Bloom Syndrome Association's Patient-Centered Research Strategy: "SECURE"

Purpose of this document:

This document has been developed by the Research Council of the Bloom Syndrome Association (BSA) to serve as a strategic framework guiding all research-related activities initiated or supported by the BSA. It outlines a patient-centered approach to understanding Bloom syndrome, addressing unmet needs, and accelerating progress toward effective treatments and a cure.

The strategy, known as the **SECURE Framework**, reflects the collective input of individuals and families affected by Bloom syndrome (BSyn), clinical experts, researchers, and rare disease advocates. It is intended to:

- Clarify the BSA's research priorities, grounded in the lived experiences and needs of the Bloom syndrome community.
- Inform the selection, funding, and evaluation of research projects, collaborations, and partnerships.
- Promote transparency and accountability in research and clinical efforts.
- Engage stakeholders across sectors, from academia to industry to policymakers and regulators.

To achieve our strategic objectives we have defined "Deliverables" for our first, two-year term of the Research Council. As a living document, this Framework, and the underlying Deliverables, will evolve over time in response to new discoveries, community feedback, and emerging opportunities.

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1. We Want to Be Safe

1.1. Identify and address key concerns of Bloom syndrome

- **What:** We want to understand what concerns individuals with BSyn and their families have about BSyn, at every step of the patient journey. From pre-natal (pregnancy), to neo-natal, baby, toddler, child, teen, young adult, adult, senior and end of life.
- **Why:** While anecdotal evidence exists within the community, the true concerns have not been explicitly and thoroughly documented. Understanding the burden of disease/ burden of illness will be critically important to guide the research strategy (as it is and must remain patient-centered) and is important for documenting the unmet need when it comes to implementing interventions, treatments, and cures.
- **How:** Collect information via the new International Bloom Syndrome Registry (IBSR) and prepare a natural history study (NHS) on patient journey, on disease manifestations, health issues, and including psycho-social aspects of the disease and how individuals feel about various risks and decisions in their life.
- **Where are we now:** Informal surveys of research priorities of the BSyn community were done before and during the 2024 Patient & Family Conference. Anecdotally, development of cancer remains the highest fear among individuals and their families.

1.2. Evaluate the effects of sunlight, x-rays, diet, alcohol, tobacco, etc. on people with BSyn

- **What:** While the chromosomal instability caused by BSyn is believed to be the major driver of cancers, other exogenous and endogenous factors (such as sunlight, radiation, inflammation, carcinogenic chemicals, dysregulated metabolism, and unhealthy lifestyle) certainly play a role in "typical" cancer development and would be expected to be an important factor in BSyn. Yet very little is known about the effects of these other factors in individuals with BSyn at a molecular, whole body, or population level.
- **Why:** Living with BSyn means living as a "previvor" to cancer and induces constant fear in individuals and their families that cancer is likely to develop at any moment. Decisions about whether or not to undergo an imaging procedure or to avoid all sunlight weigh on minds.
- **How:** a) Seek out researchers and/or CROs who are best suited to perform research in this topic, recognizing it may be a collection of researchers; b) Fund literature reviews and landscape reviews of causes of cancer in BSyn, comparing this to what is known in sporadic cancer. Fund research into carcinogenesis in "normal" cells vs Bsyn cells, describing what is known about the genetic makeup of the cells/samples. Compare what is found in related diseases such as Fanconi Anemia (FA), xeroderma pigmentosum (XP) ataxia telangiectasia (AT), and others; c) Fund in-vitro studies on UV and ionizing radiation in different Bsyn cell types and, pursuant to those studies, move to appropriate mouse or other animal models; d) Via the IBSR, undertake surveys of individuals with BSyn on lifestyle decisions (sunscreen, diet, alcohol, tobacco, etc.) as an initial source of deeper research studies.
- **Where are we now:** A request for this topic was included in our first RFP (September 2024) but no applications were received. We are currently landscaping potential researchers. Initial survey of the community was done on individual health maintenance decisions.

1.3. Evaluate the effects of anti-cancer drugs (efficacy / safety) on cancers and the risk of adverse effects (short term and long-term, where possible) in BSyn

- **What:** Determine the optimal dosing and risk-benefit profile of anti-cancer therapies in individual patients with BSyn, considering that some BSyn patients have only tolerated

significantly reduced dosages while others were successfully treated with the full dosage of standard regimens. Anti-cancer therapies can include traditional chemotherapies, targeted molecular therapies, immuno-therapies, radiopharmaceuticals, and hybrid/combo approaches.

