Bloom Syndrome

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Summary

Clinical characteristics.

Bloom syndrome (BSyn) is characterized by severe pre- and postnatal growth deficiency, immune abnormalities, sensitivity to sunlight, insulin resistance, and a high risk for many cancers that occur at an early age. Despite their very small head circumference, most affected individuals have normal intellectual ability. Women may be fertile but often have early menopause, and men tend to be infertile, with only one confirmed case of paternity. Serious medical complications that are more common than in the general population and that also appear at unusually early ages include chronic obstructive pulmonary disease, diabetes mellitus as a result of insulin resistance, and cancer of a wide variety of types and anatomic sites.

Diagnosis/testing.

The diagnosis of BSyn is established in a proband with characteristic clinical features and/or biallelic pathogenic variants in *BLM* identified on molecular genetic testing. Identification of increased frequency of sister-chromatid exchanges on specialized cytogenetic studies 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 variants in *BLM*.

Management.

Treatment of manifestations: Skin protection, including coverage of exposed skin and use of broad-spectrum sunscreen with SPF of at least 30 to reduce the sun-sensitive rash. Increased-calorie-density formulas and foods may promote weight gain. Although growth hormone treatment may improve linear growth, many clinicians caution against its use because of reports of early onset of cancer in some treated children. Developmental services and therapies as needed. Hyperglycemia from insulin resistance is treated as in type 2 diabetes. In persons with BSyn who have cancer, reduced chemotherapy dosage and duration to reduce risks of severe complications; caution should be exercised with use of ionizing radiation or alkylating agents, particularly busulfan, cyclophosphamide, or melphalan. Individuals with recurrent infections and defects in humoral immunity may be treated with gamma globulin infusions to decrease frequency and severity of infections.

Surveillance: Abdominal ultrasound examination every three months until age eight years for Wilms tumor. Screening and family education regarding signs/symptoms of leukemia and lymphoma at every health visit. Whole-body MRI every one to two years beginning at age 12-13 years for risk of lymphoma. Annual colonoscopy beginning at age 10-12 years. Fecal immunochemical testing every six months beginning at age 10-12 years. Annual breast MRI in women beginning at age 18 years. Annual fasting blood glucose and hemoglobin A1C beginning at age ten years. Annual serum TSH with reflex to T4 beginning at age ten years. Annual lipid profile beginning at age ten years.

Agents/circumstances to avoid: Sun exposure may provoke an erythematous rash, especially on the face. Exposure to ionizing radiation should be minimized.

Genetic counseling.

BSyn is inherited in an autosomal recessive manner. Identification of both pathogenic *BLM* variants in the proband is required for carrier (heterozygote) testing in at-risk families. *BLM* is included in expanded carrier screening panels, and most pathogenic variants can be identified through sequencing. Preimplantation and prenatal diagnosis are possible if the *BLM* pathogenic variants have been identified in the at-risk couple.

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Diagnosis

Suggestive Findings

Bloom syndrome (BSyn) **should be suspected** in an individual with any of the following clinical or cytogenetic findings.

Clinical findings

- Prenatal-onset growth deficiency that usually includes linear growth, weight gain, and head circumference and that persists into infancy, childhood, and adulthood
- Moderate-to-severe growth deficiency and a sun-sensitive, erythematous rash that commonly involves the face and appears in a butterfly distribution
- Moderate-to-severe growth deficiency and a diagnosis of cancer, usually occurring at an earlier age than in the general population

Cytogenetic findings

- Increased numbers of sister-chromatid exchanges
- Increased quadriradial configurations (Qrs) in cultured blood lymphocytes (a mean of 1%-2% Qrs are observed in cultured blood lymphocytes from a person with BSyn vs none in controls)
- Chromatid gaps, breaks, and rearrangements

Establishing the Diagnosis

The diagnosis of BSyn **is established** in a proband by identification of biallelic pathogenic variants in *BLM* on molecular genetic testing (see Table 1).

Note: An increased frequency of sister-chromatid exchanges (SCEs) on specialized cytogenetic studies may be helpful in circumstances where *BLM* variant analysis is inconclusive. SCE analysis alone is not sufficient to confirm a diagnosis of BSyn because increased SCEs are also observed in persons with biallelic pathogenic variants in *RMI1*, *RMI2*, and *TOP3A* [Hudson et al 2016, Martin et al 2018].

