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ORIGINAL ARTICLE

Health supervision for people with Bloom syndrome

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Bloom Syndrome (BSyn) is an autosomal recessive disorder that causes growth deficiency, endocrine abnormalities, photosensitive skin rash, immune abnormalities, and predisposition to early-onset cancer. The available treatments for BSyn are symptomatic, and early identification of complications has the potential to improve outcomes. To accomplish this, standardized recommendations for health supervision are needed for early diagnosis and treatment. The purpose of this report is to use information from the BSyn Registry, published literature, and expertise from clinicians and researchers with experience in BSyn to develop recommendations for diagnosis, screening, and treatment of the clinical manifestations in people with BSyn. These health supervision recommendations can be incorporated into the routine clinical care of people with BSyn and can be revised as more knowledge is gained regarding their clinical utility.

KEYWORDS

Bloom syndrome, cancer surveillance, chromosome instability, DNA repair, health supervision

1 | INTRODUCTION

Bloom syndrome (BSyn) is a condition marked by growth and immune deficiencies, skin sensitivity to sunlight, resistance to insulin, and a high risk for many types of cancer. BSyn is inherited as an autosomal recessive trait and is caused by loss-of-function mutations of the *BLM* gene, which codes for a RecQ helicase that helps maintain chromosome stability. Absent or nonfunctional BLM protein results in high levels of homologous chromosome recombination, and the resulting somatic mutations confer the increased risk for cancer seen in people with BSyn.

This condition was initially diagnosed through observation of high levels of sister chromatid exchanges (SCEs), but in 1995 *BLM* gene mutations were found to be causative. In the absence of treatments that address the genetic cause of BSyn, regular health supervision has emerged as a valuable tool to identify early signs and symptoms, including skin abnormalities, diabetes, and cancer, among others.

2 | BACKGROUND AND HISTORY OF BSYN

The initial report of BSyn was published in 1954 when Dr. David Bloom described three children who had telangiectatic erythema and short stature (Bloom, 1954). Later reports identified cytogenetic abnormalities such as isochromatid breaks, sister chromatid reunions,

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transverse breakage at the centromere, and quadriradial configurations, all of which suggested chromosomal instability. In 1974, high levels of SCE were reported in people with BSyn. For many years, SCE analysis was the primary diagnostic test for BSyn and remained a unique feature of the condition until 2016, when elevated SCE levels were found in siblings with a Bloom-like condition associated with mutations in the RMI2 protein (Hudson et al., 2016). Genetic studies among affected and nonaffected individuals localized the causative gene for BSyn to chromosome band 15q26.1 (German, Roe, Leppert, & Ellis, 1994), and the following year, the *BLM* gene was confirmed as the cause of BSyn after mutations were identified in 10 affected individuals (Ellis et al., 1995).

Soon after the initial description of BSyn, the BSyn Registry (BSR) was established and began collecting clinical information and tissue samples from individuals with BSyn and many of their unaffected relatives who are heterozygous for *BLM* pathogenic variants. Currently, the BSR contains information on 277 diagnosed individuals, and the medical literature contains published reports of many other affected persons from all continents. Because BSyn is encountered in any single medical center rarely, it is difficult to accumulate sufficient information to recognize and understand the medical complications and to develop diagnostic and treatment strategies that may improve clinical outcome. Yet, there remains a critical need for affected individuals and their families to have some clear guidance on how best to anticipate their medical problems and proactively address them. The purpose of this report is to propose a set of health supervision recommendations for persons with BSyn, based on published literature, information in the BSR, and expert opinion from a diverse group of clinicians and researchers with knowledge and experience in the diagnosis and treatment of people with BSyn. In particular, children with BSyn may face difficult medical and developmental issues, and these recommendations can assist physicians, therapists, and educators as they secure important services. These recommendations are intended to replace previously published recommendations (Walsh et al., 2017).

3 | DIAGNOSIS

BSyn should be suspected on the basis of its cardinal clinical features, such as growth deficiency and characteristic telangiectatic facial rash. Detection of increased SCE was for many years the only diagnostic test for BSyn, until it was largely replaced by *BLM* sequence and deletion/duplication testing. SCE analysis may still be used in circumstances where *BLM* sequencing and deletion/duplication testing are not available, but it requires some experience for proper interpretation. A definitive diagnosis of BSyn is established by identification of bi-allelic pathogenic variants of *BLM*.

