Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 1/1/24**
(See policy history boxes for previous effective dates)

Title: Genetic Testing for Bloom Syndrome

Description/Background

Bloom syndrome (BSyn) (also known as Bloom-Torre-Machacek syndrome of congenital telangiectatic erythema) is a rare genetic disorder characterized by short stature, sun-sensitive skin changes, an increased risk of cancer, and other health problems. Infants with this syndrome present with low birth weight and length. They remain much shorter and thinner than other members of their family. Full adult height is typically less than 5 feet.

Affected individuals tend to develop dilated blood vessels and reddening in the skin, particularly in response to sun exposure. These changes typically appear as a butterfly-shaped patch of reddened skin across the nose and cheeks, but the skin changes may also affect the hands and arms.

These individuals also have an increased risk of developing cancer. They can develop any of the cancers found in the general population, but the cancers tend to occur unusually early in life, and affected individuals often develop more than one type of cancer.

Other characteristics of this disorder include a high-pitched voice and distinctive facial features including a long, narrow face, small mandible, large nose and prominent ears. Other features that tend to affect people with Bloom syndrome include, but are not limited to:

- Learning disabilities
- Increased risk of diabetes
- Chronic obstructive pulmonary disease (COPD)
- Recurrent infections of the upper respiratory tract, ears, and lungs during infancy.
- Men with Bloom syndrome usually do not produce sperm, and as a result are unable to father children (infertile).
- Women with the disorder generally have reduced fertility and experience menopause earlier than usual.

Bloom syndrome is a very rare disorder in most populations, and its overall frequency is unknown. The disorder is more common in people of Central and Eastern European (Ashkenazi) Jewish background, among whom about one in 50,000 are affected. Approximately one-third of people with Bloom syndrome are of Ashkenazi Jewish descent.

Bloom syndrome is caused by mutations in the *BLM* gene, which provides instructions for making a member of the protein family called RecQ helicases. The gene for Bloom syndrome is located on chromosome 15 (gene locus is band 15q26.1). Helicases are enzymes that bind to DNA and temporarily unwind the two spiral strands (double helix) of the DNA molecule. This unwinding is necessary for copying (replicating) DNA in preparation for cell division, and for repairing damaged DNA. RecQ helicases maintain the structure and integrity of DNA. When a cell prepares to divide to form two cells, the DNA that makes up the chromosomes is copied so that each new cell will get a complete set of chromosomes. The copied DNA from each chromosome is arranged into two identical structures, called sister chromatids, which are attached to one another during the early stages of cell division. Sister chromatids exchange small sections of DNA (sister chromatid exchange) during this time. The BLM protein interacts with several other proteins involved in the maintenance of genome integrity. With the help of its partner proteins, BLM suppresses sister chromatid exchanges and helps to maintain DNA stability during the copying process.

BLM gene mutations prevent the *BLM* protein from performing its function in maintaining genomic stability. Because of the altered *BLM* protein activity, the frequency of sister chromatid exchanges (SCEs) increases about 10-fold, which is a hallmark of Bloom syndrome. Increased sister chromatid exchange is an indicator of chromosome instability. It is associated with gaps and breaks in the genetic material that impairs normal cell activities and causes the health problems associated with this condition. Cancer results from genetic changes that allow cells to divide in an uncontrolled way. Altered *BLM* protein activity may also lead to an increase in cell death, resulting in slow growth in affected individuals.[1]

Inheritance of this condition follows and autosomal recessive pattern, meaning that both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Molecular genetic testing is available to detect *BLM* gene mutations; *BLM* is the only gene in which mutations are known to cause BSyn. Mutations in *BLM* have been identified in the vast majority of persons with BSyn who have been appropriately tested. There are very few instances of affected individuals in whom *BLM* mutation(s) were not identified; these instances probably were attributable to technical limitations.[3]

Families benefit from counseling regarding the risk of cancer, a serious risk for all but clearly a much greater one for persons with BSyn. The wide variety of types and sites of cancer in BSyn, plus the unusually early onset of the so-called solid tumors (carcinomas and sarcomas), makes surveillance for cancer a life-long undertaking, requiring planning and cooperation among the affected person, the family, and the physician in charge.

