Externally-Led Patient Focused Drug Development on Wiskott-Aldrich Syndrome (WAS) and X-Linked Thrombocytopenia (XLT) Voice of the Patient Report

Meeting Date: February 3, 2023

Meeting hosted by: Wiskott-Aldrich Foundation

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Meeting Sponsors:

Partner Organizations:

Immune Deficiency Foundation and The Israeli Wiskott-Aldrich Syndrome Association (R.A.)

Wiskott-Aldrich Syndrome (WAS) and X-Linked Thrombocytopenia (XLT)

Voice of the Patient Report

The Wiskott-Aldrich Foundation is dedicated to serving children and families with Wiskott-Aldrich Syndrome (WAS) and X-Linked Thrombocytopenia (XLT) and their families worldwide, by funding research and providing educational, financial, and emotional support. This *Voice of the Patient* report was prepared on behalf of the Wiskott-Aldrich Foundation, the Immune Deficiency Foundation and The Israeli Wiskott Aldrich Syndrome Association (R.A.) as a summary of the input shared by families and caregivers living with WAS and X-Linked Thrombocytopenia (XLT) during an Externally-Led Patient Focused Drug Development (EL-PFDD) meeting, conducted virtually on February 3, 2023.

Authors and Collaborators: This report was prepared and submitted on behalf of Wiskott-Aldrich Foundation Sumathi Iyengar, MD, Co-Founder and Executive Director, Wiskott-Aldrich Foundation, Priya Stephen, MD, Board of Directors, Wiskott Aldrich Foundation and Cheryl Karow FNP-C, Board of Directors, Wiskott Aldrich Foundation, Amir Kedar, Chairman of the Israeli WAS Association, and by Chrystal Palaty, medical writer.

Consulting Partners include Larry Bauer, RN, MA, and James Valentine, Esq. and from Hyman, Phelps & McNamara, P.C.

Disclosures: The Wiskott-Aldrich Foundation is a volunteer run 501(c)(3) public charity. The Immune Deficiency Foundation is a 501(c)(3) organization. The Israeli Wiskott Aldrich Syndrome Association (R.A.) is a non-profit organization. These organizations receive funding from private and corporate sponsors including pharmaceutical and life science companies in the form of unrestricted and restricted grants and sponsorship of programs and events.

James Valentine, Esq. and Larry Bauer, RN, MA are employed by Hyman, Phelps & McNamara, P.C., a law firm that represents patient advocacy organizations and companies that are developing therapeutics and technologies to advance health.

The Wiskott-Aldrich Foundation contracted with Chrystal Palaty, PhD from Metaphase Health Research Consulting Inc. for assistance in writing this report.

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Thank you to our sponsors, CSL Behring, Orchard Therapeutics, EveryLife Foundation, and the Skrynecki Financial Planning Group (Raymond James & Associates), and to all our donors for their generous support of the February 3rd EL-PFDD meeting and this report.

Thank you to James Valentine and Larry Bauer from Hyman Phelps & McNamara, for their invaluable assistance in planning and moderating our EL-PFDD meeting. Thank you to Dudley Digital Works for their outstanding service in helping us implement our meeting.

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Thank you to all the representatives from advocacy and professional organizations, pharmaceutical companies, federal agencies, and resource centers worldwide who attended our meeting. Thank you to the many physicians and researchers working tirelessly in hospitals and labs around the world to help patients who are living with WAS/XLT. Your work has led to a solid foundation of science that is now resulting in clinical trials that are already in progress, and more that are being planned for the near future.

Our most sincere thank you goes to all of our WAS/XLT community, including patients, caregivers, family members and friends who attended our meeting and who honestly shared the lived experience of WAS and XLT. Our meeting, and this report, could not have been as impactful or enlightening without each and every one of you. Our intention is that our EL-PFDD meeting will have a lasting impact on the future of WAS/XLT research and medical product development.

Contents

Key Insights: **Wiskott-Aldrich syndrome (**WAS)/ **X-linked thrombocytopenia (**XLT)

1. **Wiskott-Aldrich syndrome (WAS)/XLT is a life-threatening disease with profound impact on the patients and their families.** WAS, the most severe form of the disease, and X-linked thrombocytopenia (XLT), the less severe form, have unpredictable and varied presentations. Immunodeficiencies and bleeding/platelet deficiencies put patients at high risk of serious infections and severe bleeding, including brain bleeds. Most patients experience eczema. As infants, many experience bloody diarrhea and food allergies, requiring special formulas and restricted diets. Patients have an increased risk of developing complications such as autoimmune disorders, leukemia, and lymphoma. Many experience psychosocial and mental health challenges as a result of the disease and/or the treatments.
2. **Life with WAS/XLT is a life of uncertainty, isolation, and terrifying worry and fear about the future.** Patients and parents worry about symptoms of life-threatening complications, the impacts of the disease and the long-term consequences of treatment. WAS/XLT severely impacts every activity of daily living and the quality of life of the patient as well as for their parents, siblings, and family members.
3. **There are no FDA approved treatments for WAS/XLT.** Experimental gene therapy (GT) and bone marrow transplant (BMT) are the only definitive treatments for WAS, are not universally available and are not FDA approved. Medications to improve platelet counts/bleeding including thrombopoietic and antifibrinolytic medications are also not approved by the FDA for WAS/XLT.
4. **Treatment for WAS can be a trade-off.** BMT, though successful, is a toxic, risky and prolonged treatment. BMT is most successful when done before the age of 5 years. The outcomes are unpredictable, patients sometimes experience severe and long-lasting side effects. Bone marrow transplants are frequently accompanied by significant drawbacks including infertility, risk of death, organ toxicity, graft versus host disease (GVHD), autoimmune disorders and malignancy. Symptomatic treatments used by patients who have not gone through BMT or GT include platelet and blood transfusions, immunoglobulin replacement therapy, steroids, prophylactic antibiotics, anti-rejection drugs, bleeding medications, splenectomy.
5. **Newer and more promising treatments such as experimental gene therapy are suspended due to financial constraints and are not available to patients.**
6. **The term XLT is a misnomer, and it is not a mild disease.** XLT is a progressive disease which is not limited to thrombocytopenia as the name indicates. Most patients develop complications such as bleeding, severe autoimmune complications, and malignancies, often starting in the second decade of life. By the time they develop complications, many are too ill to undergo definitive treatments and unfortunately some patients pass away, some just in the 3rd and 4th decade of life. Newer treatment options including experimental treatments should be made available to XLT patients.
7. **Lack of treatment consensus for XLT makes treatment decision-making difficult.** Experts widely vary in recommendations for treatment ranging from recommending a BMT to doing nothing. This leaves families in a quandary as to what is the best decision to make on behalf of their child.
8. **Patients want less risky treatment: less mortality, less toxicity and fewer long-term side effects**. They would also like to have better mental health supports and more trauma-informed care, better options to preserve fertility prior to treatment, ways to prevent transmission of the gene to future generations.

Clinical Overview of WAS and XLT[1]

Wiskott-Aldrich Syndrome (WAS) and X-linked thrombocytopenia (XLT) are life-threatening disorders characterized by bleeding, eczema, and immune deficiencies. Drs. Alfred Wiskott and Robert Aldrich independently described WAS/XLT in the first and second half of the 20th century, respectively. The causative *WAS protein (WASP)* gene was identified in 1994. The gene is located on the X-chromosome and consists of 12 exons, each of which can be affected by variants causing the disease. The WAS protein (WASp) is expressed in white blood cells and platelets and influences both immune and hematopoietic functions.

WAS and XLT exist on a disease spectrum graded on a score of 1 to 5, with disease severity related to quantity and the function of the expressed WAS protein (**Table 1**). XLT can be considered score 1-2[2] disease and is often associated with reduced expression levels of the protein. Although it is the least severe form of the disease, complications are often seen starting in the second decade of life and some patients pass away from complications in the 4th and 5th decade of life. WAS (also called Classic or Severe WAS) patients are those with a score of 3-5. Patients living with WAS who do not receive definitive treatment, which is a therapy intended to cure their disease, die in their teens.

Table 1- WAS Disease Scoring and Clinical Manifestations[3]

	XLT	WAS
Disease scores	1-2	3-5
Thrombocytopenia and small platelets	+	+
Eczema	-/+	+/++/+++
Immune deficiency and infections	-/+	+/++
Autoimmunity and or malignancies	- *	Frequent**
WASP expression	Present, but reduced quantity	Absent or truncated

WAS/XLT is passed on in an X-linked manner, predominantly affecting males, however some female carriers also report symptoms. The disease is estimated to have an incidence of approximately 1 in 250,000 live male births worldwide.

[1] Based on presentations by Drs. Sumathi Iyengar, Fabio Candotti, and Donald B. Kohn at the February 3, 2023 EL-PFDD meeting.

[2] A proposal was made to change the name of XLT to WAS score 1-2 at the 2023 Primary Immune Deficiency Treatment Consortium (PIDTC) Scientific Workshop (April 18-20, 2023).

[3] Adapted from Ochs HD, Thrasher AJ: *The Wiskott-Aldrich syndrome*. J Allergy Clin Immunol 117:725-38; quiz 739, 2006

* Patients with XLT may develop autoimmune disorders or malignancy and progress directly to a score of 5

** WAS patients who develop and autoimmune disorder or malignancy have a score of 5.

The disease typically presents in infancy and early childhood, with bruising, petechiae (rash-like red, brown or purple pinpoint bruises), bleeding, eczema and infections. WAS/XLT has heterogeneous presentation and outcomes. While some patients are affected only with thrombocytopenia, others experience severe complications like severe infections, malignancy, and autoimmunity.

- **Platelet deficiencies** are the most consistent WAS feature and include low platelet levels, small sized platelets and abnormal platelet function. Platelet levels are generally below 70,000 mm^3 as compared to normal levels ranging from 150,000 to 450,000 mm^3 in healthy children, resulting in bleeding issues which can be severe.
- **Immunological abnormalities** can include low lymphocyte counts (especially CD8+ T cells), reduced IgM antibody levels, increased IgA antibody production, and reduced or absent response to vaccines. Those living with WAS are at risk of frequent and serious infections including upper respiratory tract infections, sinus and ear infections, pneumonias and meningitis.
- **Eczema or atopic dermatitis** is experienced by 80% of WAS patients at some point in life, likely related to immune dysregulation.
- **Bloody diarrhea** and **food allergies** are often early symptoms.
- **Autoimmunity** and **malignancy** are more common seen in WAS patients and in XLT patients in their 2^{nd} to 4^{th} decade. Those living with XLT who experience either autoimmunity or malignancy, convert to WAS Score 5.

FDA-approved therapies for WAS or XLT do not currently exist. The treatment recommendations for score 1-2 and score 3-5 WAS differ. The only definitive treatments for WAS are bone marrow transplant (BMT) and experimental gene therapy, which has been offered on a limited basis in the past decade.

BMT outcomes are most successful when the transplant is conducted before the age of five years. For those living with XLT, BMT is not universally recommended as XLT is not felt to be severe enough to justify transplant when they are young. Yet, once the disease progresses to a point where BMT would be recommended, it may be too late for a successful transplant. XLT patients are excluded from gene therapy (GT) and other experimental treatments because the treatments are considered too risky compared to the perceived severity of the disease.

Note that for the purposes of this report, the term “WAS survivor” refers to one who has received definitive treatment for WAS, including BMT or GT, while “living with WAS” refers to those who have not received a BMT or GT.

WAS/XLT EL-PFDD Meeting Agenda

Meeting Date: February 3, 2023

10:00 am - 10:05 am	**Welcome and Introductions** *Sumathi Iyengar, MD*, Meeting Co-Moderator Co-Founder and Executive Director, Wiskott-Aldrich Foundation
10:05 am – 10:15 am	**FDA Opening Remarks** *Erica Glancy, MD, FACAAI*, Medical Officer, CBER, Office of Tissues and Advanced Therapies U.S. Food and Drug Administration
10:15 am – 10:30 am	**Clinical Overview of WAS and XLT** *Fabio Candotti, MD*, Head Physician, Division of Immunology and Allergy, University of Lausanne, Switzerland
10:30 am – 10:35 am	**Introduction and Meeting Overview** *Larry Bauer, RN, MA,* Meeting Moderator Senior Regulatory Drug Expert Hyman, Phelps & McNamara
10:35 am – 10:45 am	**Demographic Polling**

Session 1 – Living with WAS/XLT: Symptoms and Daily Impact

10:45 am – 11:10 am	**Patient & Caregiver Video Testimonials from Panelists**
11:10 am – 12:30 pm	**Audience Polling & Moderated Discussion** Topics: Bleeding, eczema, food allergies, infections, autoimmunity, malignancy, challenges of XLT & Classic WAS, transplant decisions, caregiver challenges, mental health challenges
12:30 pm – 1:00 pm Lunch	

Session 2 – Current and Future Treatments for WAS and XLT

1:00 pm – 1:10 pm	**Treatment Overview of WAS and XLT** *Donald Kohn, MD*, University of California, Los Angeles Distinguished Professor, Pediatric Hematology Oncology, and Molecular & Medical Pharmacology
1:10 pm – 1:35 pm	**Patient & Caregiver Video Testimonials from Panelists**
1:35 pm – 2:45 pm	**Audience Polling & Moderated Discussion** Topics: Bone marrow transplants, splenectomy, post BMT complications, GVHD, feeding challenges, 2nd transplants, Gene Therapy, IVIG, Thrombopoietics, antibiotics, infertility, mental health challenges
2:45 pm – 2:55 pm	**Summary Remarks** *Fabio Candotti, MD* Head Physician, Division of Immunology and Allergy, University of Lausanne, Switzerland
2:55 pm – 3:00 pm	**Closing Remarks** *Mike Skrynecki, CFP, RICP* Founder and President Wiskott-Aldrich Foundation

Adjourn

WAS/XLT EL-PFDD Meeting Summary

The Wiskott-Aldrich syndrome (WAS) and X-linked thrombocytopenia (XLT) Externally-Led Patient Focused Drug Development (EL-PFDD) was held virtually on February 3, 2023. The meeting was an important opportunity for the Wiskott-Aldrich Foundation to share patient and caregiver perspectives regarding the symptoms and daily impact of WAS/XLT, as well as their thoughts on current and future approaches to therapies. The meeting was cohosted by **Dr. Sumathi Iyengar**, WAS parent and the Executive Director of the Wiskott-Aldrich Foundation and **Larry Bauer**, RN, MA Hyman, Phelps, & McNamara.

Dr. Iyengar opened the meeting by welcoming all meeting attendees including the members of the US Food and Drug Administration (FDA) and by introducing the first speaker.

Dr. Erica Glancy, MD, FACAAI, CBER, USFDA, a medical reviewer at the FDA in the Office of Tissues and Advanced Therapeutics (OTAT), provided opening remarks and thanked everyone for their participation. She spoke about the importance of patient focused drug development and the FDA's commitment to facilitate the development of safe and effective medical products for rare diseases including WAS/XLT. She introduced the Rare Disease Drug Analytics Platform which can help inform drug development for rare diseases. A link to this platform as well as other FDA resources can be found in **Appendix 1**.

Dr. Fabio Candotti, MD, from the University of Lausanne, presented a scientific overview of WAS/XLT, which served as a foundation for the first half of the meeting. **Larry Bauer** provided an overview of the meeting structure and invited all caregivers and individuals living with WAS/XLT to contribute their voices through online polling, calling in by phone, and by submitting written comments through an online portal.

The online meeting was attended by 224 individuals, including three post-BMT survivors, eight individuals living with WAS, one individual living with XLT, 64 parents/caregivers, 49 family members and 12 friends. The audience included 25 attendees from the government, 23 scientists and researchers, 16 industry representatives, 14 health care providers, and eight individuals from the non-profit sector.

EL-PFDD meeting attendees used online polling to indicate meeting demographics, shown in **Appendix 2**. Not all attendees who attended the meeting may have participated in online polling.

- Most EL-PFDD meeting attendees were either caregivers/close family members of someone diagnosed with WAS (64%) or XLT (24%), and a small proportion were adults diagnosed with WAS (11%).
- Almost half of poll respondents represented someone who had been treated with BMT (46%). Other poll responses included treatments with immunoglobulin (26%), prophylactic antibiotics (15%), gene therapy (9%) and splenectomy (7%). One fifth (20%) had not received prior treatment for WAS/XLT.
- Half of meeting attendees were from the United States (52%), with representation from Eastern, Central, Mountain and Pacific time zones. Additional attendees were from Europe (23%), Canada (13%), Middle East/Asia (8%), Caribbean (2%) and other (2%).
- Most individuals living with WAS/XLT represented at the meeting were male (94%), with a small number of female (4%) and individuals who preferred not to identify (2%).