- **Why:** Due to chromosomal instability in BSyn, standard dosages of traditional chemotherapies or radiation (i.e. standard of care first line treatment in non-Bsyn cancers) may be too toxic and/or lead to secondary cancers, while on the other side, lowered dosages may be ineffective in treating the cancers. Tailored dosing could reduce harm and improve survival. Similarly, novel modalities including targeted therapies such as checkpoint inhibitors, kinase inhibitors, antibody-drug conjugates have shown promise in treating non-Bsyn cancers but little to nothing has been published on how these would be expected to perform in Bsyn cancers (even presenting the same molecular features).
- **How:** a) Collect retrospective treatment data from Bsyn cancers and publish these data as a summary of case reports; b) Write a white paper and literature review outlining the disease-biology-based hypotheses of why certain treatment modalities would or would not be expected to be particularly effective in Bsyn cancers, with a particular eye towards distinguishing within Bsyn (by type of BLM mutation, other pathogenic variants, somatic mutations and other effects identified by whole genome sequencing, etc.); c) Use Bsyn cell and animal models, Bsyn cancer organoids, and patient-derived xenografts to study dose-response of standard anti-cancer drugs[1] and approved targeted therapies[2] (where appropriate); d) use these results to both inform the ongoing Virtual Tumor Boards (VTBs) and have a set of experts review and update recommendations given in the 2017 Health Supervision paper on cancer treatment in BSyn.
- **Where are we now:** Some information on cancer treatments has been collected by the BSA, by UCLA and by the Weill Cornell Registry, but there has not been a systematic outreach campaign to collect and analyze this information.

1.4. Conduct clinical surveillance using established and new methods

- **What:** Implement regular, proactive clinical surveillance strategies to identify cancer and other health complications early in individuals with BSyn.
- **Why:** Early detection significantly improves outcomes in other high-risk cancer predisposition populations like those with BSyn, as has been shown in Li-Fraumeni and Lynch Syndrome[3]. However, the balance of benefit versus risk (e.g., radiation exposure or other potential complications) and the expected sensitivity and specificity of any screening approach must be carefully evaluated. Novel and emerging diagnostic approaches including liquid biopsies, at-home tests, and non-invasive diagnostics[4] could show promise in BSyn but have not yet been tested.
- **How:** a) understand what surveillance schedules individuals with Bsyn are currently undergoing, and what surveillance treating physicians are recommending; b) understand what cancer surveillance trials individuals may already be participating in, or otherwise have access to; c) outline data to collect via the IBSR on cancer and health surveillance; d) decide whether to implement a specific trial or to observationally collect data via the IBSR.
- **Where are we now:** Clinical surveillance recommendations were given in the 2017 Bloom Syndrome Health Supervision paper based on expert review of existing, highly limited

[1] https://my.clevelandclinic.org/health/treatments/24323-chemotherapy-drugs
[2] https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/approved-drug-list
[3] https://pubmed.ncbi.nlm.nih.gov/10784581/
[4] E.g. EsoGuard: https://www.luciddx.com/precancer-detection/esoguard

information. AACR DNA Damage Syndrome recommendations from 2024 differ slightly. Individuals seen at the UK Bsyn Centers of Excellence in London and Manchester follow a modified version of the AACR 2024 recommendations. No global consensus surveillance guidelines exist; current practices vary widely and are often determined case by case.

1.5. Report findings and recommendations to BSyn community and medical community

- **What:** As we develop a more nuanced understanding of risks in BSyn, we will share these findings with the BSyn patient & family community and the medical community.
- **Why:** Individuals with Bloom syndrome make daily decisions on lifestyle and medical choices, and these decisions need to be based in the latest knowledge in the field.
- **How:** Updates of Patient & Family Handbook; hold regular webinars (on RC activities and funded projects), and bi-annual patient & family conference; create infographics for distribution in multiple languages; encourage clinician and researcher presentations at medical society meetings.
- **Where are we now:** a 1-pager has been developed in English, Japanese, German, and Turkish. Webinars are not regularly held.

2. We Will Find Effective Treatments for BSyn

2.1. Initially screen approved drugs for efficacy in restoring BLM function (increasing lifespan, size, etc.) in BSyn. Then follow up with screening of drugs which have an established safety profile but have not completed development for their original target indication.