- In persons younger than age 20 years, leukemia is the main type of cancer. Until evidence becomes available that treatment at the earliest stages of leukemia is more effective than treatment after full-blown symptoms appear, hematologic surveillance other than that used in general pediatrics appears unnecessary, if not contraindicated.

- Close contact between individuals age 20 years and older and their physicians is advisable, and symptoms that cannot be accounted for otherwise should be evaluated promptly as potential early indicators of cancer.
- Screening for colon cancer, the most common single "solid tumor" in individuals with BSyn should begin decades earlier than in others, and should be carried out more frequently. In adults, colon cancer screening may include colonoscopy every one to two years, and stool guaiac testing for blood every three to six months.

Sun exposure to the face, particularly in infancy and early childhood, should be avoided.

The prognosis of BSyn is generally poor, with mortality in the second or third decade of life due to increased risk of malignancy. Before the age of 20 years, leukemia is the most common malignancy, although colon cancer may affect patients at any age.

Regulatory Status

There are no assay kits approved by the U.S. Food and Drug Administration (FDA) for genetic testing for BSyn, nor are any kits being actively manufactured and marketed for distribution. Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing. While FDA has technical authority to regulate home-brew tests, there is currently no active oversight or any known plans to begin oversight. Home-brew tests may be developed using reagents prepared in-house or, if available, commercially manufactured analyte-specific reagents (ASRs). ASRs are single reagents "intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens" and must meet certain FDA criteria but are not subject to premarket review.

Medical Policy Statement

The safety and efficacy of genetic testing for Bloom syndrome have been established. It may be considered a useful diagnostic option when indicated.

Inclusionary and Exclusionary Guidelines

Inclusions:
Genetic testing for Bloom syndrome (BSyn) (*BLM* mutation) is considered established in any of the following circumstances:

- For an infant/child suspected of having Bloom syndrome based on physical characteristics including, but not limited to pre- and postnatal growth retardation that persists into infancy and childhood, sun-sensitive skin which results in a butterfly rash to the face, increased susceptibility to infections and cancer, etc., elevated sister chromatid exchanges (SCEs), etc., in order to confirm the diagnosis.

- For carrier screening for BSyn in individuals with at least one grandparent of Eastern European (Ashkenazi) Jewish ancestry before/during pregnancy. (This is recommended by the American College of Medical Genetics.)
- Carrier testing of at-risk relatives when there has been prior identification of the *BLM* disease-causing mutations in the family.
- For prenatal diagnosis of at-risk pregnancies using cytogenetic or molecular genetic testing of fetal cells obtained by amniocentesis or chorionic villus sampling.

Exclusions:
Screening for Bloom syndrome in the general population

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81209 81443

Other codes (investigational, not medically necessary, etc.):

N/A

Rationale

The clinical diagnosis of, or suspicion of, BSyn can and must be confirmed by cytogenetic and/or molecular analysis of *BLM*, the gene in which mutations are known to cause BSyn. A sister chromatid exchange (SCE) analysis has become the standard test by which the clinical diagnosis of BSyn is confirmed.

Cytogenetic analysis.
The diagnosis of BSyn can be confirmed or ruled out by analysis of any cell type that can be cultured in vitro. The most commonly examined cells are blood lymphocytes in short-term culture; cultured skin fibroblasts and exfoliated fetal cells can also be studied.