- Most patients represented were under 30 years of age (84%), with patients in the 11–18-year-old age group having the greatest representation.
- Most patients were diagnosed with WAS/XLT before 1 year of age (76%), followed by 1-4 years of age (16%). A small percentage was diagnosed between 5 – 20 years of age (7%) and 2% were diagnosed over the age of 20.

The WAS/XLT EL-PFDD meeting was structured around two key topics, *Living with WAS/ XLT - Symptoms and Daily Impact,* and *Current and Future Treatments for WAS/XLT*. The meeting discussion questions are in **Appendix 3**.

The first session started with a pre-recorded panel of individuals who shared patient and caregiver perspectives on the symptoms and daily impacts of WAS/ XLT. Larry Bauer moderated a discussion between a live Zoom panel and those who dialed in by phone. Additional relevant comments entered through an online submission form were read by Dr. Iyengar.

The afternoon session was opened by **Dr. Donald Kohn MD,** from the University of California, Los Angeles and Distinguished Professor, Pediatric Hematology Oncology, and Molecular & Medical Pharmacology. He provided a WAS/XLT treatment overview, to set the stage for the afternoon's discussion. The session continued with a pre-recorded panel of patients and caregivers who described their WAS/XLT treatment experiences. Again, meeting attendees participated in online polling, called in and submitted written comments which were added to the moderated discussion by Larry Bauer and Dr. Iyengar. **Dr. Candotti,** MD, from the University of Lausanne, provided a summary of the key takeaway points. **Mike Skrynecki**, Founder and President of the Wiskott-Aldrich Foundation closed the meeting by thanking all of the meeting attendees and all others who worked so hard to make the meeting a success.

The online polling results from both sessions are included in **Appendix 4**. To include as many patient voices as possible, an online comment submission portal was open for four weeks after the meeting and comments were also collected through the registration portal. All submitted comments are included in a separate PDF document, with selected comments included in the body of this report.

WAS/XLT *Voice of the Patient* Report

This *Voice of the Patient* report is provided to all WAS/XLT stakeholders including the US FDA, government agencies, regulatory authorities, medical products developers, academics, clinicians, and any other interested individuals. The input received from the February 3, 2023, EL-PFDD meeting reflects a wide range of WAS/XLT experiences, however not all symptoms and impacts may be captured in this report.

The final report, the accompanying document containing the submitted comments and a video of the meeting are available on the Wiskott-Aldrich Foundation website at https://www.wiskott.org/pfdd.

TOPIC 1: Living with WAS/XLT: Symptoms and Daily Impact

WAS/XLT health concerns: Many individuals living with WAS/XLT experience severe health concerns as a result of disease symptoms, treatment side effects, or both

During the EL-PFDD meeting, patients and caregivers used online polling to first select all the WAS/XLT-related health concerns that they or their loved one had ever experienced, and then selected the three most troublesome (poll results are in **Appendix 4, Q1 & Q2**). Each WAS/XLT symptom is severe, yet individuals living with WAS/XLT experiences an average of ***five*** different WAS-XLT health concerns. Recurrent infections, increased bleeding, eczema, autoimmune disease were the most frequent and most troublesome symptoms. Many also experience depression and anxiety, graft-versus host disease (GVHD), food allergies, malignancy, bloody diarrhea, kidney disease and other symptoms. Sometimes it was difficult to separate disease symptoms from treatment side effects.

The following are key themes that emerged during discussion but were not captured in the polls.

- WAS/XLT has a heterogeneous presentation. Some patients experience one or two health concerns while others experience every single one.
- Many WAS-specific health concerns interfere and amplify one another: for example, scratching eczema can lead to skin infections, infections can lower platelet counts, infections can cause the onset the autoimmunity, and autoimmunity can increase the risk of malignancy.
- WAS/XLT-related health concerns are unpredictable and can result in much time spent in the hospital.

WAS/XLT-related health concerns are described in descending order of selected as troublesome in the polls and illustrated with patient quotes.

Recurrent viral, bacterial or fungal infections

Recurrent infections are experienced by most individuals living with WAS/XLT and were selected as the most troublesome health concern. Individuals with WAS/XLT experience recurrent infections resulting from WAS-related immune system impairment, or from immune suppression after BMT or splenectomy. For some individuals living with XLT, severe infection will push them to convert to classic WAS. Patients and parents described ear infections, pneumonia, urinary tract infections, and skin infections including warts and molluscum contagiosum**.** Infections ranged from mild to life-threatening, leading to severe complications such as lowered platelet counts, septic shock, difficulty breathing (as a result of lung damage from respiratory infections), brain injury, epileptic syndromes and even death.

> "*His limbs would constantly get infected from him simply scratching the surface of his skin. Scratching happens easily when you have severe eczema. The infections would get so bad, he couldn't walk*. - Parent of a WAS survivor (GT)

> *"At three months old, he caught coronavirus and landed up in hospital for six weeks. Whilst in*

hospital he also picked up CMV (cytomegalovirus) colitis and doctors were extremely worried about the chances of survival." - Parent of a 10-year-old living with XLT

"[Our son] was admitted to the hospital with Staphylococcus aureus sepsis. With such a serious infection, [our son's] diagnosis went from XLT to a classic WAS in an instant." - Parent of a son whose XLT recently converted to classis WAS

"[Our son's] killer was ultimately identified: Legionnaires' disease. He acquired it in his BMT room, while he was neutropenic. … Not a day goes by where I don't think about [our son] or talk to somebody about him. … I miss you, and will love you forever." - Parent of a son who passed at seven-and-a-half months following BMT

Increased bleeding

Increased bleeding due to low platelet counts and impaired platelet function is a symptom of both WAS and XLT, and most individuals living with WAS/XLT suffer from mild to life-threatening hemorrhages, even from minor injuries. Increased bruising is common, including petechiae, rash-like red, brown or purple pinpoint bruises, or slightly larger purpura. Bleeding is unpredictable; nosebleeds can be long and heavy, resulting in time spent in the hospital. Bleeding can even occur in joints. Children living with WAS/XLT are at high risk for brain bleeds, so many wear helmets as toddlers to protect them during daily life.

"My son suffers with low platelets, is covered in mild petechia at all times and multiple bruises. He also has occasional nose bleeds." - Parent of a son living with WAS/XLT

"The bleeding and the platelets have been a constant issue for him. It affects really everything that he can and can't do. … He has bruises all the time (which develop spontaneously because his platelets are so low) and my parents had to carry a letter from his doctor explaining that they were not abusing him because the bruising was so bad and so visible that there were concerns." - Sibling of a brother diagnosed with XLT who progressed to classic WAS

"Nosebleeds are the most disruptive and difficult to deal with aspects of [our son's] condition. They last for hours and he can lose a lot of blood in one event, often requiring hospital visits to either stop the bleeding or do a platelet transfusion. …They are highly unpredictable and almost impossible to control." - Parent of a son living with WAS

"Prior to transplant, my son's biggest issue was bleeding. When he was a toddler, he would bump his head and get huge knots on his forehead, and we were always worried about a brain bleed. My brother died at the age of 13 from a brain bleed, so that was very much on our minds." – Parent of a WAS survivor (BMT) and sister of two WAS brothers

Eczema (red patches)

Eczema is a symptom of both WAS and XLT and can be debilitating. The eczema can itch, sting and cause pain. For some, it first appears like a diaper rash while others experience drying and flaking skin that falls off in their bedsheets. For some, the skin cracks open and bleeds, making them even more susceptible

to infection. Eczema can lead to disfigurement and stigmatization as patches can be quite noticeable on different parts of the body.

> *"We noticed a mild diaper rash on [our son]. We applied diaper rash creams. At times, the rash would clear up completely, but a few days later, would come back with a vengeance."* - Parent of a son who passed away at seven-and-a-half months following BMT
>
> Before his gene therapy, *"Sometimes, he used to sit behind the furniture and curl up and scratch his feet until they bled."* – Parent of a three-year-old WAS survivor (GT)
>
> *"Equal in pain and annoyance was the eczema. The huge flaking, crusty bloody lesions [my son] experienced were [everywhere]: nose, ears, mouth, and groin. He couldn't open his mouth wide enough for a dental checkup, and when he tried a little harder, the vertical cracks in his lips and the corners of his mouth spouted blood, as he cried in pain*." - Parent of a 13-year-old XLT survivor (BMT)

Autoimmune disease

Many individuals living with WAS/XLT develop autoimmune diseases which can include immune thrombocytopenia (ITP), vasculitis, hemolytic anemia, IgA nephropathy, and irritable bowel disease (IBD). During the meeting many patients described autoimmune disorders including psoriasis, alopecia, rheumatoid arthritis, autoimmune vasculitis, IgA nephropathy and hidradenitis suppurativa. Although BMT should eliminate the risk of autoimmune disease, several experienced autoimmune diseases (Graves' disease, Hashimoto's disease or transverse myelitis), as a post-BMT complication. For individuals living with XLT, developing an autoimmune disease will convert their diagnosis to classic WAS.

> *"When our son was diagnosed at 11 months of age, we were told that gene therapy was around the corner. He had his share of bleeds and various WAS challenges, and 23 long years later, we are still waiting for gene therapy. In the meantime, he has developed three autoimmune disorders and he now has severe WAS. He has no match for a BMT and unfortunately GT trials are not available at this time"* - Parent of a son whose XLT converted to WAS
>
> *"At age six, [our son] was diagnosed with ITP, which included three months in and out of the hospital, platelet transfusions, emergency immunoglobulin infusions, and many medications."* - Parent of a son whose XLT recently converted to classic WAS
>
> Autoimmune vasculitis causes sporadic pain and swelling. *"When I was about 10, I developed swelling and intense pain in my lower legs, especially at my ankles. Sometimes I missed school. I even missed my grandfather's funeral."* – WAS survivor (BMT), and family member of others living with WAS

Depression or anxiety

Many individuals living with WAS/XLT experience a great deal of anxiety and depression and resulting from isolation and extended hospitalizations during early childhood. Others experience emotional dysregulation, panic attacks and post-traumatic stress disorder (PTSD) as a result of the BMT procedure. Several are having a hard time coping and even mentioned suicidal ideation.

"I suffered from depression from a very young age. … I still remember the feeling my body had at the time. Suicidal ideation is still something that I struggle with from time to time. Only later did I find out that these emotions and ideas were often [preceded] by some sort of panic attack. At that age, however, I didn't understand what was happening in my body nor could I convey how it felt." - 29-year-old WAS survivor (two BMTs)

"[Our son] had a successful bone marrow transplant eight years ago. …The fallout of all of his treatment and experiences is definitely anxiety. … The body can hold onto that trauma, and it can come out in other ways. He has had some severe anxiety, separation anxiety, social anxiety, all sorts of things. He has massive problems going to sleep alone, and he has general worries as well, … and he absolutely hates going to the hospital." - Parent of a 10-year-old WAS survivor (BMT)

Graft-versus host disease (GVHD)

Many WAS survivors experience GVHD as a result of BMT, which can manifest in many ways including severe skin rash, hair loss, bronchiolitis obliterans (popcorn lung), and eye damage. GVHD can become chronic.

"[Our son] also suffered skin GVHD, an extremely excruciating rash all over his body that would cause him to scream in pain." – Parent of a WAS survivor (BMT)

"My son suffered seven years after transplant with severe graft-versus-host disease on his skin. He has short stature and thyroid issues as a result of the GVHD. Even many years past the BMT, he currently still has problems with skin graft-versus-host disease when he is in the sunshine. …We have to keep his skin covered." - Parent of an 18-year-old WAS survivor (BMT) from the United States

"My son suffers from chronic skin GVHD that has caused hair loss. He has hair in front but not in the back … Nothing has helped. He's only seven years old, but this could be his life without hair." - Parent of a WAS survivor (BMT)

Food allergies and feeding difficulties

Food allergies and feeding difficulties are common symptom for those living with WAS/XLT. Allergies to food and medications mean a life of vigilance. Several described milk protein allergies or allergic colitis, which made breastfeeding impossible and required parents to buy expensive formulas. Some children even had to have feeding tubes to ensure adequate nutrition, and feeding difficulties can persist for years after transplant/gene therapy.

"One of the symptoms not discussed as often is the feeding issues associated with Wiskott. My son had a very difficult time nursing, and would scream with discomfort, which was thought to be acid reflux. He couldn't take enough to maintain his growth, and had an NG tube by 3 months of age. He eventually got a g-tube, and had to be taught to eat between age one and three. It took years before he was able to eat normally- and still takes longer than everyone else to finish his meals." - Parent of a 12- year-old WAS survivor (GT)

"[Our son] spent the first three months of his life screaming for four hours every night because of the belly pain. [We didn't know that our son suffered from a milk protein allergy that took some

time to diagnose]. It was awful for him, but also just about killed us." - Parent of two WAS survivors (BMT)

"*He has allergies to milk, egg, cheese, seafood, and wheat. So it's difficult to find foods to eat."* – Parent of a WAS survivor (GT)

Lymphoma or leukemia

There is an increased risk of blood cancers in WAS/XLT and can occasionally happen after BMT as well.

"We had been told for years that Wiskott patients who lived into or beyond their teens face a 1-in-4 chance of developing cancer. In my mid-40s I developed non-Hodgkin's large B-cell lymphoma, which first manifested itself as being short of breath with simple activities." - WAS survivor (BMT), and family member of others living with WAS

"My brother discovered he had a recurrence of B-cell lymphoma. … He passed away less than a year after finding out he had a recurrence. He left behind his wife, and his three children under the age of five." - Sibling of a brother who passed from complications of B cell lymphoma

"My brother died at the age of 51 from an infection due to a recurrence of lymphoma, which he had originally at the age of 22." – Sibling of a brother living with WAS

Bloody diarrhea

For many parents, bloody diarrhea was an early, horrifying symptom of WAS/XLT.

"*We began noticing small amounts of blood in his stool. [Our son] was breastfed and getting milk-based formula supplements and switching to a 100% soy-based formula did not remedy the symptoms*."- Parent of a son who passed at seven-and-a-half months following BMT

Kidney disease (IgA nephropathy, recurrent infections)

Kidney disease is a symptom of WAS/XLT and can also result from BMT. IgA nephropathy is an autoimmune complication of WAS. Manifestations can include blood and protein in the urine, increasing creatinine levels, recurrent infections, progressively worsening renal function eventually leading to renal failure. While experienced by relatively few, kidney disease can be life threatening. Thrombocytopenia makes it challenging to get diagnosed, receive dialysis or obtain a renal transplant.

"Two years ago … he had bleeding in the kidneys, so he had to go to hospital and then it really deteriorated quickly. He's now down only to 10% of renal function. And you see in combination with the low platelets, it's almost impossible to get a kidney transplant or even to get other medication. We are really facing the problem that now at the age of 53, we have to think about the bone marrow transplant." - Wife of an individual living with WAS who sadly passed away two months after the EL-PFDD from transplant-related complications

Other health concerns not mentioned in the polls

Individuals living with WAS/XLT experience a large number of other health concerns including fatigue, pain, slow healing after injuries, mental health challenges. Many also described delayed development secondary to isolation and multiple hospitalizations.

"*Best days, fatigue is a challenge. Worst days, mental health problems make [me] want to isolate and stay in bed."* - Individual living with XLT

"We are dealing with late effects from chemotherapy in terms of impact on learning and executive functioning. We have also navigated significant anxiety based on medical trauma." - Parent of a WAS survivor (BMT)

Many WAS/XLT carriers also experience WAS-related health concerns, as well as guilt and worry about passing the gene to their children

X-linked disease were only thought to affect males, however the impacts on female carriers are now beginning to be recognized. During the EL-PFDD many carriers described symptoms including thrombocytopenia, autoimmunity, infections, eczema, and anxiety. One described symptoms similar to lupus.

"I'm a female carrier so, I'm only really impacted by low platelets. I do have anxiety but I'm not sure if that's related to being a WAS carrier." – WAS carrier and sibling of a brother living with WAS/XLT

"*Bad days I have nose bleeds and bruising."* – WAS carrier and parent of a 15-year-old WAS survivor (BMT)

During the meeting and in the comments, a number of carriers described their guilt and worry about passing the WAS/XLT gene variant to their children.

"We found out that I, his grandmother, carried the gene that was passed on to my daughter, then as a result my grandson has Wiskott-Aldrich Syndrome. I felt awful having found out I was a carrier." – WAS carrier and grandmother of a 25-year-old WAS survivor (two BMT)

One described her, *"guilt of passing on a life-long illness to my son. Because of me he cannot live his life to the fullest."* – WAS carrier and parent of a child living with WAS

Worries include, *"financial costs for me if I do give birth to a child with WAS."* – WAS carrier and sibling of a brother living with WAS/XLT

A major impact of WAS/XLT is a life of terrifying worry and fear: for patients and for their families

When asked to select their **top three worries** about their or their loved one's condition in the future patients, parents, and family members selected **developing cancer and autoimmune disease as top worries, followed by premature death** (poll results are in **Appendix 4, Q3**).