Such pathogenic variants cause complete loss of function of the BLM helicase (German, Sanz, Ciocci, Ye, & Ellis, 2007). In this context, most if not all large indels, nonsense and frameshift variants should be considered pathogenic or likely pathogenic. To date, the only pathogenic missense variants have occurred in either the helicase or RQC domains. Caution should therefore be exercised in attributing pathogenicity to missense variants in other *BLM* domains. SCE analysis may aid in diagnosis in circumstances where someone with a clinical phenotype suggestive of BSyn has one or more variants that are not known to be pathogenic.

4 | METHODS

The BSR is the primary source for information about the natural history of BSyn, used in this report. As of January 2018, clinical information was available on 277 affected individuals. The quantity of information and the length of follow up for persons in the BSR are variable. For example, before the discovery of elevated SCE as a component of BSyn in 1974, at least 57 individuals were diagnosed with BSyn based solely on their clinical features. Since then, to be considered a confirmed case of BSyn and to be included in the BSR, individuals had either (a) a positive SCE analysis, typically at least 45 SCE metaphases; or, (b) mutation analysis that identified *BLM* mutations.

To aid in development of these recommendations, information from the BSR and from published reports was available to the authors, who represent a group of clinicians with experience in the evaluation and treatment of persons with BSyn. There are however, no clinical trials or case control studies that address medical outcomes in persons with BSyn, which limits the evidence basis for any recommendations. Using the American College of Cardiology/American Heart Association guidelines (Halperin et al., 2016), the level of evidence for these recommendations is Level C-LD and Level C-EO, comprised of limited data from the BSR and expert opinion, respectively. In developing these recommendations, we also considered recommendations for screening and surveillance in other disorders, particularly regarding cancer screening in other monogenic cancer predisposition syndromes. Below, we discuss the clinical features and basis of our recommendations. Table 1 provides a summary of surveillance and treatment recommendations.

5 | CANCER

Chief among the medical concerns for patients and families affected by BSyn is the marked increase for cancer of many types, occurring at multiple sites. Among monogenic cancer predisposition syndromes, Bloom is one of a small number of conditions with a propensity for many cancer types, as well as for multiple cancers in a single individual. Table 2 provides a list of 223 reported cancers among 144 of the 277 persons in the BSR. At least 33.4% of individuals with BSyn have developed cancer by age 25, and this number rises to 80.9% by age 40. The early onset of cancer in people with BSyn highlights the importance of thorough cancer awareness and surveillance beginning at an early age.

To address the increased risk for cancer, patients and their families can benefit from both prevention and early detection. The same general cancer prevention strategies that apply to the unaffected population are equally reasonable for people with BSyn, including avoidance of excessive sun exposure, tobacco use and other toxic exposures. However, because of the high risk of specific cancers occurring at an earlier age in people with BSyn

TABLE 1 Recommendations for surveillance and treatment of people with BSyn

Clinical condition	Screening/prevention recommendations	Treatment recommendations
Leukemia	• Awareness of symptoms of leukemia, such as pallor, abnormal bleeding, petechiae, fatigue, and unintentional weight loss	*For all cancers:* There is a possibility of increased risk for secondary cancers after chemotherapy/radiation. MRI and ultrasonography are preferred over CT scans, PET scans, and other radiography procedures. Chemotherapy should be adapted; BSR patients have typically tolerated 50% or below the normal regimen dosage. Ionizing radiation or alkylating agents (busulfan, melphalan, or cyclophosphamide) are not recommended.
Lymphoma	• Awareness of symptoms, such as enlarged lymph nodes, unexplained fevers, night sweats, fatigue, unintentional weight loss • Whole body MRI scanning every 1–2 years, starting at age 12–13	
Colorectal Cancer	• Annual colonoscopy and FIT every 6 months, starting at age 10–12 years	
Breast Cancer	• Annual breast MRI scans, starting at age 18	
Skin Cancer	• Reduce excessive exposure to sunlight • Cover exposed skin • Use a broad-spectrum sunscreen with SPF of 30 with application twice daily and every 2–3 hr if outdoors	
Wilms Tumor	• Awareness of symptoms, such as hematuria and a painless abdominal mass • Abdominal ultrasound every 3 months, starting at diagnosis to age 8	
Skin (dermatologic complications)	• Reduce excessive exposure to sunlight • Cover exposed skin • Use a broad-spectrum sunscreen with SPF of 30 with application twice daily and every 2–3 hr if outdoors	
Growth and Nutrition		Growth response, serum IGF1, and IGFBP3 levels should be monitored during GH therapy; therapy should be discontinued if there is no response.
Intelligence		Physical therapy, occupational therapy, and speech therapy can help if developmental delays are present.
Endocrine Abnormalities	• Awareness of symptoms for hypothyroidism, such as fatigue, constipation, cold sensitivity, weight gain • Fasting blood sugar measurements, glucose tolerance screening with hemoglobin A1C, thyroid function testing, and lipid profile annually, starting at age 10 • Thyroid function testing annually (with TSH and reflex to T4) is recommended	Treatment with standard protocols is recommended.
Immunity	If individual has experience recurrent, severe, or opportunistic infection: • Immunodeficiency screening, including immunoglobulin level, antibody responses to vaccines, and number of B and T lymphocytes measurements, are recommended Similar tests are recommended for individuals undergoing chemotherapy or immunosuppressive drugs	Defect 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 to for mucociliary clearance for bronchiectasis.
Fertility	• Awareness of potential early menopause in women • Awareness of azoospermia, oligospermia, and asthenospermia in men	In women, ooctye cyropreservation should be considered. ART may be beneficial if natural conception is not possible. In men, semen analysis can be conducted, and patients should consult with a fertility specialist.