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of BSyn is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with growth deficiency are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of Bloom syndrome molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *BLM* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
- **A multigene panel** that includes *BLM* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by growth deficiency, **comprehensive genomic testing** (which does not require the clinician to

determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1.

Molecular Genetic Testing Used in Bloom Syndrome

Gene [1]	Test Method	% of Pathogenic Variants [2] Detectable by This Method	
		Ashkenazi Jewish Ancestry	Non-Jewish Ancestry
BLM	Targeted analysis for c.2207_2212delinsTAGTTC	93% [3]	6% [4]
	Sequence analysis [5]	~99% [3]	87% [4]
	Gene-targeted deletion/duplication analysis [6]	1% [4]	4% [4]
Unknown [7]	NA		

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on allelic variants detected in this gene.

3. German et al [2007]

4. Bloom Syndrome Registry

5. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include: quantitative PCR, long-range PCR,

multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

7.

In nine individuals with BSyn, pathogenic variants in *BLM* were not detected, suggesting the possibility of locus heterogeneity [German et al 2007].

Sister-chromatid exchanges (SCEs). Individuals with BSyn have a mean of 40-100 SCEs per metaphase (normal SCEs: <10 per metaphase). Increased frequency of SCEs is demonstrable in BSyn cultured cells (including lymphocytes, fibroblasts, and amniocytes) allowed to proliferate in a medium containing 5'bromo-2'-deoxyuridine (BrdU). Increased SCEs are not unique to BSyn. Three additional autosomal recessive disorders (*RMI1*-, *RMI2*-, and *TOP3A*-related disorders) are associated with increased SCEs and similar clinical findings to individuals with BSyn. SCE analysis may be a useful adjunct for diagnosis of BSyn, in the circumstance where only one *BLM* pathogenic variant is identified, and molecular genetic testing finds no pathogenic variants in *RMI1*, *RMI2*, or *TOP3A*. The presence of increased SCEs alone, however, is not sufficient to confirm the diagnosis of BSyn.

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Clinical Characteristics

Clinical Description

The range of clinical features in persons with Bloom syndrome (BSyn) has been tracked through the Bloom Syndrome Registry. The clinical and genetic histories have been obtained from registered persons diagnosed between 1954 and 2018 and their clinical courses have been followed [German & Passarge 1989, German 1993, German & Ellis 2002].

The main clinical features of BSyn are the following:

- **Size and appearance.** The most consistent clinical feature of BSyn seen throughout all stages of life is growth deficiency affecting height, weight, and head circumference. Body proportions are normal. Subcutaneous adipose tissue is sparse throughout childhood and adolescence, but adults may develop central obesity. Providing increased calories in childhood and adolescence does not usually result in substantial changes in growth parameters, particularly linear growth. Plasma growth hormone concentration is normal.

  The affected fetus is smaller than normal for gestational age. The mean birth weight of affected males is 1,760 g (range 900-3,189 g) and of affected females, 1,754 g (range 700-2,892 g). The average adult height of men is 149 cm (range 128-164 cm) and of women, 138 cm (range 115-160 cm).

  The facial appearance of people with BSyn is variable and may be indistinguishable from unaffected persons of similar age and size. More commonly, the face appears narrow, with underdeveloped malar and mandibular prominences and retrognathia or

micrognathia. A paucity of subcutaneous fat may cause the nose and/or ears to appear prominent.