Worries about the survival and wellbeing of their loved ones living with WAS/XLT was a consistent theme of the WAS/XLT EL-PFDD meeting. Patients and parents worry about the possible onset of symptoms of the known life-threatening complications associated with WAS/XLT, the impacts of the disease and the long-term consequences of treatment.

"I find I am very over-protective of him to the point where I suffer with a lot of anxiety with regards to him hurting himself. … I try to ensure I don't project my worry onto him and allow him to do as much as safely possible, but I am worried how his school life will be affected and the

activities he will be able to participate in. … Because it is such a rare condition, it's difficult for people to truly understand the distress it can cause." - Parent of a son living with WAS/XLT

The WAS/XLT-related worries are listed here below in descending order as selected in the polls, and then followed by a long list of other worries mentioned during the meeting and in the submitted comments.

Worries about developing cancer, autoimmune disease and worries about XLT converting to classic WAS

Malignancy and autoimmune disease are risks for every individual living with WAS. For those living with XLT, this is a particularly strong worry; individuals living with XLT who develop autoimmune disease or malignancy immediately convert to WAS score 5 with all the unfavorable implications of such a transition.

"The chances of developing cancer… there are many fears that we have and that [we face on a daily basis]." - Parent of an eight-year-old WAS survivor (two BMTs)

"We were living on a knife edge for six and a half years before [our son] had a splenectomy. And even though now he has so much better quality of life, there's still the anxieties: he could still develop WAS, he could still get autoimmunity, he could still get leukemia or lymphoma. And it's trying to park that at the back of your mind and focus on, 'he's happy and he's healthy now'. So that's what we try to do." - Parent of a son living with XLT

"*The worry of his XLT becoming classic [WAS], lack of treatment options*." - Parent of a boy living with XLT

"When he was young, ... we were always afraid that he would fall down, or something happened to him, and today, things are changed more to worries about the future, about autoimmunities, malignancies when he will be older. So, it's a quite different situation through time." - Parent of a 14-year-old son living with XLT

Worries about premature death

Premature death is a reality for those living with WAS/XLT and during the meeting, many individuals spoke about their children and siblings who had passed.

"Both the infection risk and the mental health side of it are the things that burden me the most, and then obviously, that leads to the concern for premature death, right? I've always thought I've been cured and I think largely I can say that, but as I've gotten older I realize it's a little bit more complex than that." - Adult WAS survivor (splenectomy at six months, BMT)

"I'm really afraid of losing him each day. It's not only the kidney failure, but he had three lung infections within the last four months and is always in the hospital, on several medications. I'm really afraid of losing him each day. There is not a single second that I'm relaxed." - Wife of an individual living with WAS who sadly passed away two months after the EL-PFDD from transplant-related complications

"I was seven when my brother received his BMT (1993). … I was consistently worried he was going to die." - Sister of a WAS survivor (BMT)

"One of my worst fears was how I might bring up a child knowing his lifespan was estimated to be not more than 20 years. How do you encourage your son to study, to learn to play the same as the other kids? How do you pretend to be normal knowing that he will not live longer?" – Parent of a WAS survivor (GT)

Worries about mental health

Persistent worry as well as anxiety, depression and trauma can compromise the mental health of loved ones and family members. Many worried about the ability of their children to adapt and socialize, including the mental health of their daughters who were carriers.

"[My worry is about] his feeling that he is different from other kids." - Parent of a WAS survivor (BMT)

"*I worry about the impact of my family. They worried very much, especially through the second lymphoma that prompted the transplant five years ago."* - WAS survivor (BMT), and family member of others living with WAS

"I am concerned for his mental health specifically related to how his children/grandchildren and so on will be affected." - Sister of a WAS survivor (BMT)

"The stress of living with WAS as a single male is much different than living with it with a wife and a daughter and knowing that she is an obligate carrier, that we passed this mental burden on her to decide whether to have IVF or to have to choose between any treatments that are available to her in the future." - Adult WAS survivor (splenectomy at six months, BMT)

Worries about BMT or GT failing

Patients and parents worry about a BMT failing; many parents shared stories about initially successful BMTs which gradually failed and then had to be repeated.

"With mixed chimerism, I fear losing donor cells and becoming symptomatic again*." - WAS survivor (two BMTs)

"His chimerism had dropped to 17% and his platelets around 15 to 20. This was over a long period of 18 months, which I believe is rare. He needed a second transplant."* - Parent of a five-year-old WAS survivor (two BMTs)

"[I worry about], return of symptoms, rejection of the bone marrow transplant."- Family member of a WAS survivor (BMT)

*Chimerism in this context refers to a patient who, following a BMT has blood cells from the donor as well as his own. Over time, the proportion of donor cells can drop, necessitating another transplant.

Worries about future infertility

Fertility can be affected by the harsh conditioning treatments required for BMT and GT. As a result, many patients and their parents are worried about whether they would be able to conceive children.

"I don't have many fears for myself with the exception of never having a child of my own DNA. I am infertile from the BMT." – Adult WAS survivor (BMT)

"Given that he is cured of WAS, our greatest concern going forward for him is infertility." - Family member of a WAS survivor (BMT)

"Infertility is my greatest concern for him. We were told that would most likely be the biggest side effect of his treatment. I would hate for that to be a reason for a relationship to fail in the future for him." - Parent of a 19-year-old WAS survivor (BMT)

Worries about severe bleeding

Worries about severe bleeding, especially brain hemorrhages, are a concern for so many parents and patients. This is closely related to worries about whether or not to have platelet or blood transfusions.

"There's always this underlying fear that he'll get a nose bleed or even if it's a small one, how bad will it be? There's also a lot of worry on injuries at school or just while playing with his friends. … And for fatal accidents, let's just say I force every cell in my body not to think about those." - Parent of an eight-year-old son living with WAS

"My son was having life threatening GI bleeding and eczema. It impacted every aspect of his life- from eating to sleeping and I worried he would get sick or bleed [profusely] before he could get treatment." - Parent of a WAS survivor (BMT)

"Due to [our son's] health being so volatile, especially living with single digit platelets, [my wife] and I, we basically live in fear. Day-to-day, we constantly check in for his bruising and monitor his health whilst keeping our fingers crossed." - Parent of a 10-year-old living with XLT

Worries about making the wrong decision to transplant/not transplant

For those whose children live with XLT, this worry is constant. Parents must weigh whether to subject their child to a high-risk prophylactic procedure perhaps unnecessarily, versus waiting until the child converts to WAS score 5 later in life, when it may be too late for treatment.

"[I worry about] XLT developing into classic and us being too late for a successful BMT. I also worry about doing a BMT unnecessarily. … Best days, we can almost forget about the WAS. Worst days, we are agonizing over the decision to do a BMT or not." - Parent of a boy living with XLT

"As a parent, we lost so much sleep worrying about our decision to postpone a bone marrow transplant, worrying about what [our son] would want if he were old enough to make the choice. There's a part of me actually that wishes he was born with classic WAS, because then the decision would not be mine and the guilt would not be mine. We've spent the last 11 years in a world of waiting, because at any time, infections, autoimmunity, or a malignancy could change [our son] to a classic, and make a bone marrow transplant a necessity, except [our son] would be older with an immune system weakened by infection, autoimmunity, or a malignancy, and the chances of success would be lower." - Parent of a son whose XLT recently converted to classic WAS

> *"His doctors wanted him to go directly into a bone marrow transplant, but we refused at the time because of his XLT diagnosis. Making that BMT decision was very difficult for us. But then, he had a brain bleed, [which forced us to make the decision to have a BMT]. We couldn't risk him having another brain bleed and losing him.* - Parent of an 18-year-old WAS survivor (BMT)

Even parents of children living with WAS, for whom a BMT is necessary for survival, worry about making the decision to transplant.

> "*BMTs saved our boys, but [BMT was] described to us as 'brute force medicine'. It was nearly as risky and terrifying to choose the treatment as it would have been to choose to live with the disease. Only the sure bet that our boys' cases were so severe that they couldn't survive without the BMT made it an easy decision."* - Parent of two WAS survivors (BMT)

> "*Immediately after his diagnosis [at the age of four months], the doctors pressured us in to proceed with a bone marrow transplant. They told me this was the only treatment option and we needed to make a decision quick. [Our son] has no living donor match. The best they could find him was a six out of eight cord blood match to perform the BMT. After researching BMT I made the decision not to go ahead with the transplant."* - Parent of an eight-year-old son living with WAS

> *"We have saved his life, which was always the aim, but for some reason there always seems to be a price to pay. I would pay that price over and over to have my son, so I'm not complaining. What I have noticed as a parent of a Wiskott boy is always expect the unexpected. [Our son] has never followed a plan and when we signed that dotted line as a parent to go ahead with transplant, all you really took in that moment is a life or death. All the rest in between don't sink in and there are so many other roads that bone marrow transplant can take you down that we just don't see or understand as parents."* – Parent of a five-year-old WAS survivor (two BMTs)

Other worries selected in the polls

Other worries selected as a top three worry in the polls reflect both symptoms of the disease and the impacts of therapy. These include worries about **developing life-threatening infections**, **developing graft-vs-host disease (GVHD)**, **financial costs and/or job security, and that relationships will suffer.**

> *"[I worry about] depressed immune function due to splenectomy; worry about not knowing what impact certain bacterial infections may have on the body."* - Parent of a WAS survivor

> "*Something that worries us a lot is the uncertainty of what could happen. The return of graft vs. host to his lungs was a giant red flag that really takes our breath away."* - Parent of an eight-year-old WAS survivor (two BMTs)

> *"It's difficult financially and emotionally. Getting someone to look after him while we work and if we do, the constant worry of if that person can [care for] him well enough or what if something happens. really ill and not being able to overcome it, premature death, mental health."*- Parent of a WAS survivor (GT)

Other worries not selected in the polls: the worry that there is not a definitive treatment for WAS/XLT

This was mentioned throughout the meeting.

"Today, listening to everybody's stories and looking at the photographs, it just brought back such memories and it reignited those anxieties for the future and the worry that there isn't really a definitive treatment option that's going to cure him - God forbid - if we do need it in the future." - Parent of a son living with XLT [

"The lack of uncertainty in having a cure, I think that is the single biggest worry because we don't know what the future holds." - Parent of an adult son diagnosed with XLT who progressed to classic WAS

Life with WAS/XLT is a life of uncertainty and isolation, with every activity of daily living impacted

Patients and caregivers used online polling to choose the **top three specific activities of daily life that are important, but which they are unable to do or struggle with** because of WAS/XLT (poll results are in **Appendix 4, Q4**). These include **playing and eating freely with other children; playing sports, biking, skiing, etc.; going to school like a healthy child.**

The following are key themes that emerged during discussion but were not captured in the polls.

- Living with WAS/XLT is a life of uncertainty, due to emerging symptoms and side effects.
- Living with WAS/XLT is a life of isolation.

"*Until my son was treated, we spent our time isolated at home, only leaving the house for our doctors appointments, IVIG infusions, and when we were hospitalized. He never had a normal baptism, he didn't have a first birthday party, he never went to story time at the library. Only after he got treatment were we able to join the world and learn what normal childhood was about.*" - Parent of a 12- year-old WAS survivor (GT)

Two of the top impacts of WAS/XLT mentioned during the meeting include impacts on the entire family and much time spent in the hospital. These two impacts were not included as poll response options, but are listed below and then followed by the poll responses and illustrated with patient quotes.

WAS/XLT profoundly impacts the entire family

Although this was not a poll response, there were so many heartbreaking patient comments about the impact of WAS/XLT. Many described the stress, grief, and trauma of watching a loved one suffer, the negative effects on siblings and family dynamics, cancelled vacations and even divorces.

"*Having a sibling with a possibly terminal illness was incredibly traumatic and had long-term serious effects on my own mental health. … His immunocompromised status was also part of why my parents chose to homeschool me and my younger siblings. That resulted in severe social isolation during key developmental periods of my own life, which resulted in me becoming an adult with reduced social capabilities and holes in my own education*." - Sibling of a WAS survivor (BMT)

"Due to experiencing the pain, the heartache and the stress from doing whatever is possible to save your child …The toll of [our son] being diagnosed with XLT and then needing and receiving lifesaving treatments in the hospital, multiple times of extended periods, has not only been

exhausting for our family, but has also been detrimental to our health and our careers." - Parent of a 10-year-old living with XLT

"[Our son's] death has negatively affected my life, and that of his mother. We are no longer together." - Parent of a son who passed at seven-and-a-half months following BMT

Much time is spent in the hospital

Frequent and extended hospital stays were mentioned throughout the meeting, but not captured in polls. Hospital visits are required for acute care: to stop bleeding, to monitor for brain hemorrhage, for infection control. Patients require many appointments for blood draws for platelet checks, monitoring and routine treatments such as IVIG infusions. Hospitalization intensifies feelings of isolation and add to parents' anxieties.

"We didn't know he was born with such a complex rare blood disease, let alone a disease that could kill him, a disease that would cause his brain to bleed, a disease that would need such intense treatment. Constant hospital admissions for weeks or months at a time. Constant outpatient visits, constant doctor's visits, a constant life flipped upside down and trying to figure out what was next." - Parent of a WAS survivor (BMT)

"When my brother was four, he had a small cut on his finger that quickly turned into an infection that required hospitalization for weeks. My mother tells a story of spending every major holiday in the hospital with my brother when he was a young person." – Sibling of a brother with WAS who passed from complications of B cell lymphoma

"What impacts us the most are the hospitalizations. …The hospital implies treatments and therapies, relationships with unknown people who must be trusted, but, above all, it involves separation from the family unit and entry into a different environment. When it comes to children, all this influences emotional, cognitive, affective, and relational development, also leading to changes in the image of oneself and one's body." - Parent of two WAS survivors (GT and BMT)

Playing and eating freely with other children

Being unable to play, eat and socialize freely with other children was the top selected impact of WAS/XLT in the polls. Many parents try to balance being vigilant about infection, bleeding and allergy risks and permitting their child to have a normal childhood. Many described how isolation during early childhood created a sense of being abnormal and can lead to social and emotional difficulties later in life.

"*He cannot play with other children. He cannot socialize because of the risk of infection. He cannot play in public spaces or ride a bicycle."* – Parent of a WAS survivor (BMT)

"*Before transplants, my son was pretty much isolated from the world, so he didn't really get to do as much as what other children did. When he was able to participate, he was not able to participate fully like the other children. So, I'd seen that that made his mood very, very sad, his attitude would always change. He was very angry, unhappy*." - Parent of a 12-year-old WAS survivor (BMT)

"I could not play with other kids as a child and I believe that severely hurt my social development. I was always told that I was very mature for my age, which I viewed as a compliment at the time. But now I see it being different." - WAS survivor (BMT)

"There are activities that are important to them but at the same time risky due to low platelets such as going to school, playing with other children, playing a sport, but as a mother I sometimes prefer to take risks and make them happy and face these dangers together." - Parent of two WAS survivors (GT and BMT)

Playing sports, biking, skiing, etc.

Parents, siblings, and patients described the many activities that they were unable to do for fear of injury including combat sports like martial arts or boxing, sports that could lead to a collision like rugby, soccer, football, skating, skateboarding, sledding, or biking. Some found that even swimming is a challenge. Some described how they adapted to lower-risk, non-contact sports like tennis and golf, and activities like chess and scrabble. Even hiking can be a problem, as the areas can be remote with connectivity challenges, lack of immediate access to major medical centers, and tick-borne infections can be lethal, especially for splenectomized children.

"We kept our son from engaging in typical boy activities like riding a bike and swinging on a swing for fear of traumatic injury and internal bleeding." - Parent of a WAS survivor (BMT) from the US

"I try not to keep him too bubbled up, but the reality is that there are many sports and activities I can never allow him to play. Hockey, baseball, football, rugby, downhill skiing to name a few. It kills me to say no when he asks me to play these things with his friends. We live in a cold climate. Skiing and skating are a huge part of our culture, and yet so very dangerous. I've given up skiing myself so that I can be with him while the rest of our family goes. It breaks my heart." - Parent of an eight-year-old son living with WAS

"*He couldn't swim in chlorinated pools, because it would burn his skin. Once while playing in a lake with his cousins, he wouldn't go into the water past his groin, because it burned when it was wet. This devastated him, because among his cousins, he was the oldest and the best swimmer. He was embarrassed and sad about not being able to take advantage of water with his family, due to his eczema*." - Parent of a 13-year-old son XLT survivor (BMT)

Going to school like a healthy child

Many children are unable to consistently attend school due to illness, vaccination status, treatments or other reasons. Some described how they homeschooled their children initially and some described how the lack of social conditioning and stigma affected their children later. Several described how when their children finally attended school, they were often stigmatized because of their helmets and their appearance, including bruises and eczema.