compared to the general population, there is a need for specific surveillance strategies at earlier ages than the general population.

5.1 | Leukemia

There are 40 occurrences of leukemia in the BSR, including occurrence as a primary cancer and as a secondary cancer after chemotherapy for other tumors. The median age of diagnosis for leukemia is 18 years (range 2–40 years). Acute myelocytic leukemia is the most common primary and secondary leukemia; and when it is secondary, it is usually preceded by a diagnosis of myelodysplasia.

All patients and their families should be aware of early warning signs for leukemia, such as pallor, abnormal bleeding, petechiae, fatigue, or unintentional weight loss, and they should promptly seek medical attention if one or more is present. Among other monogenic cancer syndromes that have early-onset leukemia as one feature, such as Fanconi anemia and Dyskeratosis Congenita, annual bone marrow aspiration and biopsy are recommended (Hays et al., 2014; Savage &

TABLE 2 Cancer frequency and type in 144 of 277 individuals from the BSyn Registry

Malignancy type/tissue	Subtype	Frequency	Median age at diagnosis (years)	Mean age at diagnosis (years)	Range (years)
Leukemia		40	18	18	2–40
	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
Oro-pharyngeal		23	36	37	26–48
	Tongue	9	39	40	30–48
	Pharynx	5	32	34.8	31–45
	Tonsil	4	40	38	25–46
	Other	5	N/A	N/A	N/A
Upper gastrointestinal		13	32	33	15–48
	Esophageal	5	39	37	25–48
	Gastric	4	31	29	24–33
	Other	4	N/A	N/A	N/A
Colorectal		28	37	35	16–49
Genitourinary		14	26	29	10–47
	Cervical	5	22	21	19–23
	Other	9	N/A	N/A	N/A
Breast		23	33	35	21–52
Skin		21	34	31	18–42
	Basal cell	13	29	28	18–38
	Squamous cell (uncategorized)	4	35	35	35–36
	Other/undefined	4	N/A	N/A	N/A
Wilms tumor		8	3	3	1–8
Lung		4	37	36	32–40
All other		12	N/A	N/A	N/A

Cook, 2015). These conditions, however, are associated with bone marrow failure, and the surveillance has a dual purpose of early detection of leukemia and bone marrow failure, with treatment aimed at early hematopoietic stem cell transplantation (HSCT). Because BSyn is not associated with bone marrow failure, and early HSCT is not necessarily indicated upon diagnosis of leukemia, the benefits of annual bone marrow examination are not clearly apparent. Although, it is important to be vigilant for symptoms that are associated with leukemia and to make the diagnosis as early as possible to minimize morbidity, early diagnosis is not believed to improve long-term survival, so regular hematologic monitoring such as complete blood counts is not recommended. If someone has symptoms suggestive of leukemia however, and abnormalities such as cytopenia of one or more lineages or cells with abnormal morphology suggestive of leukemia are observed, bone marrow aspirate and biopsy with cytogenetic studies are indicated. The bone marrow should be examined for changes in cellularity, dysplasia, evidence of leukemic blasts, evolution of hematopoietic clones with abnormal cytogenetics (e.g., monosomy 7) and presence of high-risk somatic mutations.

