custom prenatal testing.”
- “Preimplantation genetic diagnosis (PGD) has been successfully utilized for one couple [Bloom’s Syndrome Registry, unpublished data], and may be an option for some families in which the BLM pathogenic variants have been identified.”
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
o No previous genetic testing of BLM, AND

• Carrier Screening:
  o Known family mutation in BLM identified in 1st, 2nd, or 3rd 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.

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 blmAsh, 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.

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 5th percentile), or
• An unusually small individual (less than 5\textsuperscript{th} percentile) who develops erythematous skin lesions in the “butterfly area” of the face after sun exposure, or
• An unusually small individual (less than 5\textsuperscript{th} percentile) who develops a malignancy, OR

• Testing for Individuals with Family History or Partners of Carriers:
  o 1\textsuperscript{st}, 2\textsuperscript{nd}, or 3\textsuperscript{rd} 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 5\textsuperscript{th} percentile), or
  o An unusually small individual (less than 5\textsuperscript{th} percentile) who develops erythematous skin lesions in the ”butterfly area” of the face after sun exposure, or
  o An unusually small individual (less than 5\textsuperscript{th} percentile) who develops a malignancy, OR

• Testing for Individuals with Family History or Partners of Carriers:
  o 1\textsuperscript{st}, 2\textsuperscript{nd}, or 3\textsuperscript{rd} 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.