"He couldn't attend any type of school or daycare with his immune system being so poor. … Anybody could get my son critically sick, not to mention we were operating in a pandemic." Parent of a WAS survivor (GT)

"*[Our son] wasn't allowed to go to preschool until he had gotten his re-vaccination program almost completed, and was four at that point. He wasn't really very socialized and it took a couple years to sort that out*." - Parent of a 10-year-old WAS survivor (BMT)

"He was wearing helmets when he was young and then when he started going to elementary school, he was called 'the boy with the helmet'." - Parent of a son diagnosed with XLT who progressed to classic WAS

"He had to be homeschooled when young due to the risk of falls at home and gradually integrated into school as he got older and more responsible."- Sibling of a brother diagnosed with XLT who progressed to classic WAS

Family get togethers/socializing

Many mentioned being unable to attend family gatherings and even important family funerals because they cannot travel.

Because he was so prone to infections, one parent isolated her son from family members who were sick including his grandmother or his father, his aunts and his uncles. *"He didn't like and he didn't understand why we were doing that. So, that was one of the biggest things for him going through Wiskott, besides getting treatment for his infections and stuff like that."* - Parent of a 12-year-old WAS survivor (BMT)

"For literally the first 12, 13 years of his life, we never went out to eat. And it was really several years when he was a teenager, when we were finally able to go out to a restaurant where the owner was very, very careful about allergies and we had the pleasure of eating out. So for our family, eating out was not an option. It was literally mom making extremely careful curated food so things wouldn't get worse for our son." - Parent of an adult diagnosed with XLT who progressed to classic WAS

"As a family, we were limited to being able take our son out to family gatherings, or attending church as we couldn't take any risk of him getting sick." - Parent of a WAS survivor (GT)

Deciding to have children

The decision to pass the WAS/XLT gene to a child is a very hard one for patients and carriers alike. Many have decided to not have children, while others have had in vitro fertilization (IVF) with a pre-implantation genetic diagnosis (PGD), to ensure that their child does not have the gene variant.

"Another impact on our family is we absolutely decided to not have any more children. We wanted two, we had one with Wiskott-Aldrich. Well, you hit the jackpot the first time, maybe not try that again. So, we are one and done for that reason." - Parent of a 10-year-old WAS survivor (BMT)

"We also decided only to have one child and we were hoping to get a boy, which would've been safe. But we got a daughter, she's perfect, but she's a carrier and she will have to make the decision to have children or not. ...Maybe I will never be a grandma." - Wife of an individual living with WAS who sadly passed away two months after the EL-PFDD from transplant-related complications

"My two daughters are carriers of WAS and both have been pregnant with males that were diagnosed with WAS in utero. They both chose termination as BMT is not offered in our province. It has been very stressful knowing that IVF is the only way to carry a healthy child and the cost are more than most families can afford."- Parent of two WAS carriers

Balancing work and health

Adults living with WAS/XLT often have to make compromises between their work and their health. Some had to make a decision to live close to caregivers at the expense of employment.

"I'm a physician, and [WAS] does limit me in some ways. There are patients that I have chosen not to see because I know that they have an infection that might be catastrophic to me if I acquire it." - Adult WAS survivor (splenectomy at six months, BMT)

"I'm no longer able to work because the constant sinus infections made it impossible. I'm on SSDI (Social Security Disability Insurance) and am single, so my limited finances make going to hockey games, out with friends, dating, etc. a thing of the past. The constant fatigue and pain leave me exhausted most of the time. I require a lot of sleep just to function. I used to be a very active person, but now I really don't do much of anything." - Individual living with XLT

"[My brother] is a successful guy. He's an engineer. He has a great job. He's independent. …He cannot take on some more physical projects at his job due to injury risk, he has to live somewhat close to my parents in a larger apartment without roommates because multiple times a year, he has medical events that require one of them to come take care of him because he can't manage alone." - Sibling of a brother diagnosed with XLT who progressed to classic WAS

Parents and caregivers often have to make hard choices regarding their employment, including giving up careers to care for their children.

"*Prior to treatment, our life was halted. [My son] was isolated and fragile. He couldn't be around other children so school or daycare wasn't an option, making me unemployed."* - Parent of a WAS survivor (GT)

"Together with my husband we are working, but it is connected with many absences at work so our effectiveness is not as good as it could be."- Parent of a WAS survivor (two BMTs)

"I had to self-employ. …Due to multiple medical appointments and / or emergencies with [our son], my husband has lost many hours of work. As parents who have children with WAS, it is really very difficult to work or dispose of our time since there is no schedule or something to infer when our child is going to get sick or how long hospitalizations or visits to the emergency room will last." - Parent of an eight-year-old WAS survivor (two BMTs)

Other WAS/XLT impacts

Planning safe vacations, sleep issues and **eating out (food allergies)** were all impacts of WAS/XLT that were selected in the polls and are described below with a few selected quotes.

"We have to plan vacations around his platelets. He can never be too far from a hospital that can deal with a rare disease. …If he gets sick before a trip, we have to cancel (and have done so frequently.)" - Sibling of a brother diagnosed with XLT who progressed to classic WAS

> *"For sure we are not able to fully use the beauty of life. We cannot travel as much as we would like to."* - Parent of a WAS survivor (two BMTs)

Additional impacts not captured in the polls but mentioned throughout the meeting include **requirements for a high level of care** and **relationship impacts**.

> *"The long-term effects of Wiskott have affected almost every relationship of mine from my parents to my sister in almost any and every one of my partners."* He described panic attacks, flashbacks. *"Wiskott and the subsequent symptoms are both such a large part of me and who I am that it feels dishonest to not come forward with these things when they happen*." - 29-year-old WAS survivor (two BMTs)

Topic 2: Current and Future Treatments for WAS and XLT

During the EL-PFDD meeting, patients and caregivers used online polling to first select all the WAS/XLT-related medications and medical treatments as well as other approaches that they or their loved one had used (currently or previously) to treat symptoms associated with WAS/XLT (poll results are in **Appendix 4, Q5 & Q6**).

The following are the key themes that emerged during discussion but not captured in the polls.

- Recommended treatments for XLT and WAS can differ. This creates challenges for families who are often unsure of the best treatment approaches.
- Families who underwent gene therapy (GT) reported much success. Although the treatment procedure is not easy, they were satisfied with the treatment and experienced less after-effects than with BMT
- BMT often feels like a trade-off for families, who often feel that they have traded one set of health concerns and worries for a different set.

Definitive treatments for WAS/XLT include gene therapy (GT) and bone marrow transplant (BMT), but there are downsides/limitations for both

Neither are FDA approved.

Gene Therapy (GT) for WAS

Experimental gene therapy for WAS patients was available on a limited basis for the last decade and has demonstrated promising results with a high survival rate. Gene therapy uses a patient's own genetically modified stem cells, so there is no need to find a matched donor, which is beneficial for those who are minorities or mixed ethnicity and are unlikely to find a matched donor. It is also a good option for older patients and those too ill to undergo BMT. Gene therapy gives the body the ability to produce the missing protein, and although the platelets may not always get up to normal levels, the risk of serious bleeding, infections, and autoimmunity are reduced.

Many families described positive gene therapy outcomes.

> *"My experience with gene therapy transformed a parent's worst nightmare, the threat to my child's health, to the greatest gift I could ever receive, a new chance for a healthy life for him."* Her son is no longer at risk for severe bleeding, his eczema has cleared and he no longer needs antibody infusions. *"Best of all, we were allowed to start interacting with the world. No more living in isolation. … Now [our son] does well in school. He snowboards and plays tennis. He plays the drums, piano, and most recently the cello. [Our son] says that when he grows up, he wants to be a doctor scientist."* – Parent of a 12- year-old WAS survivor (GT)
>
> *"Symptoms changed with the gene therapy. There is no more bleedings, infections,* eczema...*And now we are almost having a normal life. …My children go to school and play. They have no bleeding, no eczema, no infections."*– Parent of twin WAS survivors (GT)
>
> "*The treatment was a success. My boy is leading a normal life at the moment. The viruses pass, he had vaccinations, the platelets are at a safe level. Gene therapy made the difference*. …*I've*

been through the worst, it's been more than 10 years since the treatment and the boy is getting better. I sometimes have thoughts about GT's effectiveness diminishing over time, but those thoughts quickly disappear when I look at him and see that he's a normal kid. - Parent of a WAS survivor (GT)

Downsides of gene therapy

The biggest downside of gene therapy is that clinical trials have been discontinued due to a lack of commercial investment**.** When they were available, patients who had a perfect bone marrow match were ineligible and except in certain circumstances, those living with XLT were often not eligible as their disease was considered too mild for the risks of an experimental treatment. Other downsides include an arduous regimen, lots of time in the hospital before, during and after the procedure, high treatment cost, it takes weeks and months to work, patients need to return for checkups each year to the clinical trial center which, for many patients is in another country or another continent.

"Apart from the fact that all studies on GT have been discontinued, it is very unfortunate that individuals with a perfect [bone marrow] match are not admitted. GT should be available for every patient." - Wife of an individual living with WAS who sadly passed away two months after the EL-PFDD from transplant-related complications

"In the case of gene therapy, after the treatment, it took a while before we could give up the platelet supplement, I think about 6 months and the immunoglobulin supplement over one year. But it was worth the wait. Indeed, at the last monitoring visit, some values in the blood are not quite normal, but physically, the child looks very good, he leads a normal life for his age." - Parent of a WAS survivor (GT)

"*I am very happy that my son was able to receive gene therapy. Now he has to miss school every year for a follow-up examination in Italy. Still, I think that the benefits of receiving treatment are greater."* - Parent of a WAS survivor (GT)

"*We had two weeks to drop everything and move to Italy for the next five months. We spent the next two months there preparing for the procedure, doing baseline tests and scans, getting admitted to the hospital multiple times."* After the gene therapy procedure. "*It was a complicated and difficult hospital course. We had to live in an isolation ward for about eight weeks. The language barrier and very different hospital policies made things even more challenging. ... [Our son] was hooked up to multiple lines and tubes and he was at an age where he was supposed to be crawling and exploring the world, not sitting in a crib.* … He lost all his hair after the chemotherapy that was part of his regimen and felt awful a lot of the time." - Parent of a 12- year-old WAS survivor (GT)

Bone marrow transplant (BMT) for WAS

BMT is a complex procedure requiring intensive chemotherapy conditioning. A hematopoietic compatible stem cell donor is required and can be a fully matched sibling or a family member, but is most often an unrelated donor. The procedure is preferably done before the age of five years to ensure the best outcomes. Without a BMT, individuals living with WAS do not survive past their teen years.

"At six months old, [our son had] a bone marrow transplant. This was a medical emergency due to severe bleeding in his gut. He needed this to survive." - Parent of a five-year-old WAS survivor (two BMTs)

Prior to BMT, one infant experienced an intracranial hemorrhage. *"They had to revive him twice and they had to put the drain in to try and relieve the pressure on his brain. …His only hope was the transplant … so that he could start recovery. …It was his only option at that point or else he wouldn't have lived."* – Parent of a WAS survivor (BMT)

"[Our son's] WAS was very severe. BMT was his only option. … We were able to find a naive umbilical cord for a stem cell transplant. We were blessed to have him go through a successful transplant and he is now a healthy 15-year-old."- Parent of a 15-year-old WAS survivor (BMT)

Many experienced positive outcomes including survival and a reduction of symptoms.

"My experimental transplant with reduced conditioning and post-transplant cyclophosphamide went very well. No GVHD, mild infections, 100% donor. I happen to be the oldest-ever WAS transplant by at least 25 years. My only WAS-dedicated medicine today is my prophylactic penicillin." - WAS survivor (BMT), and family member of others living with WAS

"*Thankfully after my bone marrow transplant, things actually went pretty smoothly for me, thank God. I had my regular follow ups and checkups for the first several months up to a year. I was lucky enough that both of my sisters were a perfect match for me and so my oldest was my donor. So presently, penicillin is really the only thing that I am taking currently for treatment*." - 35-year-old WAS survivor (splenectomy and BMT)

"We were extremely fortunate to have a third child, a son, who was a perfect match for a bone marrow transplant (BMT). Our WAS patient had a successful BMT and is now living a relatively normal life." - Parent of a WAS survivor (BMT)

Success is not guaranteed and some patients die.

"Our son began his month-long BMT procedure. We were aware that it was an extremely dangerous procedure, and the outcome could not be guaranteed. …After his transplant, our son had high fevers which would not go down. … His sickness progressed, and he had difficulty breathing, and his oxygen levels dropped. He was moved to the pediatric intensive care unit, where his health continued to decline. … We were terrified that we would lose him. … Sadly, [our son] passed away on May 16th, 2013. He was only seven and a half months old. We were devastated." - Parent of a son who passed at seven-and-a-half months following BMT

BMT has many downsides.

BMT is a complex procedure requiring intensive chemotherapy conditioning. It can take a while for platelet levels to stabilize, and some still require medications and ongoing monitoring for platelets and chimerism (the relative proportion of blood cells from a donor and the recipient).

"Having a transplant is not like doing a simple operation. There are risks to run that are so scary and moreover it is a long and painful difficult path for the whole family." - Parent of two WAS survivors (GT and BMT)

"After 2 years of transplantation, we are still taking immunosuppression, hormones, and thyroid hormones." - Family member of a WAS survivor (BMT)

"The BMT treatment was, now 15 years later, very effective in mitigating most of the symptoms and acute health risks of WAS. However, the BMT was very arduous for about six years. First, it took some time to secure a good match (during which he was at-risk). Second, the treatment itself was life-threatening, first leaving him immuno-suppressed and occasionally suffering from severe infections requiring emergency hospitalization." - Parent of a WAS survivor (BMT)

Despite BMT success, some patients experience residual trauma and PTSD.

"He is not the carefree child now that he was pre BMT." - Parent of a WAS survivor (BMT)

"I think there's mental health issues with everything that's happened. Every time to this day, I say at some point, 'We have to talk about it.' He just says, 'I don't want to know,' and walks away. It's very difficult." - Parent of a WAS survivor (BMT)

"[My son] suffers badly from PTSD due to the bone marrow transplant. He remembers the pain. He remembers all of the medications being put into his mouth. He remembers the syringes going near his face. He remembers being poked constantly as if he were a human pin cushion. … [My son] is five years post bone marrow transplant and is still very much so traumatized." - Parent of a WAS survivor (BMT)

Finding a matched donor can be challenging for minorities or those with mixed ancestry as minorities are underrepresented in national and international bone marrow registries. Patients must be in adequate health before they receive a BMT. Unfortunately, those who don't have a BMT have few other treatment options.

One family used *in-vitro* fertilization to select a perfect match and collected his cord blood. "*The process was long, exhausting and extremely costly one."* Despite extending their family with a perfect match for their XLT child*, "at present, we cannot subject him to the risk involved around a BMT pre and post preparation.*" - Parent of a 10-year-old living with XLT

Denied a BMT due to the lack of a matched donor, *"Now the situation is just about management. He sometimes bleeds everyday from the nose. It continues for months like this; even he bleeds for 3-5 hours [at a time]."* - Parent of a son living with WAS

In addition, BMT can potentially fail and must be redone (page 41). The many other significant BMT side effects are described later in the report (page 40).

Bone marrow transplant (BMT) for XLT

BMT is typically not recommended for XLT unless there is a matched sibling donor. This situation creates a lot of worry and difficult decision-making for XLT families, as was described in a previous section (page 18).

"My son was diagnosed at 4 months with WAS. After getting a second opinion they said he has XLT, but after contracting HSV (herpes simplex virus) while on antiviral medication we decided to

go for a stem cell transplant. Even though it was rough we have not looked back. Our son is doing amazing 5 months post transplant." - Parent of a XLT survivor (BMT)

"With an XLT diagnosis, without a 10+ matched related donor, BMT was not recommended until it was very late in the disease." - Parent of an XLT survivor (BMT)

"XLT cases are routinely not recommended to pursue a bone marrow transplant, unless there is a fully matched sibling. Neither my brother nor my son achieved that." – Parent of a 13-year-old living with XLT

Some were denied the opportunity.

"We were looking for possible treatments for XLT and we were encouraged to go down the path of a bone marrow transplant. … After searching both the Australian and international database, it was clear that the closest match that we could find was a six out of 10. Our doctors explained that research showed that XLT children receiving a BMT from a six out of 10 match was not a viable and not a sensible pathway to explore. …After receiving this news regarding an irrelevant match, we found ourselves at another dead end. At the time, gene therapy trials were not available for patients with XLT. We knew that in reality a BMT was our only hope for our son." - Parent of a 10-year-old living with XLT

The downsides of BMT for XLT are the same as BMT for WAS and are not described here again.

Patients try many different medications and medical treatments to address WAS/XLT symptoms, including platelet and blood transfusions, immunoglobulin replacement therapy, steroids, and prophylactic antibiotics

Individuals with WAS and XLT try many other treatments to manage symptoms (poll results are in **Appendix 4, Q5**). Poll respondents indicated that they each used an average of 5.2 different medications and medical treatments. Some patients and families have tried every single treatment available.