5.2 | Lymphoma

There have been 37 occurrences of lymphoma, at a median age of onset of 20 years (range 4–49 years). With the exception of two people with Hodgkin lymphoma, all others have had the non-Hodgkin type, and most of those had the B-cell subtype, which is similar to the distribution in the general population. Lymphoma was the first malignancy in 29 people and was the second or third malignancy in seven others. While not all lymphomas lead to the development of a characteristic constellation of symptoms, awareness of commonly associated features such as enlarged lymph nodes, unexplained fevers, drenching night sweats, fatigue, and unintentional weight loss are important for early detection. In particular, multiple and readily palpable lymph nodes should be investigated promptly. Among other monogenic disorders that predispose to lymphoma, such as autoimmune lymphoproliferative syndrome, combined CT and PET scans are recommended every 2 to 3 years for early detection (Rao & Oliveira, 2011). For persons with BSyn, such repeated radiation exposure is a concern, as it may provide an increased risk for malignancy. MRI scanning is not likely to pose an increased risk for malignancy and is the preferred imaging method when lymphoma or other tumors are suspected. Because lymphoma is generally a fast-growing malignancy, performing MRI scans more frequently than every 2 to 3 years may be a better option. Regarding the age to begin screening, the risks of anesthesia or sedation, particularly in medical settings unaccustomed to treating children, is a consideration. Most children are able to have MRI scanning without sedation by age 12 to 13 years, so this is a reasonable age to begin, with repeat imaging every 1–2 years. Because

individuals with BSyn have risks for other malignancies amenable to detection by MRI scanning, the most comprehensive approach is to obtain whole body MRI scans at each interval.

5.3 | Colorectal carcinoma

Following leukemia and lymphoma, the next most common tumor type is colorectal cancer, accounting for 28 of the 223 malignancies reported. The median age of diagnosis is 37 years (range 16–49 years). Tumors have been reported throughout the colon, from the cecum to the rectum. Of the 14 individuals in the BSR that were affected by colon polyps, six of them also developed colorectal cancers. Although the earliest diagnosis of colorectal cancer is age 16 years, polypectomy at an earlier age may prevent or delay the onset of cancer. For these purposes, annual colonoscopy and fecal immunochemical testing (FIT) every 6 months, beginning at age 10–12 years is a reasonable approach, with the potential for less intensive therapy and improved outcomes in those who are diagnosed early. A similar approach has been advocated for persons with Lynch syndrome, which has a lifetime risk of approximately 50%–80% for development of colorectal carcinoma (Kohlmann & Gruber, 1993).

5.4 | Breast cancer

Breast cancer has been observed in 16 of the 132 women in the BSR at a median age of 33 years (range 21–52 years). One woman had bilateral breast tumors diagnosed concurrently. Another woman had a contralateral breast tumor associated with metastasis. Four women were diagnosed with a second breast tumor month to years after their first incidence of breast cancer. Whether these were recurrences or multiple primary tumors is unknown. As in the general population, most breast cancer has been ductal carcinoma.

In high-risk populations such as those with *BRCA1* and *BRCA2* mutations, the addition of MRI to mammography improves sensitivity of breast cancer detection, identifies tumors in an earlier stage than mammography alone, and improves metastasis-free survival. In such populations, MRI is recommended because of its significantly higher sensitivity for cancer detection with comparison to mammography or ultrasonography alone (Sardanelli et al., 2011). Furthermore, in the Dutch MRI Screening Study, tumors were also smaller at detection, more frequently node negative, and patients required less chemotherapy and hormonal therapy (Saadatmand et al., 2015). However, due to the potential for ionizing radiation to increase cancer risk in persons with BSyn, we do not endorse mammography for screening. Because whole body MRI scans may not be sufficient to diagnose breast cancer, we recommend annual breast MRI scans beginning at age 18 years.

5.5 | Skin cancer

Skin cancers are commonly reported in individuals with BSyn. Basal cell (n = 13) and squamous cell cancers (n = 4) have been observed, but melanoma has not yet been identified in any person entered into the BSR. For prevention and early detection, steps should be taken to reduce excessive exposure to sunlight and other UV radiation sources, and suspicious skin lesions should be reported promptly. Annual dermatologic examinations for skin cancer screening may be beneficial. Recommendations for reducing UV exposure include (a) seeking the shade, particularly between 10 a.m. and 4 p.m., (b) covering exposed skin with clothing, including a broad-brimmed hat and UV-blocking sunglasses, and (c) using a broad-spectrum (UVA/UVB) sunscreen with an SPF of 30 or higher every day, with application twice daily and every 2–3 hr if participating in outdoor activities.

5.6 | Wilms tumor

Wilms tumor was diagnosed in eight individuals in the BSR, at a median age of 3 years (range 16 months to 8 years). This includes the child reported by Berger et al. (1996), the 2 children reported by Moreira et al. (2013), and 2 of the 3 children reported by Cairney et al. (1987). The prevalence of Wilms tumor in people in the BSR therefore is approximately 3%–4%, which is lower than the 5% risk threshold that has been proposed as a cutoff point for recommending routine ultrasound surveillance in persons with a genetic predisposition to Wilms tumor (Dome & Huff, 2003). The rate of 3%–4% is, however, several orders of magnitude higher than the general population risk, and ultrasound examination is the imaging modality of choice for diagnosis. Therefore, abdominal ultrasound examination is recommended at diagnosis and every 3 months through age 8 years. Parents should also be aware that hematuria or presence of a painless abdominal mass is also suggestive of Wilms tumor, and these findings should be reported promptly to the patient's primary care physician.