- **Feeding problems.** Most parents report that feeding is an issue for their newborns, infants, and young children. The child with BSyn characteristically feeds slowly, has a decreased appetite, and eats a limited variety of foods. In a minority of infants with BSyn, nursing and eating are normal. Because of their slow growth and weight gain, many children are prescribed formula with increased caloric density and later are prescribed nutritional supplements that provide extra calories. Many infants have had gastrostomy tubes placed. Despite these maneuvers, weight gain continues to be modest, and children are rarely in the normal range for growth. Gastroesophageal reflux is common and may contribute to the feeding issues.
- **Skin lesions.** The skin at birth and during early infancy appears normal; however, typically following sun exposure during the first or second year of life, a red, sun-sensitive rash appears on the nose and cheeks and sometimes also on the dorsa of the hands and forearms. This rash varies in severity and extent among affected individuals; in some, it is minimal. It is usually characterized by telangiectasia but in others is described as poikiloderma. In severely affected individuals, the lesion can be bright red and can extend onto adjacent areas. Additional dermatologic manifestations include cheilitis, blistering and fissuring of the lips, eyebrow and eyelash hair loss, alopecia areata, and vesicular and bullous lesions with excessive or intense sun exposure. Café au lait macules and areas of hypopigmented skin are more numerous and larger than in those without BSyn.
- **Immunodeficiency.** In children and adults who have had laboratory evaluation of their immune system, the concentration of one or more of the plasma immunoglobulins is usually abnormally low. IgM and IgA levels are most commonly affected. Although the numbers of T and B cells are usually normal, variable abnormalities of the adaptive immune system suggest a possible role in the frequent infections reported in affected individuals.
- **Infections.** Parents of children with BSyn report that their affected children have more childhood infections than their sibs and peers; none, however, has had an opportunistic infection, and few persons with BSyn have had bacterial sepsis, meningitis, or pneumonia.
- **Fertility.** Most men with BSyn appropriately examined have had azoospermia or severe oligospermia. There is, however, one confirmed case of paternity [Ben Salah et al 2014]. Women with BSyn, although often fertile, may enter menopause prematurely. Eleven women with BSyn followed in the Registry have become pregnant at least once; seven of them have delivered a total of 11 healthy babies of normal size.
- **Intelligence.** There are no systematic studies of academic achievement or cognitive performance in persons with BSyn. The great majority appear to perform within the normal range of intellectual development. Some have required academic support for attention-related issues and task orientation, but it is not clear that the prevalence of these problems is different from that seen in the general population. Many others have excelled in school, with some earning graduate degrees.
- **Other clinical features.** Major anatomic defects are not increased in frequency. In the 281 persons in the Registry as of 2018, only single examples of the following have occurred: tracheoesophageal fistula, cardiac malformation, absent thumbs, and absence of a toe and malformation of a thumb.

Medical complications of BSyn, all serious, in order of increasing frequency are the following:

- **Chronic obstructive pulmonary disease.** Chronic bronchitis and bronchiectasis are common, and pulmonary failure has been the cause of death in six persons.
- **Myelodysplasia** has been diagnosed in 23 persons in the Registry at a median age of 22.1 years (range 3-47), and it has progressed to acute myelogenous leukemia in at least seven. In all but three, the myelodysplasia was preceded by some form of cancer for which chemotherapy and/or radiotherapy had been administered.
- **Diabetes mellitus.** Abnormalities in insulin release and glucose tolerance have been detected in the eight healthy children (ages 9 months to 13 years) and the three healthy young adults with BSyn (ages 22, 28, and 28 years) appropriately studied [Diaz et al 2006]. Because of insulin resistance, the diabetes mellitus of BSyn resembles type 2 diabetes but has a much earlier age of onset than in the general population. Paradoxically, diabetes in persons with BSyn commonly occurs in the setting of low body mass index (BMI), rather than high BMI. Diabetes has been diagnosed in 47 of 281 persons in the Registry (16.7%) at a mean age of 26.6 years (range 4-45 years). Although most individuals do not have severe complications, 16 have required insulin, and retinopathy has developed in two. Lipid profile abnormalities were also identified by Diaz et al [2006] in five of the ten subjects tested.
- **Cancer** is the most frequent medical complication in BSyn and the most common cause of death. Although the wide distribution of cell types and anatomic sites of cancer resemble that in the general population, it occurs more frequently and at much earlier ages in BSyn. Development of multiple cancers in a single individual is also much more common. Table 2 summarizes the cancers diagnosed in individuals followed in the Registry.

Table 2.

The 226 Malignant Neoplasms Diagnosed in 145 Persons in the Bloom Syndrome Registry (1954-2018)

Malignancy Type / Tissue	Subtype	Frequency	Age at Diagnosis (years)		
			Median	Mean	Range
Leukemia	Acute myeloid	17	21	19	6-32
	Acute lymphoblastic	11	14	17	4-40
	Other/biphenotypic/undefined	12	18	19	2-40
Lymphoma	--	37	20	21	4-49
Oropharyngeal	Tongue	9	37	37	30-48
	Pharynx	6	32	34.8	31-45
	Tonsil	4	40	38	25-46
	Other	5	NA	NA	NA
Upper GI	Esophageal	5	39	37	25-48
	Gastric	5	31	29	24-33
	Other	4	NA	NA	NA
Colorectal	--	28	37	35	16-49