"*I found myself checking most of those boxes that were presented in the polling questions*." - Parent/caregiver of a WAS survivor (BMT)

Platelet and blood transfusion for XLT and WAS

Platelet or blood transfusion was the top medical therapy selected in the polls. This is one of the only therapies for patients living with XLT and is also used to treat WAS patients prior to BMT. Many reported receiving many transfusions.

"During his hospital stay, he received over 20 platelet blood and albumin transfusions. …It was devastating to watch our infant child in this state as we clung onto his life as the weeks passed." - Parent of a 10-year-old living with XLT

"A bone marrow transplant was urgently needed and his only option as his body was destroying platelets and red blood cells quickly. [Our son] survived off of red blood cells and platelet transfusions until it was time for his transplant." - Parent of a WAS survivor (BMT)

"He had over 60 blood or platelet transfusions in his first nine years of life. …He became the poster child for Florida Blood Services and American Blood Centers for a little while so that we could help give back and promote blood and platelet donation." - Parent of an adult WAS survivor (two BMTs)

Downsides of platelet and blood transfusions.

Parents are forced to make difficult decisions, as platelet transfusions can lead to the development of autoantibodies. This can reduce the effectiveness of future transfusions, cause a reaction during a future transfusion and may compromise future treatments including BMT. For this reason, knowledgeable physicians are cautious and try to avoid platelet transfusions even when platelet counts are very low unless there is a significant bleed.

"There's a constant discussion about if we should get platelets or not, because we understand that platelets as an emergency should be given if he has very low platelets. On the other hand, if he's going to have a [BMT] later, this may create problems with antibodies that may have developed. " - Parent of a 14-year-old son living with XLT

Immunoglobulin replacement therapy for WAS

Immunoglobulin replacement therapy (IVIG) is a treatment for many individuals living with WAS, and in some XLT patients. Different types of antibodies can be used to address different symptoms. Intravenous immunoglobulin (IVIG) and subcutaneous immunoglobulin (SCIG) are composed of normal human immunoglobulins, administered prophylactically to fight infections in patients who are immunocompromised due to WAS/XLT, BMT conditioning or splenectomy. Many reported that they worked very well. Recombinant monoclonal antibodies such as Remicade (infliximab) block the activity of inflammatory molecules, reducing inflammation and may be used for some autoimmune conditions.

"Infections were constant prior to transplant. My wife would take him as often as twice a week for treatment." - Parent of a 19-year-old WAS survivor (BMT)

"My son had monthly infusions of Sandogloblulin as a therapy to prevent infections before and for a while after his BMT." - Parent of a WAS survivor (BMT)

"IVIG, prophylactic antibiotics…for the most part, they manage his XLT." - Parent of a boy living with XLT

IVIG and SCIG downsides.

Although widely used, IVIG can require time for administration, can incur significant costs and some feel poorly after administration. In some cases, post-IVIG reactions tip the balance towards pursuing a BMT.

"[Our son] was having massive reactions when he was having the IVIG. We basically came to the conclusion that we had no choice, but to go with BMT." -Parent of a WAS survivor (BMT) from Australia

"Monthly IV immunoglobulin therapy meant missed work, missed school and life, lots of needles. Switching to weekly SubQ immunoglobulin at home was better, but it comes with its own challenges. [Our son] has missed out on being able to just be a kid." - Parent of a son whose XLT recently converted to classic WAS

After a splenectomy, "*I went on monthly IVIG for 20 plus years, and while it reduced the incidence of the dangerous septic spells, ongoing insurance authorization hassles and thousands of dollars in deductibles remain a perennial burden to me and my family."* – WAS survivor (BMT), and family member of others living with WAS

Steroids for WAS and XLT

Oral steroids are used occasionally to increase platelet counts, to treat autoimmune conditions and to treat GvHD. Topical steroids are used for eczema as well as skin GVHD. While steroids are effective, they can have serious side effects.

"Whenever the skin got that bad and they gave him steroids. The steroid cream, that was the most effective. …It's something that you question you don't want them on, but it was actually the most effective." - Parent of a three-year-old WAS survivor (GT)

Many years post-BMT, *"He currently still has problems with skin graft-versus-host disease... If he is in the sunshine for an extended amount of time, his GvHD flares up and then we have to go back to applying the topical steroids again."* - Parent of an 18-year-old WAS survivor (BMT)

Steroid downsides.

Steroids downsides include immunosuppression, bone loss, short stature, and dependency, as well as long term side effects such as adrenal insufficiency.

"We would cover him with so much steroids, eventually he went into adrenal insufficiency where his body stopped making its own steroids." - Parent of a WAS survivor (BMT)

Prophylactic antibiotics for WAS and XLT

Prophylactic antibiotics are used to prevent infections in anyone who is immune compromised, due to WAS/XLT, BMT conditioning or splenectomy. They are generally effective and are necessary in conditions such as splenectomy. However, they can cause the generation of antibiotic-resistant pathogens that can be difficult to treat.

"*My son takes prophylactic antibiotics. We are very conscious about who he is around and on constant high alert if he gets ill."* - Parent of a child living with WAS

"Presently, penicillin is really the only thing that I am taking currently for treatment. … I've had no real reactions or negative adverse effects from being on penicillin for this many years." – 35-year-old WAS survivor (splenectomy and BMT)

"No treatment except antibiotic prophylaxis for splenectomy." - Parent of a son living with XLT from Ireland

Immunosuppressive medications for WAS survivors

Immunosuppressant medications are used to prevent autoimmune diseases including GVHD after transplant. An obvious downside is that they cause patients to be even more immunocompromised.

"[Our son was on] immunosuppressants for almost two years after transplant because of his skin GVHD, which forced us to isolate for a lot longer than we had hoped for. So, a difficult journey." - Parent of a WAS survivor (BMT)

Anti-rejection drugs for WAS survivors (BMT)

Antirejection medications can be used at the time of transplant, as well as longer term, after a BMT. A downside is that anti-rejection drugs, like many other oral medications, can be difficult to administer to small children.

> *"[Our son's pre-BMT] chemotherapy regimen consisted of fludarabine, Campath and busulphan." After his BMT, he experienced skin GVHD. [Our son] was on immunosuppressants for his rash for almost two years. It took a very long time to wean him off the medication."* - Parent of a WAS survivor (BMT)

Medications to prevent bleeds (Amicar/Eltrombopag/Romiplostin) for WAS and XLT

Some families have tried many types of medications to stop the bleeding, particularly nose bleeds. This includes thrombopoietin mimetic drugs (eltrombopag, romiplostim, oprelvekin) to improve platelet counts, as well as antifibrinolytic medications (tranexamic acid, aminocaproic acid) to help control bleeding. The downsides are that they do not always work well, they are not approved in all jurisdictions and long-term effects in WAS and XLT patients have not been well studied.

> *[Our son] has very intense nose bleeds. We did, thanks to Sumathi, fight for trying eltrombopag. that this is not an approved treatment at the moment and definitely not in Canada. Unfortunately, we don't really think it's helping at all. He still continues to bleed. We just basically sit around and wait for the next one. We go to the hospital, they give platelet transfusions and that's it."* - Parent of an eight-year-old son living with WAS

> *"Presently, [our son] is taking eltrombopag. …. If he suffers with substantial bruising or a fall he will have a short course of tranexamic acid for 2-3 days."* - Parent of a son living with WAS/XLT

> *"Received Neumega daily to stimulate platelet counts but that stopped working and monthly IVIG infusions stopped working. "*- WAS survivor (two BMTs) living with mixed chimerism

Not currently using medications/lifestyle changes: post GT, post BMT and for XLT

While some patients who undergo BMT are able to be off medications completely in a few years, many need medications and or lifestyle changes to deal with complications, some even a decade after. Thus far, patients who undergo gene therapy seem to have lesser need for medications a few years out. XLT is often managed with lifestyle changes such as living with extreme caution to avoid any activity that causes exposure to infections or potential bleeding.

> After XLT diagnoses, *"Although [our son's] platelets were extremely low, the bleeding could be managed with lifestyle changes."* - Parent of a son whose XLT recently converted to classic WAS

> *"Avoiding any activity that may increase bleeding. Be active in all cases of viral or non viral infections for early identification of the cause and giving the correct treatment (like early testing for influenza and giving Tamiflu etc..)."* - Parent of a 14-year-old son living with XLT

> *"Watching his every step."* - Parent of a child living with WAS

> *"My parents even got rid of most of our furniture since when he was little he could fall off it or bump himself and get a head bleed. Guests sat on the floor in our living room for years."* - Sibling of a brother diagnosed with XLT who progressed to classic WAS

Splenectomy for WAS or XLT

Although this is no longer common, splenectomy may permit platelet survival and decrease the bleeding risk. A downside is that splenectomy further increases the risk for bacterial sepsis and requires very strict compliance with prophylactic antibiotics like daily penicillin.

> *"I did have a splenectomy when I was three years old, about six years before my bone marrow transplant."* – 35-year-old WAS survivor (splenectomy and BMT)

> *"[Our son's] spleen was removed post-transplant as he continued to have low platelets. They now sit in low normal range around 100,000. A miracle jump from around 4-15,000!"* - Parent of a 17-year-old WAS survivor (BMT)

Other medications and medical treatments not captured in the polls

Patients and parents mentioned other medications and medical devices that they had used to manage symptoms.

Medications include immune modulators such as IL-2 for GVHD, thyroid medications, antiviral and anti-fungal medications, selective serotonin reuptake inhibitors (SSRIs) for depression and anxiety, proton pump inhibitors to address vomiting and reflux issues, pain medications including fentanyl for chronic pain, and medications for renal failure.

Medical devices included pain pumps, as well as nasal and gastric tubes for feeding difficulties or for administering essential medications to children.

> *"[Our son] suffered immensely during his transplant and developed severe mucositis. He stopped eating completely and became so malnourished because the pain was so bad. Even with the pain pump, he could not hold in any nutrition at all and eventually needed a feeding tube. [Our son] required 24/7 feedings. To this day, even at age seven, [Our son] has a G-tube and still requires tube feedings*." - Parent of a WAS survivor (BMT)

Individuals living with WAS/XLT use a variety of non-medical modalities to help manage WAS/XLT related symptoms including skin remedies, ice packs to control bleeding and dietary modifications

Meeting attendees used online polling to select everything that they or their loved one used to help manage the symptoms of WAS/XLT, besides medications and treatments. Poll respondents each selected an average of 3.6 response options (poll results are in **Appendix 4, Q6**).

Skin remedies (oatmeal baths, lotions, creams)

This was the top selected option for dealing with both WAS/XLT-related eczema and manifestations of skin graft-versus-host-disease. Many described using skin remedies in combination with topical steroids.

> *"They both had eczema and had to be medicated and rubbed down in Aquaphor several times a day."* - Parent of two WAS survivors (BMT)

> After losing his BMT engraftment, *"He had eczema really bad, so we were using Alpha-Keri oil in the bath. I don't know how I found that, but it seemed to work really well to help with the eczema."* - Parent of an adult WAS survivor (two BMTs)

Skin problems were a big problem after transplant and included skin GVHD. In addition to steroids, "*We would try every adjunct topical cream to go on top of that. He had horrible diaper rash. We would cover him in different Vaseline type products, Aquaphor, Eucerin, and try anything that would work."* -Parent of a WAS survivor (BMT)

After experiencing topical steroid withdrawal, "*We started using lemongrass and calendula for my son's eczema."* - Parent of a WAS survivor (BMT)

One parent even used emu oil. *"I applied it to keep his skin supple so it wouldn't crack and bleed and he'd get infections and lose his skin. …Yes, it helped. I used a lot of other different topicals and the emu oil used with the topical steroid was the most effective."* - Parent of an 18-year-old WAS survivor (BMT)

Ice packs to control bleeding

Many described the using icepacks for nosebleeds, cuts and to reduce bruising. Other solutions included hemostatic sponges to pack the nostrils, humidifiers and nasal ointments. Most of these were *insufficient.*

"Every time he gets even a minor injury (like a small cut or bruise) he usually has to ice it for about 2 days straight, or it gets worse. This level of treatment for such a small injury sometimes made it hard for him to go to school." - Sibling of a brother diagnosed with XLT who progressed to classic WAS

"*[There is] no medicine available to address nosebleeds. This results in very frequent hospital visits, platelet transfusions, and many hours each day spent on managing a heavy nosebleed."* - Parent of a son living with WAS

Dietary modifications (aside from for allergy)

Although dietary modification was the third most selected poll response option, there were very few comments. Several mentioned iron supplements and vitamins.

"I strictly adhere to my medicine protocol as well as utilize vitamins and zinc. Rest is a very important variable. It is necessary to have a plan and to be prudent." - Living with WAS

Support groups, counseling or psychotherapy

Many patients rely on support groups, counseling, or psychotherapy, especially to deal with residual emotional and mental health impacts of early treatment. Some reported mixed success.

"I used to have difficulty with my parents and people who made decisions for me when I was so young. After a lot of therapy and such, I have come to terms with their decisions. … Best days, it is something to be proud of how far I have come, and it gives me pause to think about how grateful I am to be alive and to have survived." - Adult WAS survivor (two BMTs)

"He has had some severe anxiety, separation anxiety, social anxiety, all sorts of things. He went to a whole year with a psychologist for treatment for that. As it is, he still has certain types of separation anxiety." - Parent of a 10-year-old WAS survivor (BMT)

Therapies: physical, occupational, speech and feeding therapies

Physical, occupational, speech and feeding therapies are necessary for children who have spent so much time confined to the hospital. Parents sometimes had to provide these therapies themselves when none were available.

> *"[My son] also deals with speech delay from being in the hospital for so long. He was isolated due to BMT for a very long time and stopped talking. He currently requires speech therapy and occupational therapy as well. He never regained his willingness to eat food after transplant and eventually will need feeding therapy."* - Parent of a WAS survivor (BMT)

> *"In the first half of his life we was fairly isolated due to his condition, he was homeschooled and out of the mainstream. We compensated with some additional educational enrichment Taekwondo training, which helped mitigate his earlier isolation and build his confidence despite being 'different.'"* - Parent of a WAS survivor (BMT)

Additional treatments mentioned in the polls

Patients and parents selected other options including **avoiding scented products**, **CBD**, and **papaya leaves** and **not doing anything to help manage symptoms**. These choices speak to the desperation of WAS/XLT families who are willing to try anything to help stop their child's bleeding. One parent described using papaya leaves, which supposedly increase the platelet counts of patients with dengue fever.

> *"You make sure and clean the leaves properly, wash it with soap and you put a little water and strip leaves and crush it until you get little juices from it. You squeeze it out into a cloth and that green stuff, you drink it."* There is not published evidence to support this approach. *"All of the doctors that I spoke to thus far about it, they told me it's not proven to work, but it would not hurt. That's what we were told."* - Parent of a three-year-old WAS survivor (GT)

> *"Our son's skin was like sandpaper. We had to do the wraps, the bleach bath, no scented laundry detergent. We could not wear perfume. We had to look at the type of clothes we get for him because it irritates the skin. The oatmeal. We tried everything possible for the eczema."* - Parent of a three-year-old WAS survivor (GT)

Treatment for WAS/XLT is a trade-off; most treatments are accompanied by significant drawbacks

Meeting attendees used online polling to indicate how well their current treatment regimen treated the most significant symptoms of WAS/XLT, and to select the biggest drawbacks of current treatment approaches (poll results are in **Appendix 4, Q7 and Q8**). Patient comments about how well some of the specific treatments worked as well as the drawbacks are described in previous sections of the report. Additional drawbacks are described below.

Infertility

Infertility is one of the biggest drawbacks and results from the chemotherapy used for the initial BMT conditioning. When parents are selecting a treatment and hoping that their critically ill child survives, fertility implications seem far in the future. Despite this, some adult BMT survivors felt that the choice and opportunity to have children were taken away from them without consent.

"I was made aware of the possibility that I could be infertile because of the chemotherapy that I had had as an infant. … This has prohibited me from having my own natural born child. I've worked through the topic quite often and while I know that there are many options, it's ultimately not about having options. It's about not having them. It's about having had them taken away without my consent or understanding well before I could have ever known what was going on." - Adult WAS survivor (two BMTs)

"*Fertility is a really, really big thing that isn't touched upon and it's a scary thought. Everybody's dream is to one day have a family, have kids. To have that taken away from you at such a young age, it's scary to think about. Hindsight now is 20/20. I did go through fertility treatment and now do have three kids of my own, but I never had any direction when it came to that. I know that's a scary thought for a lot of parents."* - 35-year-old WAS survivor (splenectomy and BMT)

"Chemotherapy has a long term impact on his life, including likely sterility. I wish he did not lose so much to get a chance to survive." - Grandparent of a WAS survivor (BMT)

Some parents considered testicular cryo-preservation prior to BMT, yet this option comes with the risk of infection, is not always available and does not guarantee future viable sperm. This procedure is also very new and wasn't available to families until the last decade.