5.7 | Other cancers

While the above cancers types are most common, individuals in the BSyn Registry have also been diagnosed with a variety of other tumors, as detailed in Table 2.

5.8 | Recommendations

- Patients and their families should be aware of the general signs and symptoms of cancer and seek prompt medical attention if they appear. Such symptoms include presence of mass, unintentional weight loss, fatigue, changes in bowel or bladder habits, and persistent and unexplained pain, among others.
- Patients and their families should be aware of early warning signs of leukemia such as pallor, petechiae, abnormal bleeding, fatigue, or unintentional weight loss and should be evaluated if these signs or symptoms appear.
- A complete blood count (CBC) with peripheral smear should be obtained if any signs or symptoms of leukemia are observed. If abnormalities such as cytopenia of one or more lineages or cells with abnormal morphology suggestive of leukemia is observed, bone marrow aspirate and biopsy with cytogenetic studies should be performed.
- Patients and their families should be aware of the signs and symptoms of lymphoma such as enlarged lymph nodes, unexplained

fevers, drenching night sweats, fatigue, and unintentional weight loss.

- Lymph node biopsy is recommended for any lymph node that is rapidly growing, associated with systemic signs or symptoms, or is provisionally diagnosed as infected but not responding to antibiotics.
- Whole body MRI scan is recommended every 1–2 years, beginning at age 12–13 years, to screen for all tumors, including squamous cell carcinoma and lymphoma.
- For surveillance of colorectal cancer, we recommend annual colonoscopy and semi-annual (every 6 months) FIT beginning at age 10–12 years.
- Breast cancer surveillance should include annual breast MRI scans beginning at age 18 years. This strategy is superior to mammography and avoids the use of radiation, which may increase the risk for cancer.
- Patients and their families should be aware of the early signs of skin cancer and seek medical attention if such signs are observed, including changes in color or size of moles, itching, tenderness, or pain. Prevention strategies include minimizing sun exposure, using protective clothing and use of UVA/UVB protective sunscreen.
- For Wilms tumor surveillance, we recommend renal ultrasound examination at diagnosis and every 3 months through age 8 years.

5.9 | Cancer treatment

In the situation where persons with BSyn require medical treatment for their tumors, medical providers should be aware of the concern for an increased risk for secondary malignancies after chemotherapy or therapeutic radiation. There is conflicting evidence from animal models and cell culture studies regarding toxicity of ionizing radiation (El Ghamrasni et al., 2015), and there is insufficient human data from the BSR or published literature to guide recommendations in the circumstance where radiotherapy is contemplated. Until there is more conclusive evidence, radiotherapy should be avoided if possible, recognizing that use of radiation may be the best alternative in some circumstances. For disease staging and residual disease monitoring, MRI and ultrasonography are preferable to CT scans and other radiographic procedures and should be used whenever feasible. However, CT and/or PET scans may be necessary in some circumstances for tumor staging and selection of appropriate treatment regimens. Standard chemotherapy regimens should be modified for individuals with BSyn because in many circumstances the usual weight-based dosing has resulted in severe and sometimes life-threatening toxicity, including severe mucositis and prolonged neutropenia (Adams et al., 2013; Fedhila-Ben Ayed et al., 2016). Affected individuals in the BSR have usually tolerated doses at or below 50% of the standard chemotherapy dosage, with no clear evidence that this has resulted in poorer outcomes. Furthermore, when planning a therapeutic regimen, we do not recommend use of ionizing radiation or alkylating agents such as busulfan, melphalan, or cyclophosphamide, as persons with BSyn have proven hypersensitive to these therapeutic agents. HSCT has been performed in three persons in the BSR. One person had over 5 years of disease-free survival before succumbing to another cancer, and the other two persons died in the immediate post-transplant period.

5.10 | Recommendations

- Exercise caution and use decreased weight-based dosing for chemotherapy. A dose reduction of 50% for most chemotherapeutic agents is a reasonable beginning point, and the dose can be adjusted upward or downward, depending on patient response. For some chemotherapeutic drugs such as steroids and tyrosine kinase inhibitors however, full weight-based dosing may be appropriate.
- Where possible, avoidance of radiotherapy is recommended.
- In circumstances where MRI or ultrasound examinations can replace CT scans or other radiographic procedures, they are preferred for disease staging and residual disease monitoring.
- If HSCT is being contemplated, nonmyeloablative transplantation is likely to be tolerated more readily than other regimens. Total body irradiation or use of alkylating agents such as busulphan or melphalan is not recommended.