Malignancy Type / Tissue	Subtype	Frequency	Age at Diagnosis (years)		
			Median	Mean	Range
Genitourinary	Cervical	5	22	21	19-23
	Other	9	NA	NA	NA
Breast	--	24	33	33	21-52
Skin	Basal cell	13	29	28	18-38
	Squamous cell (uncategorized)	5	35	35	35-36
	Other/undefined	4	NA	NA	NA
Wilms tumor	--	8	3	3	1-8
Lung	--	4	37	36	32-40
All other	--	12	NA	NA	NA

GI = gastrointestinal

Adapted from Cunniff et al [2018]

Genotype-Phenotype Correlations

Homozygotes and compound heterozygotes. A similar phenotype is produced by either homozygosity or compound heterozygosity for any of the more than 60 pathogenic variants in *BLM* identified to date.

Prevalence

Few individuals with BSyn have been reported in the medical literature since its description half a century ago [Bloom 1954], and fewer than 300 are known to the Bloom Syndrome Registry.

Although rare in all populations, BSyn is relatively less rare among Ashkenazi Jews. Sixty-seven of the 281 persons in the Registry are of Ashkenazi Jewish ancestry. The predominant *BLM* pathogenic variant identified in Ashkenazi Jews is c.2207_2212delinsTAGATTC, a 6-bp deletion/7-bp insertion in exon 10 of *BLM*, often (for brevity) designated blm^{Ash}; the second most common pathogenic variant is c.2407dupT.

The approximate carrier frequency of the blm^{Ash} allele:

- One in 100 Ashkenazi Jews dwelling both in New York City [Li et al 1998] and in Israel [Peleg et al 2002]
- One in 37 Ashkenazi Jews dwelling in Israel, all four of whose grandparents were from Poland [Shahrabani-Gargir et al 1998]

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Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *BLM*.

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Differential Diagnosis

Table 3.

Other Genetic Etiologies of Interest in the Differential Diagnosis of Bloom Syndrome (BSyn)

Gene(s) / Genetic Mechanism	Disorder	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/BSyn	Distinguishing from BSyn
RMI1 [1]	RECQ-mediated genome instability 1 (OMIM 610404)	AR	• ↑ SCE • Small size • Multiple café au lait macules in persons w/*TOP3A* & *RMI2* pathogenic variants	• Cancer not observed, but reported persons are all relatively young: cancer predisposition may be identified in future. • No abnormal skin findings in persons w/*RMI1* pathogenic variants • No malar rash in persons w/*TOP3A* pathogenic variants
RMI2 [1]	RECQ-mediated genome instability 2 (OMIM 612426)	AR		
TOP3A [1]	Microcephaly, growth restriction, & increased sister-chromatid exchange 2 (OMIM 618097)	AR		
Chromosome 11p15 hypomethylation or matUPD7	Russell-Silver syndrome	See footnote 2	Growth deficiency	• Not associated w/↑ SCE • Ophthalmalogic abnormalities
ATM	Ataxia-telangiectasia	AR	• Small stature • Evidence of excessive genomic instability • Telangiectasis	• Progressive cerebellar ataxia from early childhood • ↑ alpha-fetoprotein levels

Gene(s) / Genetic Mechanism	Disorder	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/BSyn	**Distinguishing from BSyn**
			• Sinopulmonary infection • Immunodeficiency	
BRCA2 *BRIP1* *FANCA* *FANCB* *FANCC* *FANCD2* *FANCE* *FANCF* *FANCG* *FANCI* [3]	Fanconi anemia	AR (AD XL)	• Small stature • Evidence of excessive genomic instability • ↑ cancer susceptibility • Cutaneous abnormalities (café au lait macules, hyper- or hypopigmentation) • ↓ fertility • Endocrinopothy	• Skeletal malformations • Bone marrow failure
MRE11	Ataxia-telangiectasia-like disorder (OMIM 604391)	AR	• Small stature • Evidence of excessive genomic instability	• Progressive cerebellar degeneration • No telangiectasias or immunodeficiency
NBN	Nijmegen breakage syndrome	AR	• Small stature • Evidence of excessive genomic instability • Immunodeficiency • Café au lait macules • Predisposition to lymphoid malignancy	• Decline in intellectual performance • No telangiectasias
WRN	Werner syndrome	AR	• Small stature	• Premature artherosclerosis