Serious side effects (organ toxicity, risk of death, GVHD, etc.)

Many of the side effects of treatments, especially BMT are already well described, including autoimmune disease (page 15), graft versus host disease (page 16), malignancy (page 17), kidney disease (page 17).

The list of additional treatment side effects was very long and includes dental issues, feeding issues, constant pain, growth restriction (short stature), hip necrosis, spastic paraplegia, severe mucositis, acute kidney failure, liver issues, thyroid issues, tachycardia, neurological toxicity, sensitivity to the sun, potential ADHD, autism, sensory processing disorder, social and psychological effects including suicidal ideation.

"The chemotherapy treatment our son received for his BMT led to the failure of him to grow normal adult teeth requiring a complicated orthodontic regime we are just starting. Our son also suffers from ADHD which may be a side effect of the treatment. He is also sterile as a direct side effect of the chemotherapy." - Parent of a WAS survivor (BMT)

"My son's white matter in his spine was disrupted and he is suffering from spastic paraplegia, cannot walk or stand on his own and uses a walker and a wheelchair." - Parent of a WAS survivor (BMT)

"Because [our son] was on so many harsh medications during BMT, he went into acute kidney failure as well as his liver taking a hit. His liver is still very sensitive and has to be watched closely." - Parent of a WAS survivor (BMT)

Lack of treatment consensus for XLT and Waiting until XLT converts to Classic WAS to treat

These two downsides are closely related. With no XLT treatment consensus, parents are left on their own to make treatment decisions for their children, including the decision to have a BMT. Previous sections of this report describe worries about making the wrong decision to transplant or not (page 21).

BMT is most effective when done before the age of five, yet sometimes children are older before they convert to classic WAS.

> *"Last year, the diagnosis changed to severe WAS, unfortunately they don't have a match. 24 years we've been looking."* - Parent of a son living with XLT who progressed to classic WAS

This lack of treatment consensus for XLT can lead to disagreements with medical professionals.

> *"The need for going to ER each time the fever is high, the need for bloodwork in such cases, the constant arguments with doctors about their wish to transfuse platelets while understanding that for long term it is not good."* - Parent of a 14-year-old son living with XLT

> *"The antibiotic keeps the sinus infections somewhat at bay. The other meds keep me alive, but do not manage the symptoms: depression, anxiety, etc."* - Individual living with XLT

Potentially fail and must be repeated

BMT failure, requiring a second procedure is uncommon, however this was mentioned by many WAS survivors. The second procedure is much more risky and more difficult to endure than the first.

> *"The [BMT] procedure did not take as we expected it to. My body went through a period of mixed chimerism. This is a state in which a body has two different kinds of bone marrow in it. While my sister's transplanted bone marrow was doing its job correctly of keeping me alive, not all of my faulty bone marrow had been eradicated through the dosages of chemo, there was still a significant amount of my bone marrow left. … Four years later, I had a second bone marrow transplant with my sister again as the donor. Two months later, the treatment was deemed successful."* - Adult WAS survivor (two BMTs)

> *"He needed a second bone marrow transplant. He received it, but has been very, very difficult for us and for him*." - Parent of a WAS survivor (two BMTs)

May not fully correct problems

Many described how their treatments didn't really address the symptom of interest, only solved one of multiple symptoms that they experience, or resolves one symptom at the expense of another. This is closely related to the results of the poll question (**Appendix 5, Q7**) where 24% of poll respondents said that their current treatment regimen only helps "very little" or "not at all".

> "*I'm merely surviving every day. Not living. Certainly not enjoying life. My symptoms are not controlled. My "treatments" are simply enough to keep me alive. … I've already done IVIG with little improvements. Prednisone improved my platelets significantly, as well as my pain and fatigue, but after 8 years, I was taken off of it. It's been a steady decline ever since then. Now I'm on a daily antibiotic and a ton of other meds."* - Individual living with XLT

> *"Unfortunately for our case, nothing has really been effective at all. …The bottom line is that every intervention is coping, nothing more. Coping, and hoping that something will work, nothing substantial so far."* - Parent of an eight-year-old son living with WAS

> *"For [our son], the transplant recovery process has been very long. It seems his BMT has solved strictly his bone marrow issue - his white cells, red cells and platelets - but has caused so many side effects post-transplant. I'm truly grateful that we no longer have to worry about him falling*

and bleeding to death. I'm also grateful he no longer needs to wear a helmet to protect his head. However, [our son] still continues to need continuous treatment and follow up with many specialists as a result of his transplant." - Parent of a WAS survivor (BMT)

Other treatment downsides

Several other treatment downsides selected in the polls. This includes **limited availability or accessibility**, which is an issue for gene therapy especially, and also for BMT for those who are unable to find a matched donor. **Route of administration (including needle-phobia)** and **high cost or co-pay, not covered by insurance** were offered as poll options.

> *"He was only two at the time, so he couldn't swallow pills. So that was another difficult thing is to try and get your child to take not very good tasting medication. He actually had to be discharged from the hospital with an NG tube because he wasn't able to take most of those medications by mouth."* - Parent of a WAS survivor (BMT)

Treatment downsides that were not selected in the polls but already described as impacts include frequent and extended hospitalizations and isolation (page 24). Another downside is that oral medications can be difficult to administer to small children.

In addition to a cure, the WAS/XLT community needs less risky treatment: less mortality, less toxicity and fewer long-term side effects

Poll respondents were asked to select their top three aspects of an ideal treatment for WAS/XLT, short of a complete cure (poll results are in **Appendix 4, Q9**). Many emphasized the need for a more humane treatment.

> *"As a mother who lost a son from WAS disease and is currently planning a life-threatening procedure for another little one, I feel there is more that could be done to help these children survive and have the ability to live normal lives. Before my son passed away, I witnessed him suffer for years, many traumatizing events that I would never wish upon any parent. These children live their lives in isolation, not being able to experience life the way a normal child does. In my opinion, it is inhumane to allow these children to suffer in this way when something could be done. Every WAS parent is willing to fight for as long as it takes."* - Parent of one son living with WAS/XLT and another who passed away from the disease

The WAS/XLT community needs a cure

Although "cure" was not offered as a poll response, many patients and their families would like a cure for this disease. Many parents specifically asked for gene therapy, to permit their children to have a normal life.

> *"To be honest, I think the [poll] question here is really flawed. Any ideal treatment of a disease would be a cure of that disease."* - WAS survivor (BMT), and family member of others living with WAS

> *"Even his treatment options were so scary and carry lifelong risks/uncertainties. He has gotten an unrelated bone marrow transplant. I would have loved to pursue gene therapy as a safer option if more research had been done and it was more available."* - Parent of a WAS survivor (BMT)

"We live in hope that there will be a less invasive treatment such as gene therapy becoming safer and more readily available in the future, that has trialed, and has been tested with high favorable outcomes." - Parent of a 10-year-old living with XLT

No mortality

In the polls, parents selected no mortality as their top wish for a future treatment. Currently, a top transplant center can expect a five-year mortality rate of 10%.

"No mortality, reduce the toxicity, preserve the fertility. I think that sums up where we are and what we want for our families." - Parent of an 18-year-old WAS survivor (BMT)

"The BMT is a dangerous procedure. We survived -- but some patients do not. So less mortality for our community, please. Also, if possible, less toxicity for the chemotherapy; and research into GVHD treatments with fewer side effects than steroids." -Parent of a WAS survivor (BMT)

Fewer side effects and less toxicity during treatment and Fewer long-term side effects such as GVHD and infertility

Throughout the meeting, parents described the treatment toxicity and side effects that their children experienced, both short and long term. They would like the benefits to outweigh the treatment risks.

"It is my hope that in the future, treatments are developed for WAS that have little to no side effects, that these kids will not have to endure what our son went through. No pain, no suffering, no delays that they receive a complete cure and nothing less. Simply fix their cells." - Parent of a WAS survivor (BMT)

"But for future, less toxicity would be awesome. No GVHD. The way that my son has suffered so much with graft versus host disease on his skin. … Those things would be great for the future if we could eliminate some of these really toxic medical procedures." - Parent of an 18-year-old WAS survivor (BMT)

Adequate platelets to prevent bleeding

Many parents would like a treatment that results in adequate platelets to prevent WAS/XLT-related bleeding issues, including nosebleeds and bruising. Some would like a drug that would prevent platelet levels from dropping, which could help minimize transfusions. Some viewed gene therapy as the path.

"I pray that gene therapy will continue to improve and be an option for him. … How many more years do we have to suffer and live in fear until there's some sort of treatment for these nose bleeds? - Parent of an eight-year-old son living with WAS

"Drugs that could keep platelet counts from dropping or that can bolster the immune system would have been game changers for us." - Parent of two WAS survivors (BMT)

"Medicine to improve platelets that will last for months or a year so number of transfusions are minimized." - Parent of a son diagnosed with XLT who progressed to classic WAS

Many responded to the question in the online comments; "*If a platelet treatment were offered, at what platelet level would you or your loved one feel safe and comfortable?"* Answers covered the range, with

fairly equal representation from those who asked for "over 50K" and for those who asked for "over 100K". Additional responses are shown below.

> "*My goal for my brother would be over 100k. In every hospital I have practiced in (as an internist) neurosurgical teams will take a patient for brain/spine surgery if their platelets are over 100, so I think that if that is their threshold, he would be safe to do any regular life activity he wanted. I would settle for a platelet threshold of 50 (at which general or cardiothoracic surgery would still take him for a major chest/abdominal surgery if he needed it) because he could probably still do most activities like casual sports and travel at 50k*." - Sibling of a brother diagnosed with XLT who progressed to classic WAS

> *"This wouldn't be a number for us, it would be the point where there is no more active bleeding."*- Parent of a boy living with XLT

> "*100K, and knowing this will stay like this."* - Grandmother an individual living with WAS/XLT

Prevention of conversion of XLT to Classic WAS

In addition to preventing the conversion of XLT to classic WAS, many would like better treatments for XLT, including the opportunity to participate in clinical trials.

> *"Nothing has changed for our XLT boys in 10 years. Our only option is to be aggressive and risk a bone marrow transplant, or wait and see, and hope that if they do become a classic, they are well enough to survive a bone marrow transplant. My hope is that one day, our XLT boys have other options."*- Parent of a son whose XLT recently converted to classic WAS

> *"He does not have a bone marrow match and gene therapy is not available. We hope that there will be a treatment for him before his health deteriorates further. [Our son] is just one among the hundreds of WAS patients worldwide facing these struggles."* - Parent of an individual diagnosed with XLT, now living with severe WAS

Other options selected in the polls

Other treatment options selected in the polls included a treatment that **decreased the risk of serious infection**, **prevents disease progression**, **resolves eczema and allergies,** and has **better administration options (including oral)** that can be taken at home.

> *"Maybe use a small molecule, to take on an everyday basis, versus a one and done treatment. Maybe XLT can be converted to a disease where you can take medications every day."* -Parent of a 14-year-old son living with XLT

> *"To bring his platelets over 50, to be able to take it at home, that it has no side effects and does not suppress his development and health in any way."* - Parent of a child living with WAS

> "*Affordable and less time in the hospital."* - Grandparent of a child living with WAS

Other potential treatment options not selected in the polls

The WAS/XLT community shared their other treatment goals. These include greater mental health supports and trauma informed care for patients and families undergoing BMT procedures, better options to preserve fertility before BMT, preventing the transmission of the *WAS* gene variants to the

next generation, treatment options for carriers including gene therapy, improvement to the quality of life, better vaccination protocols for individuals with WAS/XLT.

> *"Being a psychologist and an educator, I constantly emphasize mental health as a priority. … I strongly urge … that mental health support should start as soon as you become aware of the patient or the caregiver facing this issue. Making the funds available for such support and creating options for clinical trials in the United States (and other countries) to provide BMT or gene therapy with least complicating side effects should become a priority."* - Family member of a boy living with WAS/XLT

> *"When we asked about cryopreservation, one of our doctors brought up "the ethics of preserving fertility when one is a carrier of such a disease". I find this so hurtful when I look back on this conversation- I think all families should be given the choice to preserve fertility, even if this was said as an academic, theoretical point, it takes away choices from families."* - Parent of a 12-year-old WAS survivor (GT)

Incorporating Patient Input into a Benefit-Risk Assessment Framework

The WAS/XLT EL-PFDD meeting helped to increase the understanding of how WAS and XLT impact patients and their loved ones and reinforced the urgent need for effective treatments for these diseases.

Table 2 speaks to the challenge of having a lifelong disease burden that patients living with WAS/XLT endure. It serves as the proposed introductory framework for the Analysis of Condition and Current Treatment Option to be adapted and incorporated in the FDA's Benefit-Risk Assessment. This may enable a more comprehensive understanding of these disorders for key reviewers in the FDA Centers and Divisions who would be evaluating new treatments for WAS/XLT. The data resulting from this meeting may help inform the development of WAS- and XLT-specific, clinically meaningful endpoints for current and future clinical trials, as well as encourage researchers and industry to investigate more effective treatment.

The information presented captures the perspectives of patients and families living with WAS/XLT presented at the February 3, 2023 EL-PFDD meeting. We hope that this meeting will encourage future research and successful new product development for people living with WAS and XLT who urgently need treatment options.

Note that the information in this sample framework is likely to evolve over time.

> *"I want to impart on you that WAS may be rare for a population, but it's constant and unyielding for those who live with it."* - Parent of an eight-year-old son living with WAS

TABLE 2: Benefit-Risk Table for WAS/XLT

	EVIDENCE AND UNCERTAINTIES	CONCLUSIONS AND REASONS
ANALYSIS OF CONDITION/IMPACTS ON ACTIVITIES OF DAILY LIVING	**Wiskott-Aldrich syndrome (WAS)/XLT is a life-threatening disease in children, with profound impact on the patients and their families.** WAS, the most severe form of the disease, and X-linked thrombocytopenia (XLT), the less severe form, have unpredictable and varied presentations including immunodeficiencies, bleeding/platelet deficiencies, eczema. As infants, many experience bloody diarrhea and food allergies. Patients have an increased risk of autoimmune disorders, leukemia, and lymphoma. Many experience psychosocial and mental health challenges. **The term XLT is a misnomer.** XLT is a progressive disease which is not limited to thrombocytopenia as the name would indicate. Importantly**, XLT is not a mild disease**. Most XLT patients develop life-threatening complications such as bleeding, severe autoimmune complications, and malignancies. By complications arise, many are too ill to undergo definitive treatments.	**Life with WAS/XLT is a life of uncertainty, isolation, and terrifying worry and fear about the future.** Patients and parents worry about the life-threatening symptoms, the impacts of the disease and the long-term consequences of treatment. WAS/XLT severely impacts every activity of daily living and the quality of life of the patient as well as for their parents, siblings, and family members.
CURRENT TREATMENT OPTIONS/PROSPECTS FOR FUTURE TREATMENTS	**There are no FDA approved treatments for WAS/XLT.** Bone marrow transplant and Experimental gene therapy are the only definitive treatments for WAS and are not universally available. Medications to improve platelet counts/bleeding are also not approved by the FDA. **Treatment for WAS can be a trade-off.** BMT, though successful, is a toxic, risky and prolonged treatment. Gene therapy seems promising with potentially less mortality and morbidity. Symptomatic treatments used by patients include platelet and blood transfusions, immunoglobulin replacement therapy, steroids, prophylactic antibiotics, anti-rejection drugs, bleeding medications, splenectomy. **Newer and more promising treatments such as experimental gene therapy are suspended due to financial constraints and are not available to patients and is unacceptable. Patients lose lives waiting for such treatments.**	**Patients want less risky treatment: less mortality, less toxicity and fewer long-term side effects**. They would also like to have better mental health supports and more trauma-informed care, better options to preserve fertility prior to treatment, ways to prevent transmission of the gene to future generations. **Lack of treatment consensus for XLT makes treatment decision-making difficult.** This leaves families in a quandary as to what is the best decision to make on behalf of their child. **They are too well to have a BMT when younger and often too old, have complications and too ill to receive definitive treatment when older.** Newer treatment options including experimental treatments should be made available to XLT patients as many lose their lives in the 3rd to 5th decade of life.
	See the Voice of the Patient report for a more detailed narrative.	

Appendix 1: FDA Resources

These resources were shared by Dr. Glancy during the WAS/XLT EL-PFDD meeting.