6 | SKIN

Among the most common symptoms facing individuals with BSyn is the development of sun-sensitive skin rashes, hypopigmented macules, and café au lait spots, with 184 of 277 individuals in the BSyn Registry reporting some type of dermatologic complication. Facial erythema and telangiectasias commonly appear in infancy or early childhood and involve the eyelids, ears, nose, and cheeks in a butterfly distribution. Many individuals also report similar findings on the tops of the hands and forearms. Although not universal, sun exposure tends to worsen the rash, so most people with BSyn should reduce exposure to sunlight. Sensitivity to sunlight should be examined on a case-by-case basis, as some persons have developed intense rashes upon normal sun exposure while others with more extended time spent in direct sunlight have demonstrated more mild rashes. The café au lait spots with surrounding areas of hypopigmentation may be present on any area of the body, but they rarely involve the face. Poikiloderma and cheilitis may also be exacerbated by sun exposure.

6.1 | Recommendations

- Minimizing direct sun exposure is recommended whenever possible. This is best accomplished by seeking the shade, especially during times of peak sun intensity. Furthermore, it is reasonable to cover exposed skin with clothing, including a broad-brimmed hat and UV-blocking sunglasses, and to use a broad-spectrum UVA/UVB sunscreen with an SPF of 30 or higher every day with more frequent applications when participating in outdoor activities.

7 | GROWTH AND NUTRITION

Individuals with BSyn usually present with prenatal onset growth deficiency. In the largest published survey of growth in persons with BSyn, the mean (*SD*) birth length was 43.4 (±4.4) cm in boys and 43.8

(±2.8) cm in girls (Keller, Keller, Shew, & Plon, 1999), compared to 50.5 (±2.5) cm and 49.9 (±2.7) cm in unaffected boys and girls, respectively. In the same investigation, the mean (*SD*) birth weight was 1.89 (±0.35) kg in boys with BSyn and 1.87 (±0.35) kg for girls, compared to 3.27 (±0.44) kg in unaffected newborn boys and 3.23 (±0.53) kg in unaffected girls. These growth problems persist into adulthood, with a mean (*SD*) final adult stature of 148.5 (±7.6) cm for males and 141.5 (±6.6) cm for females, and a mean weight of 41.3 (±8.8) kg in males and 36.6 (±8.6) kg in females (Keller et al., 1999). The reasons for this generalized growth deficiency are unknown. The secretion of growth hormone (GH) appears to be normal, as are the serum concentrations of IGF-1 and IGFBP-3 (Diaz, Vogiatzi, Sanz, & German, 2006). Nonetheless, some individuals have been treated with GH, with varying effects on growth. A supraphysiologic rise in serum IGF-1 concentrations with GH therapy has been described (Renes, Willemsen, Wagner, Finken, & Hokken-Koelega, 2013). There are published reports of children treated with GH who developed leukemia or lymphoma at particularly young ages (Brock, de Zegher, Casteels-Van Daele, & Vanderschueren-Lodeweyckx, 1991; Renes et al., 2013), and the BSyn Registry is aware of one other person who developed lymphoma after 6 years of treatment. Because people with BSyn are already at a high risk for cancer, it is difficult to establish a causal relationship between GH and cancer, but many clinicians consider a diagnosis of BSyn to be a contraindication to the use of GH (Renes et al., 2013). The Pediatric Endocrine Society Drug and Therapeutics Committee has examined the issue of GH treatment in children with disorders that increase the risk for cancer and found the current evidence to be insufficient to conclude whether or not GH further increases cancer risk (Raman et al., 2015). They suggested that such children should be critically analyzed on an individual basis, and if GH is prescribed, appropriate surveillance for malignancies should be initiated.

In younger populations, especially children and infants, feeding problems are common and there is often a marked reduction in adipose tissue. There is no evidence of malabsorption (Diaz et al., 2006). Many parents have reported problematic feeding behaviors that include irregular eating schedules, small portion sizes, and a general lack of interest in eating. In addition, many infants and toddlers have had gastrointestinal symptoms including frequent emesis, diarrhea, and gastroesophageal reflux (Keller et al., 1999). There have been no systematic studies of feeding interventions or treatments in persons with BSyn.

7.1 | Recommendations

- 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 feeding specialist, use of high calorie diets, institution of reflux precautions and use of anti-reflux medications.
- Caution should be exercised in the use of GH in persons with BSyn. If GH 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.