Gene(s) / Genetic Mechanism	Disorder	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/BSyn	**Distinguishing from BSyn**
			• Evidence of excessive genomic instability • ↑ incidence of diabetes	• Prematurely aged appearance

AD = autosomal dominant; AR = autosomal recessive; matUPD7 = maternal uniparental disomy for chromosome 7; MOI = mode of inheritance; SCE = sister-chromatid exchange; XL = X-linked

1. *RMI1*, *RMI2*, and *TOP3A* encode proteins that make up the BTRR complex. The **B**LM protein forms the BTRR complex with topoisomerase III alpha (**T**opIIIa) and RecQ-mediated genome instability proteins 1 and 2 (**R**MI1 and **R**MI2, respectively). Together, these proteins process double Holliday junctions that arise as a result of homologous-recombination-mediated repair of double-stranded DNA breaks during DNA synthesis.

2. Russell-Silver syndrome has multiple etiologies including: epigenetic changes that modify expression of genes in the imprinted region of chromosome 11p15.5, maternal UPD7, and (infrequently) autosomal dominant or autosomal recessive inheritance.

3. Listed genes represent the most common genetic causes of Fanconi anemia. For other genes associated with this phenotype (20 genes have been identified), see Fanconi anemia.

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Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Bloom syndrome (BSyn), in addition to the routine medical history, family history, and physical examination, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4.

Recommended Evaluations Following Initial Diagnosis in Individuals with Bloom Syndrome (BSyn)

System/Concern	Evaluation	Comment
Gastrointestinal	Consultation w/gastroenterologist &/or feeding specialist	Evaluation for gastroesophageal reflux & problem feeding behaviors
	Colonoscopy & fecal immunochemical testing	In probands age ≥10 yrs
Dermatologic	Careful history & skin examination for sun-sensitive skin rash & for moles or nevi suspicious for basal cell or squamous cell carcinoma	
Immune	• Immunodeficiency screening incl immunoglobulin level, antibody responses to vaccines, & number of B & T lymphocytes • Referral to immunologist as needed	If patient has experienced severe &/or recurrent infections
Endocrine	Fasting blood glucose & hemoglobin A1C concentration	In probands age ≥10 yrs to evaluate for evidence of diabetes mellitus
	Thyroid function testing: TSH w/reflex to T4	At any age
	Lipid profile	Beginning at age 10 yrs
Renal	Abdominal ultrasound examination for Wilms tumor	In probands age ≤8 yrs
Lymphoreticular	Whole-body MRI scan for lymphoma	In probands age ≥12 yrs
Breast	Breast MRI scan	In female probands age ≥18 yrs
Developmental	Developmental assessment	If indicated based on developmental history
Other	Consultation w/clinical geneticist &/or genetic counselor	

Treatment of Manifestations

Health supervision recommendations that address diagnosis, treatment, and surveillance for complications in persons with BSyn have been published [Cunniff et al 2018].

Skin. Reduce excessive exposure to sunlight by seeking shade, particularly between 10 am and 4 pm. Cover exposed skin with clothing, including a broad-brimmed hat and UV-blocking sunglasses. Apply a broad-spectrum sunscreen with SPF of 30 twice daily, or every two to three hours if outdoors.

Psychosocial. Family and teachers are encouraged to relate to persons with BSyn appropriately for their chronologic age rather than the younger age suggested by their unusually small size.

Growth. Growth hormone administration to children with BSyn has not consistently increased growth rate in most persons, but some have experienced improved linear growth. Use of growth hormone has been approached cautiously in this population because of concerns regarding an increased risk of developing tumors as a result of their treatment. If growth hormone is prescribed, the growth response and serum IGF-1 and IGFBP-3 levels should be closely monitored, and unless there is an increase in growth velocity while under treatment, it should be discontinued.

Nutrition. Until additional information is available regarding treatment of problematic feeding behaviors and gastrointestinal symptoms, standard treatment for these concerns is recommended. This may include consultation with a gastroenterologist or feeding specialist, use of high-calorie diets, institution of reflux precautions, and use of anti-reflux medications. Studies of small cohorts of individuals with BSyn have shown that supplemental feeding may result in increased fat deposition but not in improved linear growth. Because abnormalities have been identified in the lipid profile of persons with BSyn, caution should be exercised in the use of high-fat and/or high-cholesterol diets.