- **What:** Systematically evaluate existing, approved drugs that may restore BLM protein function or compensate for its loss in individuals with Bloom syndrome.
- **Why:** Repurposing existing drugs offers a faster, more cost-effective path to treatment. These drugs have known safety profiles and may alleviate symptoms or slow disease progression. Such an approach may have a low likelihood of success, but it also represents an opportunity to establish high throughput assays and validated disease models. It may also point us towards a better understanding of disease biology that can be targeted with novel therapies.
- **How:** a) Decide which cell models, animal models, and functional assays show phenotype and are amenable to high-throughput screening; if none, fund the development of said tools and assays; b) Engage a CRO (contract research organization) or NIH TRND (the US NIH Therapeutics for Rare and Neglected Diseases program) to perform high throughput screening (HTS), with advice on initial libraries based on expert opinion, hypotheses (e.g. readthrough molecules for premature codon termination variants), and possibly findings from surveying the BSyn patient community (e.g. for any current drugs being prescribed off-label); c) For any hits, further test in pre-clinical models and organize compassionate drug use on a named patient basis or implement small clinical studies (in partnership with treating physicians) to test efficacy in Bloom patients.
- **Where are we now:** Not a clear understanding of which cell lines, in vitro, and functional assays would be used.

2.2. Evaluate anti-cancer drugs for appropriate dosage (efficacy & safety) in BSyn → see 1.3 above

2.3. Find a cure for BSyn

- **What:** Identify and develop curative therapies for Bloom syndrome, such as gene therapy, gene editing, or targeted molecular interventions.
- **Why:** A definitive cure would eliminate disease burden, prevent cancer, and normalize life expectancy and quality of life for people with BSyn. While there are substantial challenges in developing a cure that could reach all cell/tissue types throughout the body, we will need to consider the pros and cons of partial "cures", e.g. treatment of the bone marrow but not full body. Note that *treatments* (interventions that can alleviate symptoms or delay disease onset or progression) are differentiated from *cures,* with our approach to treatments described in 2.1 and 4.3.
- **How:** a) Perform an analysis to list all the known pathogenic variants in the BLM gene and their frequency in the Bloom population; c) Considering individual pathogenic variants present in the BLM gene or the nature of the targets identified via the "omics" approach, systematically outline which curative approaches are potentially viable. Explore gene therapy, gene editing, mRNA therapy, ASO treatments; d) Fund pre-clinical seed projects to demonstrate potential feasibility in cell and animal models; e) create partnerships with translational researchers and biotech companies to further develop.
- **Where are we now:** Early-stage interest exists in gene therapy approaches, with small projects in AAV-based gene therapy delivery and lentivirus approaches underway. Omics discovery studies have been proposed but not yet funded.

3. We Will Communicate – Collaborate with Stakeholders

3.1. Within the BSyn community

- **What:** Build trust, awareness, and engagement within the global BSyn patient and family community.
- **Why:** A strong, connected community is the foundation of patient-centered research. It enables shared learning, recruitment into studies, and ensures patient voices are central in setting research priorities.
- **How:** a) Continue to hold biannual patient/ family conferences and seek opportunities for local gatherings between conferences; c) Establish peer support and ambassador programs; d) Foster dialogue between families and researchers via the Research Council and informal interactions.
- **Where are we now:** Engagement through the 2024 Family Conference and online presence is growing; ongoing work is needed to reach families globally and across language barriers. BSA is establishing a Global Ambassador program.

3.2. With the BSyn clinician / researcher community

- **What:** Maintain strong and communicative relationships with clinical experts and researchers working on BSyn.
- **Why:** Partnerships with clinicians and scientists are essential for advancing research and translating findings into care improvements, and clinicians and scientists can learn from ultra-rare patients, as well.
- **How:** a) Host BSyn-specific workshops / symposia or satellite meetings at conferences; b) Develop a webinar series for clinicians / researchers; c) Provide funding opportunities for our research priorities; c) offer IBSR and natural history data to collaborators under guidance of Registry Advisory Board; d) Act as a catalyst to facilitate multi-institutional projects such as global network of Centers of Excellence.

- **Where are we now:** Relationships exist with several researchers and clinicians, but the network needs to grow and be formalized into a stronger consortium.

3.3. With other ultra-rare disease communities

- **What:** Collaborate with other rare and ultra-rare disease organizations to share knowledge, advocate collectively, and align research efforts. Groups to consider are those that support other RECQ diseases and those that support other cancer predisposition syndromes (e.g. Rothmund Thomson syndrome, Fanconi anemia, Li-Fraumeni syndrome, etc.)
- **Why:** Ultra-rare diseases share common challenges. Collaboration increases visibility, access to shared infrastructure, research findings, and policy impact.
- **How:** a) Participate in rare disease alliances and umbrella organizations such as NORD, Global Genes, and FORCE and actively reach out to related disease organizations; b) Seek opportunities to collaborate on tools (registries, data platforms) and/or Centers of Excellence, where appropriate; c) Advocate jointly for research funding and research collaboration.
- **Where are we now:** Preliminary connections made to individual groups such as the RTS Foundation. BSA is a member of NORD, Global Genes, and FORCE. Participation in Chromosomal Instability Think Tank at UPenn in 2025. No formal partnerships with any other patient advocacy organizations established yet.