8 | INTELLIGENCE

There are no published studies of early development, academic performance, or intelligence in persons with BSyn. Children with BSyn have a head circumference significantly below the mean (*SD*) at birth: 28.9 (±1.2) cm for males and 30.1 (±0.7) cm for females (Keller et al., 1999). This compares to 34.8 (±1.3) and 34.3 (±1.3) cm for unaffected boys and girls, respectively. While a small head circumference is commonly associated with cognitive impairment, it is clear that individuals with BSyn do not have the kind of moderate to severe impairment that might be expected in individuals with a head circumference that is typically 2 to 3 standard deviations below the mean. In fact, many individuals with BSyn have normal intelligence and good academic achievement, including those who have completed college and obtained graduate degrees. At the same time, many people in the BSyn Registry have reported early motor and speech delays, enrollment in special education programs and difficulties with job placement.

8.1 | Recommendations

- Infants, toddlers, and preschool-age children with BSyn should have close developmental monitoring and referral for early intervention services such as physical therapy, occupational therapy, and speech therapy if they do not meet their developmental milestones.
- School performance should be assessed regularly, and parents should be aware of educational support that is available for children whose academic performance is limiting their academic progress.

9 | ENDOCRINE ABNORMALITIES

People with BSyn are at risk for a variety of endocrine abnormalities, including abnormal carbohydrate metabolism, dyslipidemia, hypothyroidism, and insulin resistance with susceptibility to type 2 diabetes (Diaz et al., 2006). The presence of insulin resistance is not related to obesity or adiposity, since people with BSyn have a paucity of fat and are often underweight. Insulin resistance may be related to fetal growth restriction, as it has been observed in other individuals born small-for-gestation (Giapros et al., 2017). Nonetheless, as they age, individuals with BSyn show an improvement in BMI along with an increasingly impaired glucose tolerance and a tendency to develop overt type 2 diabetes (Diaz et al., 2006). Using an oral glucose tolerance test in a cohort of 11 otherwise asymptomatic children and young adults with BSyn, Diaz et al. identified impaired glucose tolerance in four and diabetes in one. These data suggest that carbohydrate abnormalities in BSyn start at a young age. Dyslipidemia in the form of elevated concentrations of total cholesterol, low-density lipoprotein (LDL), and triglycerides have been identified, as well as low

serum high-density lipoprotein (HDL), but it is unclear if this is an independent phenomenon or the result of impaired carbohydrate metabolism. Type 2 diabetes has been reported in 48 of 277 patients in the BSyn Registry, with a median age of diagnosis of 26 years (range 4–48 years). Diaz et al. (2006) identified compensated hypothyroidism in 2 of 11 persons studied, and hypothyroidism has also been diagnosed in at least 10 of the 277 individuals in the BSyn Registry. This problem has not been under regular surveillance by the Registry, so the true incidence may be higher. Onset has been variable, from childhood to adulthood.

9.1 | Recommendations

- Fasting blood sugar measurements and screening for impaired glucose tolerance (i.e., pre-diabetes) with hemoglobin A1c are recommended annually beginning at age 10 years. Patients and parents should be aware of symptoms of diabetes such as polyuria and polydipsia, especially if they are associated with weight loss. If a patient develops diabetes, treatment with standard protocols is recommended.
- A lipid profile is recommended annually, beginning at age 10 years. For those individuals who have unfavorable lipid profile results, treatment by standard protocols is recommended.
- Thyroid function testing should be obtained beginning at age 10 years.
- Parents and patients should be aware of the signs and symptoms of hypothyroidism such as fatigue, constipation, cold sensitivity, and weight gain, and those showing symptoms should have thyroid function testing to include TSH, with reflex to T4.

10 | IMMUNITY AND INFECTION

The BLM protein plays a role in the development and function of the immune system (Babbe et al., 2009), and it can be predicted that the genomic instability from BLM deficiency might compromise the development, maintenance, and function of leukocytes. Individuals with BSyn have been reported to have immune abnormalities that place them at risk for recurrent infection, but there is very little information about the frequency or severity of immune defects in an unselected cohort. Very few individuals have had severe immune problems such as opportunistic infection, abscess requiring drainage, sepsis, meningitis, or bacterial pneumonia, but they are often reported to have a pattern of recurrent upper and lower respiratory and gastrointestinal infections. B-cell and T-cell numbers are usually normal, but decreased numbers of CD4-positive T-cells and impaired T-cell function have been identified, as have deficiencies of at least one of the serum immunoglobulin classes, usually IgM or IgA (Hutteroth, Litwin, & German, 1975; Kondo et al., 1992; Van Kerckhove et al., 1988). A recent investigation of six individuals with BSyn confirmed low levels of serum immunoglobulins, an increased number of infections, and the absence of severe or opportunistic infections (Schoenaker et al., 2017). They also identified mild abnormalities in somatic hypermutation and class switch recombination.