The cytogenetic features of BSyn cells in mitosis are increased numbers of the following:
- Chromatid gaps, breaks, and rearrangements
- Quadriradial configurations (Qrs); a mean of 1%-2% in cultured BSyn blood lymphocytes (vs. none in the controls)
- Sister-chromatid exchanges (SCEs); a mean of 40-100 per metaphase (vs. <10 in controls). A greatly increased frequency of SCEs is demonstrable in BSyn cells allowed to proliferate in a medium containing 5'bromo-2'-deoxyuridine (BrdU). BSyn is the only disorder in which such evidence of hyper-recombinability is known to occur. In an individual with BSyn the mean and range of SCEs per metaphase are higher in lymphocytes than in fibroblasts, but the differences from controls in both types of cells are so great that interpretation of findings is not a problem (i.e., the normal and abnormal ranges do not overlap significantly). Note: In a minority of persons with BSyn, varying numbers of lymphocytes with normal SCE rates circulate in the blood alongside cells with the characteristically greatly increased SCE frequency and presumably are the result of

mutation back to normal in a stem cell. In theory, low (normal) SCE cells could predominate, even to the exclusion of the high-SCE cells. Therefore, when the clinical phenotype of an individual strongly suggests the diagnosis of BSyn and when no lymphocytes freshly removed from the circulation display the high number of SCEs per metaphase characteristic of BSyn, cytogenetic examination of cultured dermal fibroblasts may be necessary; low (i.e., normal) rates of SCE in fibroblasts have never been found in an individual with BSyn.

Table 1. Summary of Molecular Genetic Testing Used in Bloom's Syndrome

Gene	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method
BLM	Targeted mutation analysis	c.2207_2212delinsTAGATTC	100%
	Sequence analysis	Multiple BSyn-causing mutations	90%
	Deletion/duplication analysis	Exonic and whole gene deletions	Unknown

Testing strategies include:

- Confirming/establishing the diagnosis Bloom's syndrome
  - Cytogenetic demonstration of a characteristically greatly increased SCE frequency OR
  - Molecular demonstration either of homozygosity for a BSyn-causing mutation in *BLM* or of compound heterozygosity for two different BSyn-causing mutations. Sequence analysis should be performed first. If neither or only one mutation in *BLM* is identified, deletion/duplication analysis should be considered.
- Carrier testing for at-risk relatives requires prior identification of the *BLM* disease-causing mutations in the family. Note: Heterozygotes (i.e., carriers of a *BLM* disease-causing mutation) exhibit no features of BSyn.
- Population screening. Because of a carrier rate of approximately 1% for the blm^{Ash} allele in Ashkenazi Jews, individuals who are Ashkenazi Jewish and of reproductive age may choose to be tested [ACOG Committee on Genetics 2009].
- Prenatal diagnosis of at-risk pregnancies is possible by cytogenetic analysis, specifically by an SCE analysis. Prenatal diagnosis by molecular genetic testing and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the *BLM* disease-causing mutations in the family.

Confirming a suspected case of Bloom syndrome is important in that affected patients have an increased risk of developing cancer. They can develop any of the cancers found in the general population, but the cancers tend to occur unusually early in life, and affected individuals often develop more than one type of cancer. Confirmation of Bloom syndrome can lead to more frequent surveillance of the patient and earlier intervention in the case of suspected cancer, as susceptibility to multiple forms of cancer usually is the cause of death.

Identifying carriers for Bloom syndrome may be important in reproductive planning for parents who do not wish to pass this devastating disease on to their children. Alternatively, it may

be important for both parents and medical personnel to alert them to the possible need for additional medical support before, during and after delivery.

Government Regulations

National:

There is no NCD on this specific topic. Genetic tests used to diagnose or determine treatment in the presence of signs and symptoms of disease can be covered by Medicare. BLM gene testing (81209) is covered in that Bloom syndrome patients have a high mutation rate and therefore are at high risk of developing malignancies. Early and accurate diagnosis results in them being entered into appropriate cancer screening protocols.