Cognitive. Infants, toddlers, and preschool-age children with BSyn should have close developmental monitoring and referral for early intervention services. If developmental delays are present, physical, occupational, and speech therapy can help. School performance should be assessed regularly and parents made aware of available educational support.

Diabetes mellitus. Treatment of diabetes mellitus in BSyn is the same as in other persons.

Hypothyroidism. Thyroid hormone replacement therapy is recommended according to standard protocols.

Dyslipidemia. Dietary treatment according to standard protocols is recommended.

Cancer. The hypersensitivity of persons with BSyn to both DNA-damaging chemicals and ionizing radiation ordinarily necessitates modification of standard cancer treatment regimens, which usually includes a reduction of both dosage and duration. Individuals with BSyn have usually tolerated doses at or below 50% of the standard chemotherapy dosage, with no clear evidence that this has resulted in poorer outcomes. However, full weight-based dosing may be appropriate for some chemotherapeutic drugs such as steroids and tyrosine kinase inhibitors. Absence of information as to the ideal dosages makes such treatment particularly challenging to the physician; nevertheless, the fact that the cancers themselves often appear unusually responsive to the treatment justifies the special effort.

Bone marrow transplantation (BMT). Hematopoietic stem cell transplantation (HSCT) has been performed in three persons in the Bloom Syndrome Registry. One person had more than five years of disease-free survival before succumbing to another cancer, and the other two persons died in the immediate post-transplant period. If HSCT is being contemplated, nonmyeloablative transplantation is likely to be tolerated more readily than other regimens. Additionally, the required ablative therapy prior to BMT often may require modification of standard protocols because of the hypersensitivity of persons with BSyn to DNA-damaging agents.

Immune. Defects in humoral immunity can be managed with weekly subcutaneous or monthly intravenous infusions of gamma globulin. Cough assist devices, vibration vests, and

daily nasal lavage can be used for mucociliary clearance for bronchiectasis. If an individual with BSyn experiences recurrent, severe, or opportunistic infection, immunodeficiency screening (including immunoglobulin level, antibody responses to vaccines, and quantitative B- and T-lymphocyte measurements) is recommended.

Fertility

- **Men** with BSyn can undergo semen analysis to reveal azoospermia, oligospermia, or asthenospermia. Those who wish to conceive should consider consulting a fertility specialist. It is unclear if assisted reproductive technology (ART) may be helpful in persons with oligospermia or other abnormalities.
- **Women** with BSyn should be aware of signs of early menopause. Oocyte cryopreservation can be considered. Additionally, ART may be beneficial if natural conception is not possible; the authors are not aware of any prior use of ART in this population.

Surveillance

Health supervision recommendations for surveillance in persons with BSyn have been published [Cunniff et al 2018]. It should be recognized, however, that these recommendations are based on limited data from the Bloom Syndrome Registry and on expert opinion. There are currently no clinical trials or case-control studies that address outcomes in people with BSyn. Because of the unusually high risk for early development of cancer, much of the health supervision effort is directed to early detection and treatment.

Table 5.

Recommended Surveillance for Individuals with Bloom Syndrome (BSyn)

Manifestation	Evaluation	Frequency
Wilms tumor	• Abdominal ultrasound • Screen for signs/symptoms incl hematuria & a painless abdominal mass	Every 3 mos from time of diagnosis to age 8 yrs
Leukemia	Screening & family education on signs/symptoms incl pallor, abnormal bleeding, petechiae, fatigue, unintentional weight loss	Every health visit
Lymphoma	Screening & family education on signs/symptoms incl enlarged lymph nodes, unexplained fevers, drenching night sweats, fatigue, unintentional weight loss	Every health visit
	Whole-body MRI	Every 1-2 yrs from age 12-13 yrs
Colorectal cancer	Colonoscopy	Annually from age 10-12 yrs
	Fecal immunochemical testing	Every 6 mos from age 10-12 yrs

Manifestation	Evaluation	Frequency
Breast cancer	Breast MRI in females	Annually from age 18 yrs
Skin cancer	Skin examination w/dermatologist for any suspicious skin lesions	On recognition of suspicious lesions & annually thereafter
Diabetes mellitus	• Fasting blood glucose & hemoglobin A1C • Screening & family education on signs/symptoms of polyuria, polydipsia, weight loss	Annually from age 10 yrs
Hypothyroidism	• Serum TSH w/reflex to T4 • Screening & family education on signs/symptoms incl fatigue, constipation, cold sensitivity, weight gain	Annually from age 10 yrs
Dyslipidemia	Lipid profile	Annually from age 10 yrs

Agents/Circumstances to Avoid

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

Exposure to ionizing radiation should be minimized.