The Rare Disease Cures Accelerator-Data and Analytics Platform (RDCA-DAP®)

RDCA-DAP | Critical Path Institute (cpath.org)

This integrated database and analytics hub is designed to be used in building novel tools to accelerate drug development across rare diseases. It is being developed by the Critical Path Institute (C-Path) and NORD through a collaborative grant from the FDA, with the goal of using data to accelerate clinical development, lower costs and encourage even more companies and researchers to get involved in rare disease research and innovation. To learn more about the technical components and vision, please visit C-Path's site.

Past FDA Workshops and Webinar Series highlighting how patients and patient advocacy organizations can help advance regenerative medicine, such as cell and gene therapies and other medical products.

FDA CBER OTAT Patient-Focused Drug Development Listening Meeting -Patient Perspectives on Gene Therapy Products November 15, 2022

Natural History Studies to Support Retrospective Medicines: A How-To Webinar October 27, 2022

Annual Patient Engagement & Regenerative Medicine Meeting 2022: An FDA CBER Workshop for Patient Advocates May 24, 2022

RegenMedEd Webinar: The Critical Role of Patients in Advancing Gene Therapy Treatments for Rare Diseases March 9, 2022

Regenerative Medicine 101 Webinar: Information for Patients, Caregivers & Advocates November 16, 2021

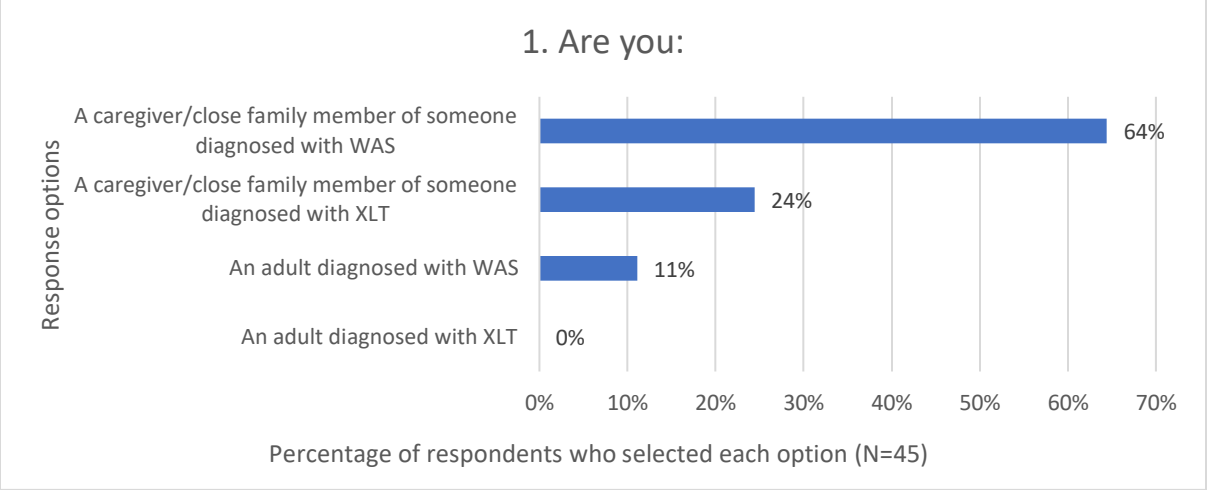
Patient Engagement and Regenerative Medicine: An FDA CBER Workshop for Patient Advocates May 6, 2021

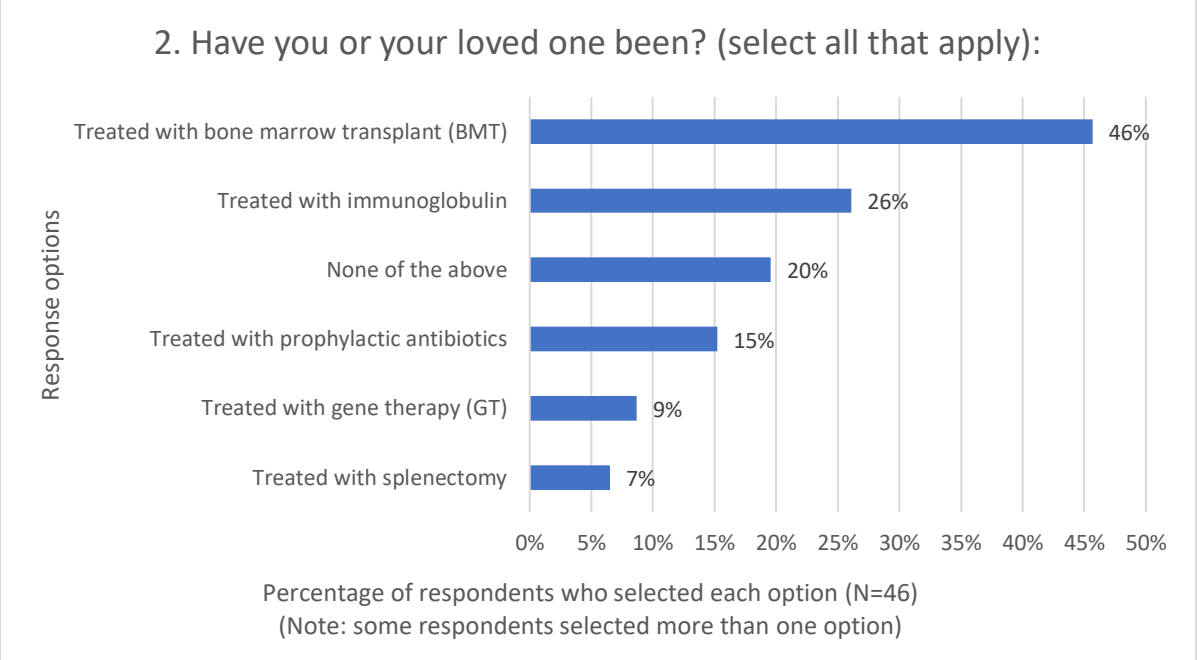
www.fda.gov

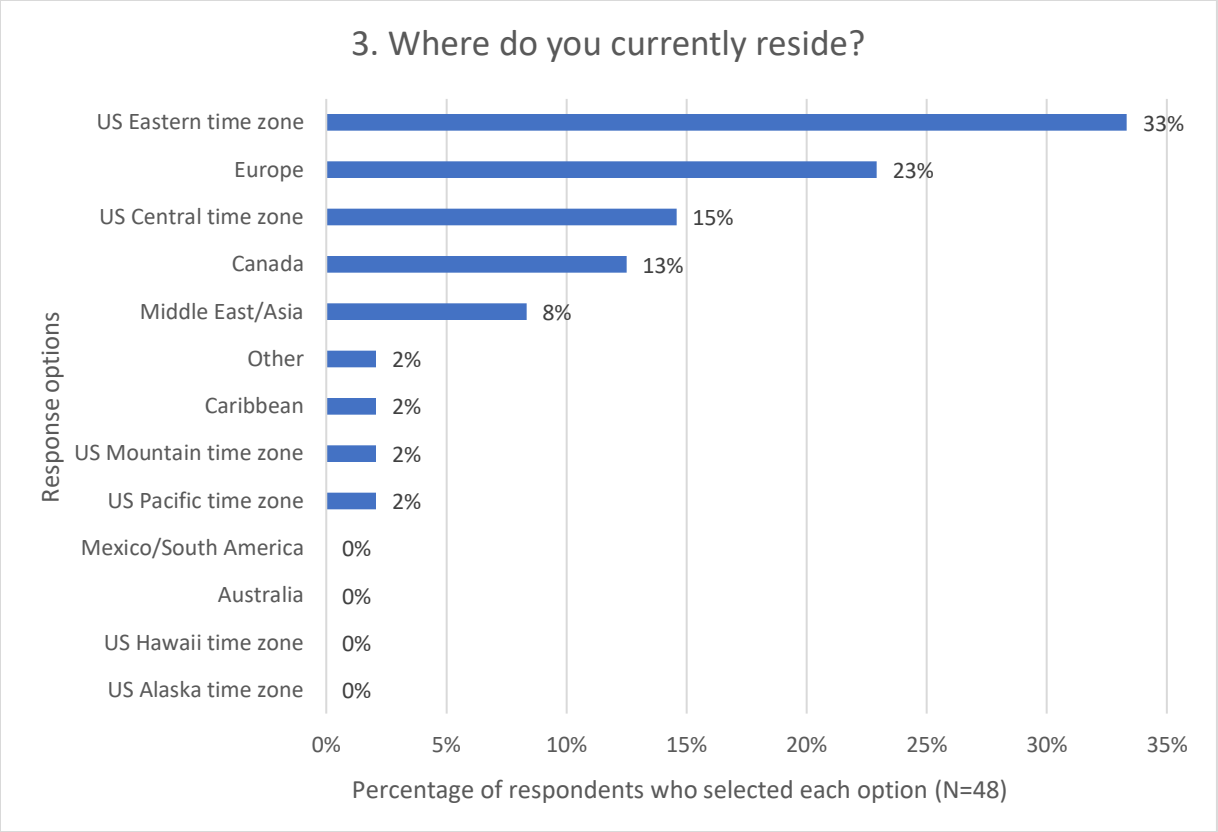
Appendix 2: Demographics

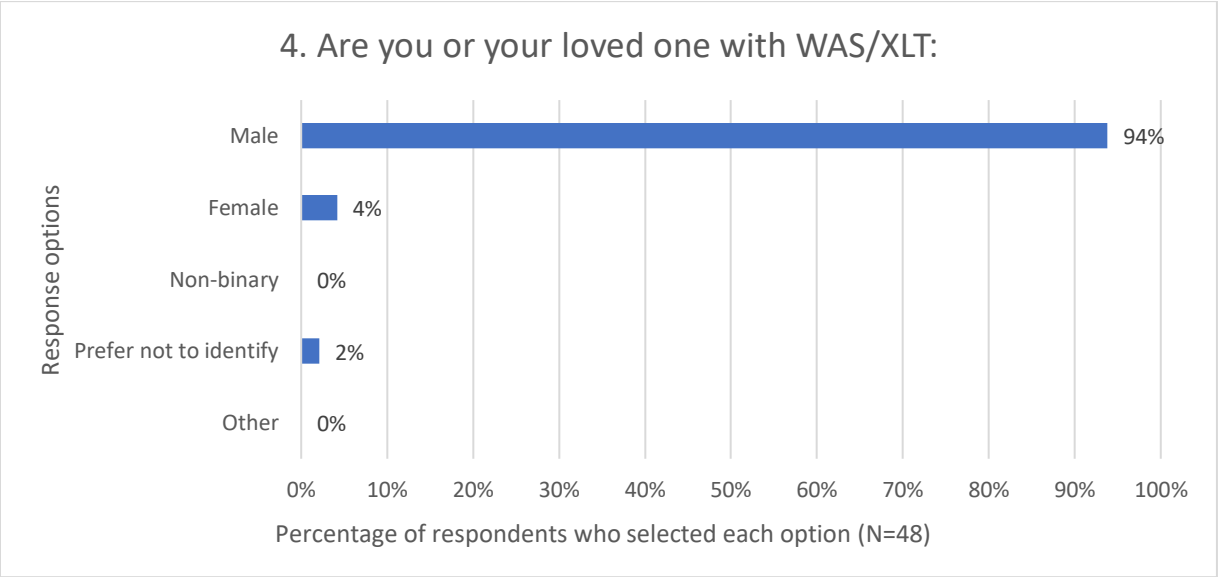
The graphs below include patients, parents and caregivers who chose to participate in online polling at the February 3, 2023 meeting. The number of individuals who responded to each polling question is shown below the X axis (N=x).

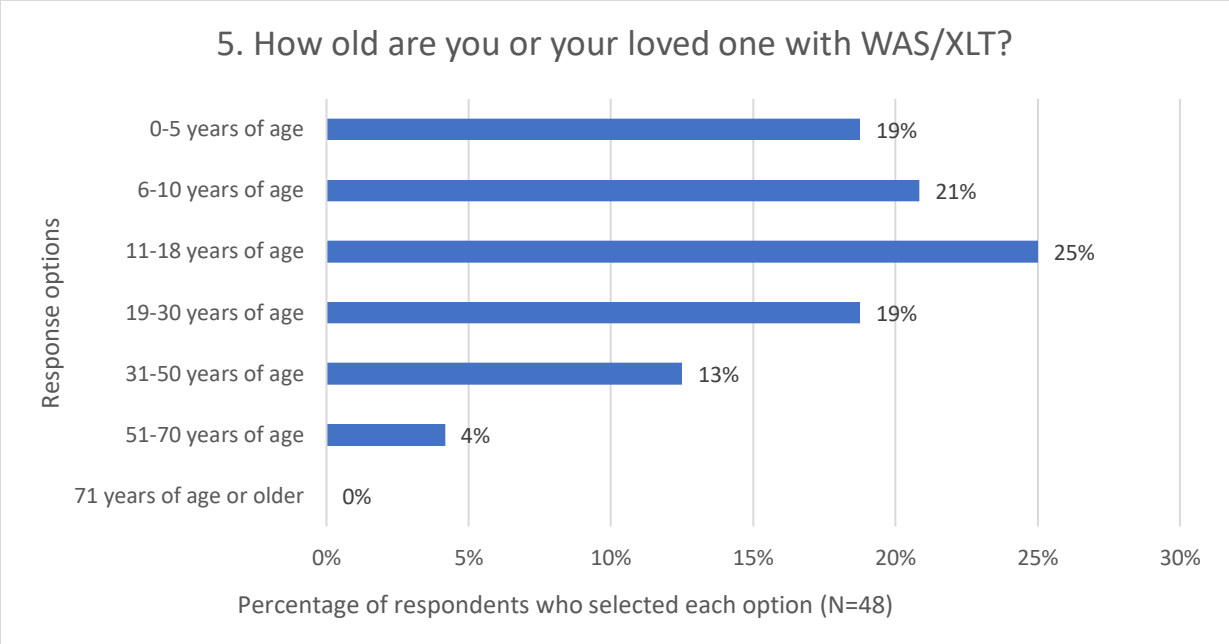
While the response rates for these polling questions is not considered scientific data, it provides a snapshot of those who participated in the WAS/XLT EL-PFDD meeting. Note that meeting demographics are dynamic and may have changed as more individuals joined the meeting.

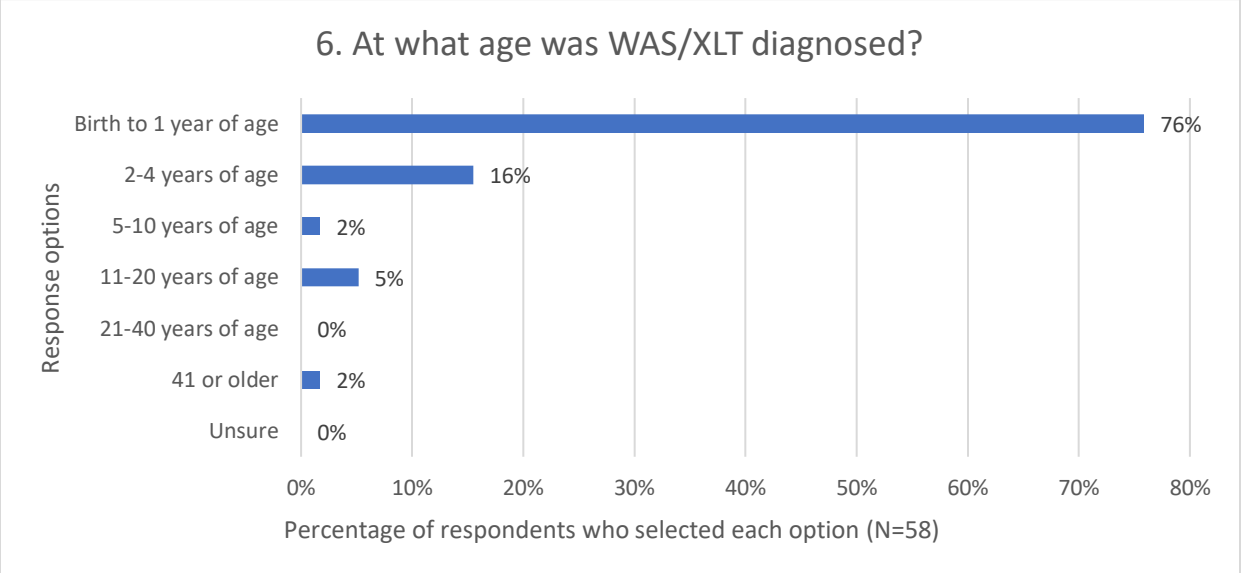





3. Where do you currently reside?
US Eastern time zone
Europe
US Central time zone
Canada
Middle East/Asia
Other
Caribbean
US Mountain time zone
US Pacific time zone
Mexico/South America
Australia
US Hawaii time zone
US Alaska time zone
33%
23%
15%
13%
8%
2%
2%
2%
2%
0%
0%
0%
0%
Response options
0%
5%
10%
15%
20%
25%
30%
35%
Percentage of respondents who selected each option (N=48)


4. Are you or your loved one with WAS/XLT:
Male
Female
Non-binary
Prefer not to identify
Other
94%
4%
0%
2%
0%
Response options
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Percentage of respondents who selected each option (N=48)


5. How old are you or your loved one with WAS/XLT?
Response options
0-5 years of age
6-10 years of age
11-18 years of age
19-30 years of age
31-50 years of age
51-70 years of age
71 years of age or older
19%
21%
25%
19%
13%
4%
0%
0%
5%
10%
15%
20%
25%
30%
Percentage of respondents who selected each option (N=48)


6. At what age was WAS/XLT diagnosed?
Response options
Birth to 1 year of age
2-4 years of age
5-10 years of age
11-20 years of age
21-40 years of age
41 or older
Unsure
76%
16%
2%
5%
0%
2%
0%
0%
10%
20%
30%
40%
50%
60%
70%
80%
Percentage of respondents who selected each option (N=58)

Appendix 3: Meeting Discussion Questions

Session 1 – WAS/XLT Symptoms and Daily Impacts

1. Of all the symptoms and health effects of Wiskott-Aldrich syndrome/ XLT, which 1-3 have the most significant impact on you or your loved one's life?
2. How does Wiskott-Aldrich syndrome/ XLT affect you or your loved one on best and on worst days?
3. How has your or your loved one's symptoms changed over time? How has the ability to cope with the symptoms changed over time?
4. Are there specific activities that are important to you or your loved one that you/they cannot do at all or as fully as you or they would like because of Wiskott-Aldrich syndrome/XLT?
5. What do you fear the most as you or your loved one gets older? What worries you the most about you or your loved one's condition?