3.4. With regulators, politicians, industry and media

- **What:** Engage external stakeholders who influence policy, funding, and public awareness related to BSyn research.
- **Why:** Achieving progress in rare disease research requires partnerships with government, media, and industry. Awareness can drive investment, access to care, and innovation. Broader awareness via media can also support the finding of additional patients.
- **How:** a) Share patient stories and research needs with media; b) Establish ICD-10 and ICD-11 codes unique to BSyn, which will be important for regulators; c) Educate elected officials on the value of BSyn research via participation in organizations like NORD and Everylife; d) As research progresses, seek out industry partnerships for therapies.
- **Where are we now:** Minimal engagement to date. Opportunity exists to significantly expand outreach and advocacy, yet other activities are of nearer-term priority.

4. We Want To Understand BSyn

4.1. Define the "Status Quo" of BSyn in 2024 → Completed

4.2. Build a registry to better understand the daily life and clinical reality of people with BSyn

- **What:** Establish and maintain a secure, global patient registry (International Bloom Syndrome Registry, IBSR) that captures patient-reported, caregiver-reported and clinician-reported outcomes, clinical and genetic / genomic information on individuals with BSyn.
- **Why:** Registries provide a foundation for natural history studies, clinical trial readiness, and a better understanding of disease burden and variability. They may also inform individual decisions regarding care of self or affected child.
- **How:** Document needs and conduct a technical assessment of registry solutions; select and implement a registry platform for the BSA.
- **Where are we now:** Planning underway with data platform providers for the various data sources and establishing a Registry Advisory Board.

4.3. Conduct research into the underlying mechanisms of BSyn to find effective treatments for BSyn and Bsyn cancers

- **What:** Support more exploratory research to identify points of therapeutic intervention within the biological framework of BSyn and the cancers that develop in BSyn.
- **Why:** The underlying biological mechanisms of Bloom syndrome and its associated cancers remain poorly understood. This knowledge gap is a barrier to developing targeted treatments or preventive strategies. Understanding the specific pathways by which genomic instability leads to different cancers in BSyn can reveal intervention points not just for this syndrome, but potentially for cancer biology more broadly.
- **How:** a) Fund the creation of validated cell lines and animal models that display BSyn phenotype and BSyn cancers (including blood and solid tumors); b) Fund work into Bsyn tumor and blood cancer characterization for understanding genetic signatures that may be amenable to targeted treatments or otherwise shed light on cancer development and how it may be avoided or delayed; c) Perform broad 'omics' studies in cell models to identify therapeutic targets; d) Where needed, support projects to clarify disease biology, with BSA funds used only for the most immediate "must-know" questions in order to design a treatment.
- **Where are we now:** A few exploratory studies have been published (e.g. showing frequency of Clonal Hematopoiesis of Indeterminate Potential in Bsyn and carriers is higher than in normal populations), but no comprehensive effort has yet been made to build reliable BSyn cancer models or perform deep molecular characterization of tumors and cancer development in BSyn individuals. Interest is growing, as seen in new collaborations and the 2025 project led by Dr. de Voer, which marks an important step toward understanding BSyn cancer biology at the genomic level.

4.4. Evaluate BSyn as an important model of cancer development in general

- **What:** Explore how insights from BSyn can inform our understanding of cancer biology and genomic instability more broadly.
- **Why:** BSyn may serve as a natural model for studying mechanisms of cancer initiation, which could benefit oncology research more generally, and could attract broader interest and funding for Bsyn research.
- **How:** a) Engage cancer researchers to include BSyn in genomic studies; b) Encourage comparative biology research, e.g. with other cancer predisposition syndromes; c) Present BSyn as a relevant model of cancer development at cancer-focused scientific meetings.
- **Where are we now:** This concept is identified but not properly established yet. No studies have yet specifically positioned BSyn as a cancer model.