Evaluation of Relatives at Risk

It is appropriate to evaluate sibs of a proband in order to identify as early as possible those who would benefit from avoidance of sun exposure to the face and early surveillance for cancer (see Surveillance).

- Molecular genetic testing can be used to evaluate sibs if the *BLM* pathogenic variants in the family are known.
- An unusually low birth weight followed by short stature throughout childhood is typically present in affected sibs; sibs of normal stature are likely unaffected and may not need further testing.

See Genetic Counseling for issues related to the testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Eleven women with BSyn followed in the Registry have become pregnant at least once; seven of them have delivered a total of 11 healthy babies of normal size.

See MotherToBaby for more information on medication use during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

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Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Bloom syndrome (BSyn) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- Both parents of an individual with BSyn may be assumed to be heterozygous for a pathogenic variant in *BLM*. However, a single example of uniparental disomy has been reported [Woodage et al 1994], suggesting that molecular testing of parents may be warranted to confirm their genetic status.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing BSyn.
- The cancer risk of heterozygotes as a group has been examined in association studies but is yet to be determined [Antczak et al 2013, Prokofyeva et al 2013].

Sibs of a proband

- At conception, each sib of an individual with BSyn has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier of a *BLM* pathogenic variant, and a 25% chance of being unaffected and not a carrier.
- The cancer risk of heterozygotes as a group has been examined in association studies but is yet to be determined [Antczak et al 2013, Prokofyeva et al 2013].

Offspring of a female proband

- Children born to a woman with BSyn are usually heterozygous for a *BLM* pathogenic variant. However, because approximately 1% of individuals of Ashkenazi Jewish descent carry a *BLM* pathogenic variant, the risk for BSyn in the children of a union between a woman with BSyn and an Ashkenazi Jewish man whose BSyn carrier status has not been determined is 1/200.

- Children born to a woman with BSyn and a reproductive partner who is a carrier of a pathogenic variant have a 50% chance of having BSyn and a 50% chance of being carriers.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *BLM* pathogenic variant.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the *BLM* pathogenic variants in the family.

Population Screening

Individuals of Ashkenazi Jewish heritage. Because of the relatively increased carrier rate of the blm^{Ash} allele in Ashkenazi Jews, individuals of Ashkenazi heritage should be aware of their carrier risk, and practitioners should consider screening in this population [ACOG Committee on Genetics 2017].

Expanded carrier screening. Bloom syndrome is included on most expanded carrier screening panels.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Molecular genetic testing. 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. Preimplantation genetic diagnosis has been successfully utilized in a single family [Bloom Syndrome Registry, unpublished data].

Note: Ultrasound measurements are not reliable for estimating gestation age if prenatal diagnosis confirms the diagnosis of BSyn in the fetus.

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Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Bloom's Syndrome Association (BSA)**

  P.O. Box 727

  Hanover NH 03755-0727

  Phone: 603-643-2850

  Email: info@bloomssyndromeassociation.org

  www.bloomssyndromeassociation.org

- **Bloom's Syndrome Foundation (BSF)**

  7095 Hollywood Boulevard

  #583

  Los Angeles CA 90028

  Email: info@bloomssyndrome.org

  www.bloomssyndrome.org

- **National Library of Medicine Genetics Home Reference**

  Bloom syndrome

- **Center for Jewish Genetics**

  Ben Gurion Way

  30 South Wells Street

  Chicago IL 60606

  Phone: 312-357-4718

  Email: jewishgeneticsctr@juf.org

www.jewishgenetics.org

- **Xeroderma Pigmentosum Society, Inc (XP Society)**

  XP Society has material on their site related to UV protection/avoidance.

  437 Syndertown Road

  Craryville NY 12521

  Phone: 877-XPS-CURE (877-977-2873); 518-851-2612

  Email: xps@xps.org

  www.xps.org

- **Bloom Syndrome Registry**

  Weill Cornell Medicine

  505 East 70th Street

  3rd floor, Box 128

  New York NY 10021

  Phone: 646-962-2205

  Bloom Syndrome Registry

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Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A.