10.1 | Recommendations

- There are not enough data available at this time to suggest that all individuals with BSyn be screened for immunodeficiency, but this should be done for any individual who has recurrent (e.g., chronic or recurrent sinusitis despite anatomically corrective surgery, more than one pneumonia in a 10-year period, multiple episodes of bronchitis per year or bronchiectasis), severe (e.g., pneumonia with empyema or blood-borne infection), or opportunistic infections. Particular attention should be paid to measuring immunoglobulin (IgG, IgA, and IgM) levels, antibody responses to biologically relevant (pneumococcal and influenza) vaccines, and numbers of B (CD19) and T (CD4, CD8) lymphocytes.
- Similar tests should be performed in any person with BSyn who is undergoing chemotherapy or prolonged treatment with immunosuppressive drugs such as prednisone, to allow early detection of immunodeficiency.
- Immunology referral is indicated for individuals with laboratory or clinical features of immunodeficiency, with treatment directed to the functional abnormality identified. The most commonly reported deficiency, a defect in humoral immunity, often can be managed with weekly subcutaneous (preferred) or monthly intravenous infusions of gamma globulin to provide IgG antibodies. Though there are no published studies documenting the efficacy of this treatment in BSyn, there are many such studies documenting the effectiveness of gamma globulin replacement therapy in people with a variety of other diagnoses such as Common Variable Immunodeficiency (Martínez García et al., 2001) and Agammaglobulinemia (Aghamohammadi et al., 2004), both of which lead to antibody deficiency. Results are best if such therapy is started before there is end-organ damage, for example, bronchiectasis or chronic sinusitis with squamous metaplasia of the mucosal surface.
- If bronchiectasis occurs, strategies for improving mucociliary clearance should be employed. This may require the use of cough assist devices or vibration vests in pediatric sizes. People with chronic sinusitis may derive benefit from daily nasal lavage with saline. An epidemiologic study of immune function is needed to determine the prevalence and severity of immune deficiency in a cross section of people with BSyn. These data will provide information about the cost:benefit ratio of screening every person with BSyn whether or not they have a history of infections.

11 | FERTILITY

Individuals with BSyn may have infertility or subfertility. Some females have had delayed puberty and early menopause (Masmoudi et al., 2012). However, there are reports of women with BSyn having successful delivery of healthy infants (Mulcahy & French, 1981; Chisholm, Bray, & Karns, 2001), and there are individuals in the BSyn Registry who have had healthy offspring. There is a single case report of confirmed paternity in a man with BSyn (Ben Salah et al., 2014). There are no men in the BSyn Registry who have had offspring, and in those who have been studied, all have had azoospermia, oligospermia,

and/or asthenospermia. Therefore, while it may be possible for women with BSyn to achieve natural conception, this is unlikely for men with BSyn. Assisted reproductive technologies (ARTs) may provide a helpful alternative, but there are no reports of successful ART in men with BSyn, and there is no experience with ART reported to the BSyn Registry.

11.1 | Recommendations

- Women with BSyn should be aware of the possibility of early menopause and may wish to consider oocyte cryopreservation. If natural conception cannot be achieved, ART may be beneficial.
- Men with BSyn who wish to have children should first have semen analysis and consult with a fertility specialist if the analysis is abnormal. It is unclear if ART may be helpful in persons with oligospermia or other abnormalities.

12 | FUTURE DIRECTIONS

Like many other very rare genetic conditions, the full range of health consequences for people with BSyn is not fully characterized. To address this concern, the systematic study of problems such as immune compromise, pulmonary complications, intellectual development, and cancer pathogenesis and treatment are important goals of the BSyn Registry. The study of health problems, particularly cancer risk, in heterozygotes is an area for future investigation, although it is difficult because the small number of heterozygotes in any population is insufficient to adequately power analyses of risk. There is also a critical need for study of the genomic abnormalities of tumors occurring in people with BSyn, to identify targets for treatment and to understand better how *BLM* may contribute to the pathogenesis of tumors in those who are neither affected with BSyn nor heterozygous for *BLM* pathogenic variants. Although the ultimate goal is to identify treatments that can restore some BLM protein function, none has yet been identified. Until this can be achieved, it is important for parents and medical providers to be aware of the specific health complications that occur in persons with BSyn and act quickly when such complications are suspected. We hope that careful attention to these health supervision measures will standardize clinical assessment and assist in prevention, early diagnosis, and improved outcome.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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