Local:

Local CMS Article, A55148, effective 11/25/2021. Billing and Coding: MolDX: BLM Gene Analysis
The clinical diagnosis of Bloom (**BLM** syndrome, BSyn), characterized by severe pre and postnatal growth deficiency, highly characteristic sparseness of subcutaneous fat tissue in infants and children, is confirmed through cytogenetic testing. Molecular genetic testing identifies **BLM** gene mutation carriers at risk for conceiving offspring with the disease. Therefore, **BLM** genetic testing is not a Medicare benefit and is a statutorily excluded service. In addition to single gene testing, MolDX will also deny panels of tests that include the **BLM** gene as a statutorily excluded service.

To receive a **BLM** gene test service denial, please submit the following

- CPT code 81209 or 81443
- An Advance Beneficiary Notice (ABN) is not required for statutorily excluded services
    - For a voluntary issued ABN, append with GX modifier
    - To indicate a statutorily excluded service, append with a GY modifier
- Labs may either use the SV101-7 or SV202-7 (preferred) or the NTE field to submit this required information
- Enter the appropriate DEX Z-Code™ identifier adjacent to the CPT code in the comment/narrative field for the following Part B claim field/types:
    - Loop 2400 or SV101-7 for the 5010A1 837P
    - Box 19 for paper claim
- Enter the appropriate DEX Z-Code™ identifier adjacent to the CPT code in the comment/narrative field for the following Part A claim field/types:
    - Line SV202-7 for 837I electronic claim
    - Block 80 for the UB04 claim form

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Genetic Testing and Counseling

References

1. Genetics Home Reference: Bloom syndrome. Reviewed April 2015. Available at http://ghr.nlm.nih.gov/condition/bloom-syndrome. (Accessed August2022).
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3. Monnat RJ. Human RECQ helicases: Roles in DNA metabolism, mutagenesis and cancer biology. Semin Cancer Biol. 2010; 20:329–39. [PMC free article: PMC3040982] [PubMed: 20934517]
4. ACOG Committee on Genetics; ACOG Committee Opinion No. 442: Preconception and prenatal carrier screening for genetic diseases in individuals of Eastern European Jewish descent. Obstet Gynecol. 2009t; 114:950–3. Available at https://www.acog.org/Search?Keyword=preconception+and+prenatal+carrier+screening. (Accessed August 2019).
5. Arora H, Chacon AH, Choudhary S, McLeod MP, Meshkov L, Nouri K, Izakovic J. Bloom Syndrome. Int J Dermatol. 2014 Jul; 53(7):798-802.
6. Gross SJ, Pletcher BA, Monaghan KG. Carrier screening in individuals of Ashkenazi Jewish descent. ACMG Practice Guideline. January 2008, 10(1). Available at https://www.acmg.net/docs/Published_Carrier_Screening_PG.pdf . (Accessed August 2019).
7. Garcia AM. Loss of the bloom syndrome helicase increases DNA ligase 4-independent genome rearrangements and tumorigenesis in aging *Drosophila.* Genome Biology. Available at https://genomebiology.biomedcentral.com/articles/10.1186/gb-2011-12-12-r121. (Accessed August 2019).

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through August 2023, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/1/15	12/9/14	12/29/14	Joint policy established
12/10/15	12/10/15	12/10/15	Routine policy maintenance, updated references. No change in policy status.
1/1/17	10/11/16	10/11/16	Routine policy maintenance. Removed blue cross complete references.
1/1/18	10/19/17	10/19/17	Routine policy maintenance, no change in policy status.
1/1/19	10/16/18	10/16/18	Routine policy maintenance, no change in policy status.
1/1/20	10/15/19		Routine policy maintenance, no change in policy status.
1/1/21	10/20/20		Routine policy maintenance, no change in policy status.
1/1/22	10/19/21		Routine policy maintenance, no change in policy status.
1/1/23	10/18/22		Added code 81443 as established, routine policy maintenance, no change in policy status.
1/1/24	10/17/23		Routine policy maintenance, no change in policy status. Vendor managed: N/A (ds)

Next Review Date: 4th Qtr. 2024

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR BLOOM SYNDROME

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply.
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.