Bloom Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
BLM	15q26.1	Bloom syndrome protein	BLM database BLMbase: Mutation registry for Bloom Syndrome	BLM	BLM

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B.

OMIM Entries for Bloom Syndrome (View All in OMIM)

210900 BLOOM SYNDROME; BLM
604610 RECQ PROTEIN-LIKE 3; RECQL3

Molecular Pathogenesis

Bloom syndrome (BSyn) is the prototype of the class of human diseases sometimes referred to as the chromosome breakage syndromes [German 1969]. These include BSyn, Fanconi anemia, ataxia-telangiectasia, ataxia-telangiectasia-like disorder (OMIM 604391), Nijmegen breakage syndrome, and Werner syndrome. These clinically disparate disorders are caused by pathogenic variants in genes encoding enzymes comprising pathways of DNA replication and repair that are responsible for the maintenance of genomic stability. In all of these disorders, the diagnostic cytogenetic abnormalities are accompanied by an increased rate of spontaneous reversion (mutation) to the normal state in somatic cells. This hypermutability explains the cancer predisposition shared by these disorders.

Gene structure. A 4,528-bp cDNA sequence defines *BLM*, which contains a long open reading frame encoding a 1,417-amino-acid protein, BLM. *BLM* comprises 22 exons and is located at chromosome band 15q26.1. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Most individuals of Ashkenazi Jewish heritage with BSyn have the pathogenic variant c.2207_2212delinsTAGATTC [Ellis et al 1998]. A second, rarer pathogenic variant segregating in the Ashkenazi Jewish population, c.2407dupT, has been identified [Ellis et al 1998, German et al 2007].

Pathogenic variants identified in several studies of individuals with BSyn fall into the following four broad classes [German et al 2007, Amor-Guéret et al 2008, Shastri & Schmidt 2015]:

- **Nucleotide insertions and deletions** that result in frameshifts and elimination of the C terminus of the protein where the nuclear localization signals of BLM are located; BLM is therefore absent from the nucleus (~1/3 of all pathogenic variants)
- **Nonsense variants** that convert sense codons to nonsense or chain-terminating codons that predict translation of a truncated BLM protein (~1/3 of all pathogenic variants)
- **Intron variants** that cause splicing defects (~1/6 of all pathogenic variants)
- **Missense variants** that result in the production of nonfunctional BLM protein (~1/6 of all pathogenic variants)

Table 6.

BLM Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.2207_2212delinsTAGATTC [2] (2281del6/ins7) (blm^{Ash})	p.Tyr736LeufsTer5 [2]	NM_000057.2 NP_000048.1
c.2407dupT (insT2407)	p.Trp803LeufsTer4	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions

2. Also known as the blm^{Ash} allele

See Table 7 (pdf) for pathogenic variants identified in registered persons of various nationalities and ethnic groups.

Normal gene product. The 1,417-amino acid protein named BLM contains an amino acid domain consisting of seven motifs characteristic of DNA and RNA helicases. The helicase domain of BLM is 40%-45% identical to the helicase domain in the RecQ subfamily of DNA helicases and is known to be important in other species for the maintenance of genomic integrity. Molecular and genetic evidence implicates BLM in the cellular mechanisms that maintain genomic stability [Hickson et al 2001, Monnat 2010, Larsen & Hickson 2013, Suhasini & Brosh 2013, Cunniff et al 2017].

BLM is a cell cycle-regulated protein that is distributed diffusely throughout the nucleus but also is concentrated in nuclear foci, many of which have been identified as PML (promyelocytic leukemia protein) bodies [Sanz et al 2000]. DNA-dependent ATPase and DNA duplex-unwinding activities have been demonstrated for BLM; the nucleic acid substrates that it acts on in the cell remain to be identified.

Abnormal gene product. The major consequence of loss of BLM function for a somatic cell is an abnormally high rate of recombination and mutation. The pathogenic variants that arise in the cells of a person with BSyn are of several types and affect many regions of the genome. Thus, although the cancer predisposition in BSyn is attributable to the cellular hyper-recombinability and hypermutability, the proportional small size – the constant feature of BSyn – remains unexplained, as do the important medical complications of BSyn other than cancer.

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References

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