5. We Will Recruit

5.1. More individuals with BSyn globally through publicity, early diagnosis, dialogue with experts

- **What:** Expand global identification of individuals with BSyn through increased awareness, global patient-to-patient outreach, global outreach to clinicians, clinician education, and diagnostic access.
- **Why:** More diagnosed individuals lead to stronger research, more accurate data, and a better understanding of Bloom syndrome's variability and burden. A minimum of 300 individuals is thought to be required to create meaningful data.

- **How:** Identify all possible sources of BSyn referrals, e.g., clinical geneticists, cancer predisposition clinics, genetic societies, Bloom syndrome clinics, and conduct outreach for BSA referrals. This will require the establishment of Centers of Excellence.
- **Where are we now:** Some materials and outreach efforts exist; further global outreach and formal partnerships are needed.

5.2. More expert researchers, clinicians, and MDTs (multi-disciplinary teams)

- **What**: Attract and support a broader, global network of experts working collaboratively across disciplines to advance care and research in BSyn.
- **Why:** Due to BSyn's complexity, multi-disciplinary teams (MDTs) are essential for effective management and for building comprehensive research approaches.
- **How:** Establishment of a global network of ~15-20 Centers of Excellence, with the BSA's evaluation of and designation as a Center of Excellence, integrating clinical care, research, and patient & family engagement. a) Define the minimum requirements (must-have) and desired components (ideal) for an institution to be designated as a Bloom Syndrome Center of Excellence; b) Work with PIs at institutions to formally establish CoE; c) Publish CoEs on BSA website, FB group, and include in infographics, welcome letter, etc. to raise awareness and drive patients to these centers; d) Establish and maintain a network of CoEs who share best practices of BSyn patient care; e) Track and evaluate outcomes.
- **Where are we now:** Two formal BSyn centers exist in the UK; initial connections and discussions in the US, Germany, the Netherlands, Australia etc. in progress.

5.3. More friends, volunteers, and donors who support us

- **What:** Grow a larger network of advocates, volunteers, and donors to support the mission of improving life for people with BSyn.
- **Why:** Sustainable research and advocacy require a strong, engaged base of supporters beyond just BSyn persons and affected families.
- **How:** a) Create compelling storytelling and social media campaigns; b) Offer volunteer roles with clear impact; c) Launch donor engagement programs; d) Partner with influencers and rare disease champions.
- **Where are we now:** Initial community support is strong; room to grow with more structured outreach and fundraising infrastructure.

6. We Will Actively Engage in BSyn Research

6.1. Through discussion, study participation, provision of our data and samples

- **What:** Encourage and support individuals with BSyn and their families in actively participating in research activities.
- **Why:** Patient and family engagement in research ensures relevance, quality, and accelerates scientific discovery.
- **How:** a) Provide clear, accessible information about IBSR and additional study opportunities; b) Offer support via care coordinator during participation; c) Provide feedback/ results of ongoing IBSR or other studies to show benefits of participating.
- **Where are we now:** Participation is growing through the Research Council and conferences; need to scale and streamline engagement pathways.

6.2. Through fundraising

- **What:** Generate financial support for research, outreach, and operations through individual giving, grants, and partnerships.
- **Why:** Sustained funding is critical to advancing the SECURE strategy and building infrastructure for long-term impact.
- **How:** a) Develop a fundraising plan; b) Cultivate individual donors; c) Apply for grants; d) Explore partnerships with foundations, corporations, and philanthropy networks.
- **Where are we now:** Initial fundraising successes achieved, largely through community donations. Need to diversify and scale efforts.

6.3. Through participating priority setting, study planning, and evaluation of study outcomes

- **What:** Empower patients and families to help shape future research directions, plan studies, and interpret study findings.
- **Why:** Co-creation of knowledge ensures that the outcomes matter to those most affected and promotes transparency and trust.
- **How:** a) Convene advisory panels and working groups that include patients and families (e.g. Research Council, Registry Advisory Board, Deliverable teams and working groups); b) Include patients in study design and evaluation; c) Use surveys and feedback loops via IBSR to inform priorities moving forward.
- **Where are we now:** Early-stage patient involvement has begun, e.g. through community surveys and Research Council. Structures for continuous engagement still in development.

6.4. By documenting the impact of research outcomes on our own lives

- **What:** Capture and share the real-world effects of research and medical advances on people with BSyn and their families.
- **Why:** Documenting impact helps researchers, funders, and policymakers understand the value of investing in BSyn research.
- **How:** a) Collect testimonials and case studies; b) Include quality-of-life metrics in IBSR; c) Publish community reports highlighting personal stories and milestones.
- **Where are we now:** Some personal stories have been shared through conferences and social media; more systematic collection and dissemination are needed.