Session 2 – Current and Future WAS/XLT Treatments

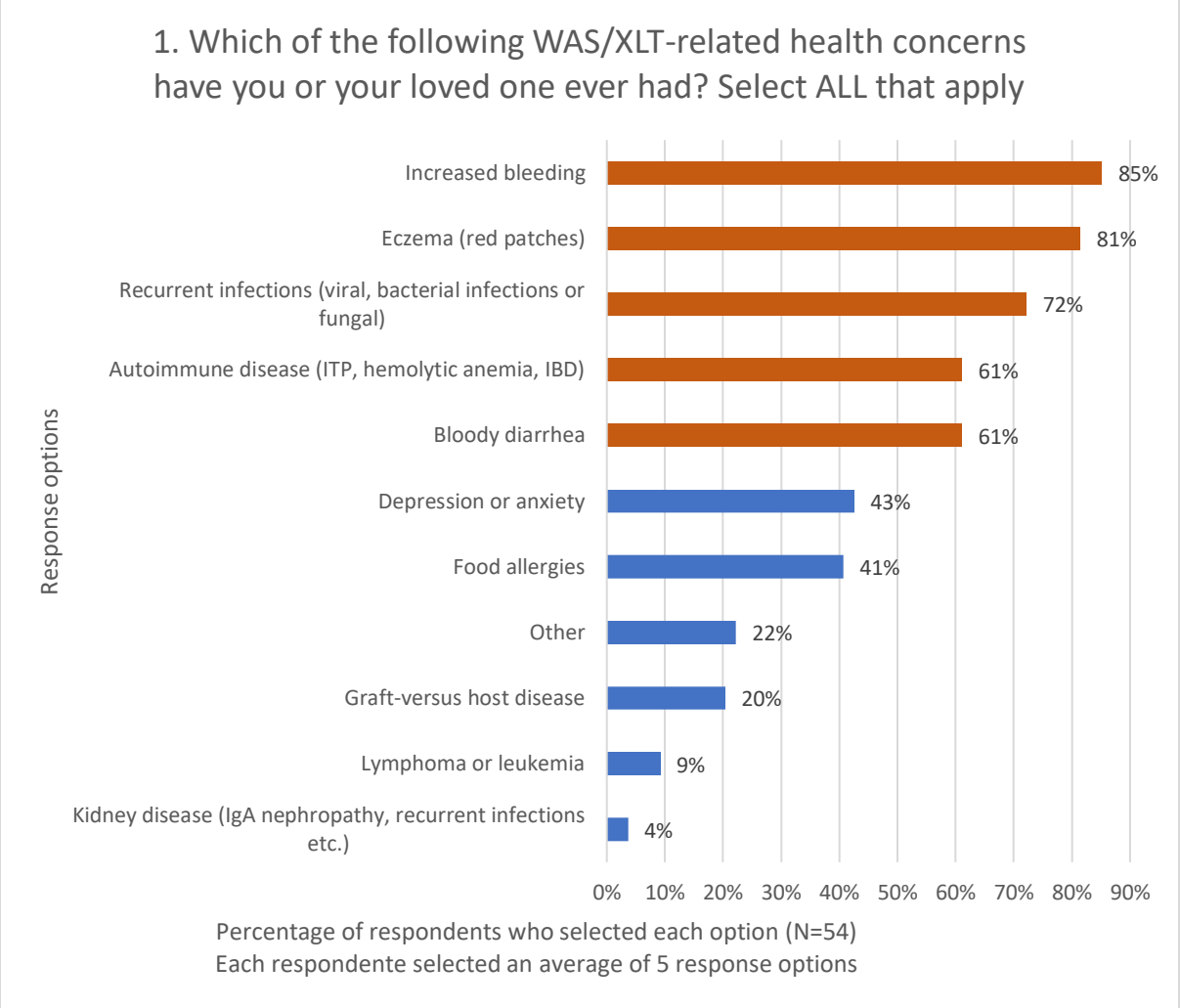
1. What are you currently doing to manage Wiskott-Aldrich/XLT symptoms?
2. How well do these treatments treat the most significant symptoms and health effects of Wiskott-Aldrich syndrome/XLT?
3. What are the most significant downsides to your or your loved ones' current treatments and how do they affect daily life?
4. Short of a complete cure, what specific things would you look for in an ideal treatment for Wiskott-Aldrich syndrome/XLT?
5. If you were offered a treatment for platelets, what platelet level would you or your loved one feel safe and comfortable with?

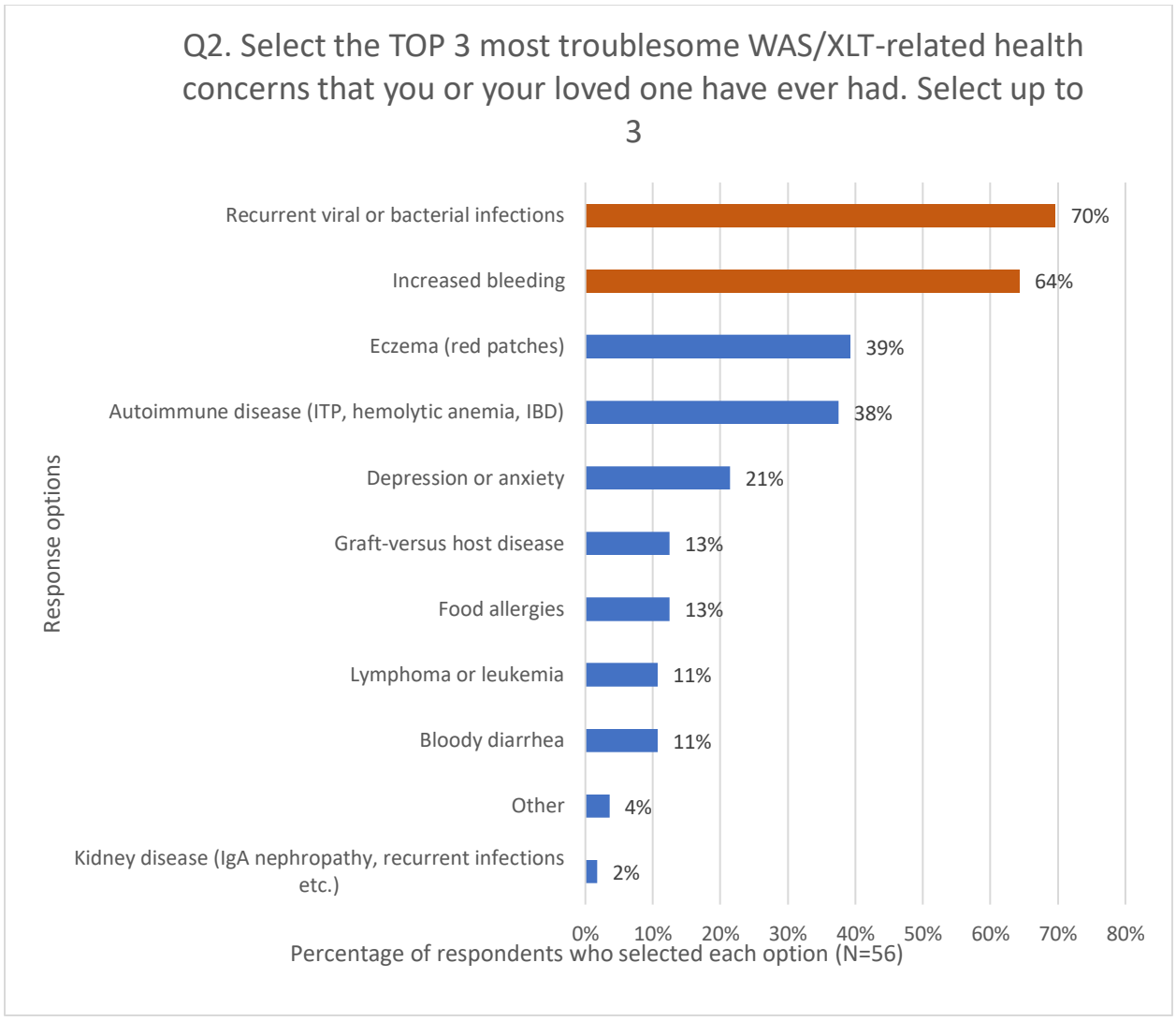
Appendix 5: Online Poll Results

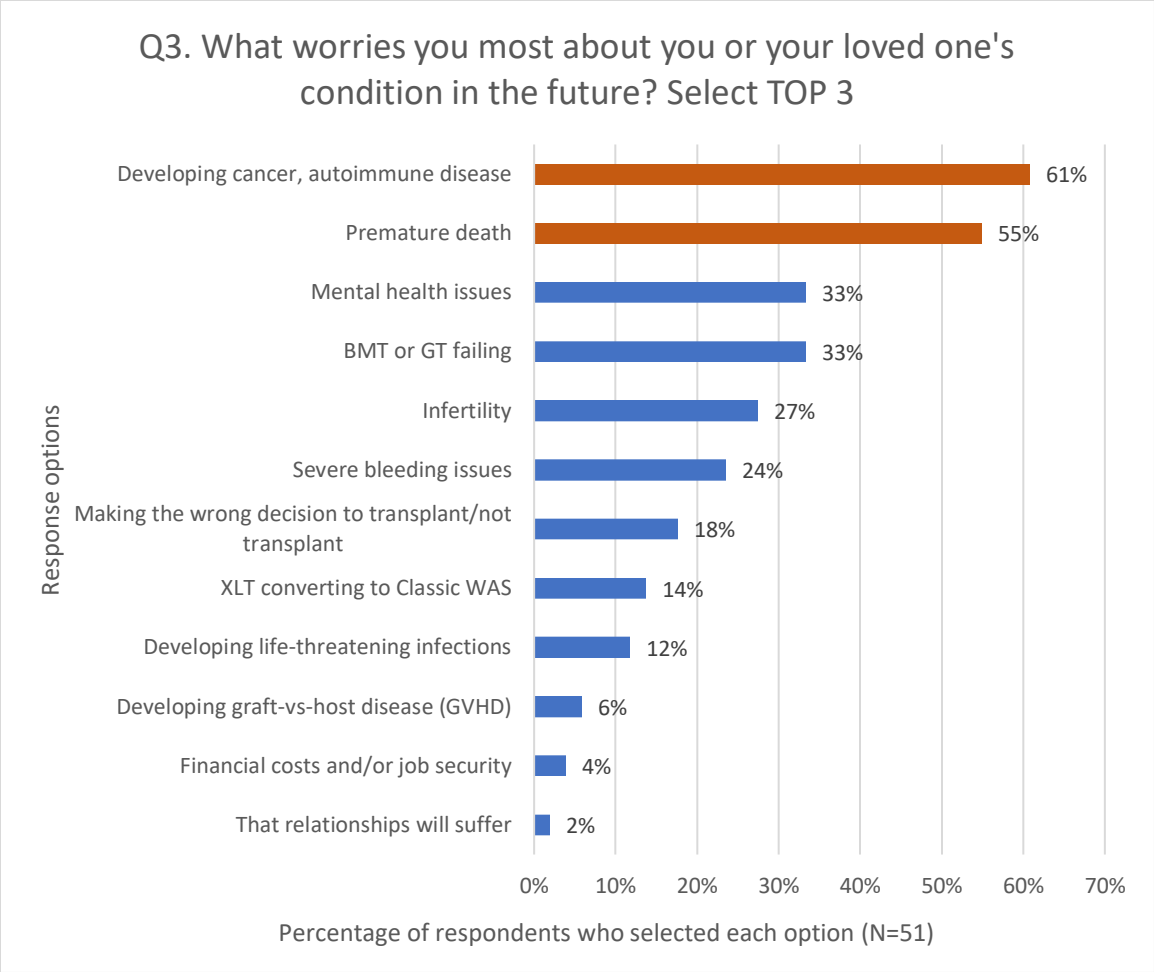
The graphs below include patients, parents and caregivers who chose to participate in online polling. The number of individuals who responded to each polling question is shown below the X axis (N=x).

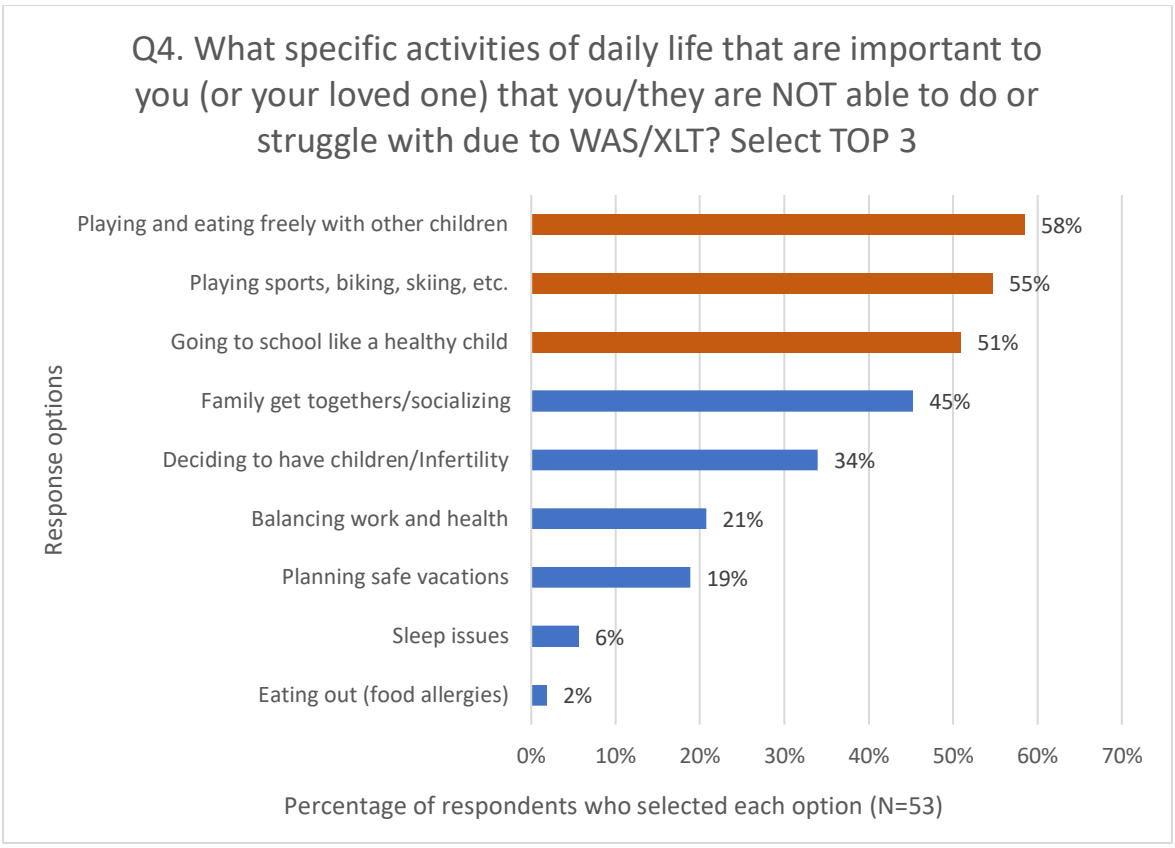
The responses for these polling questions are not considered scientific data. These are intended to complement the patient comments made during and after the meeting.

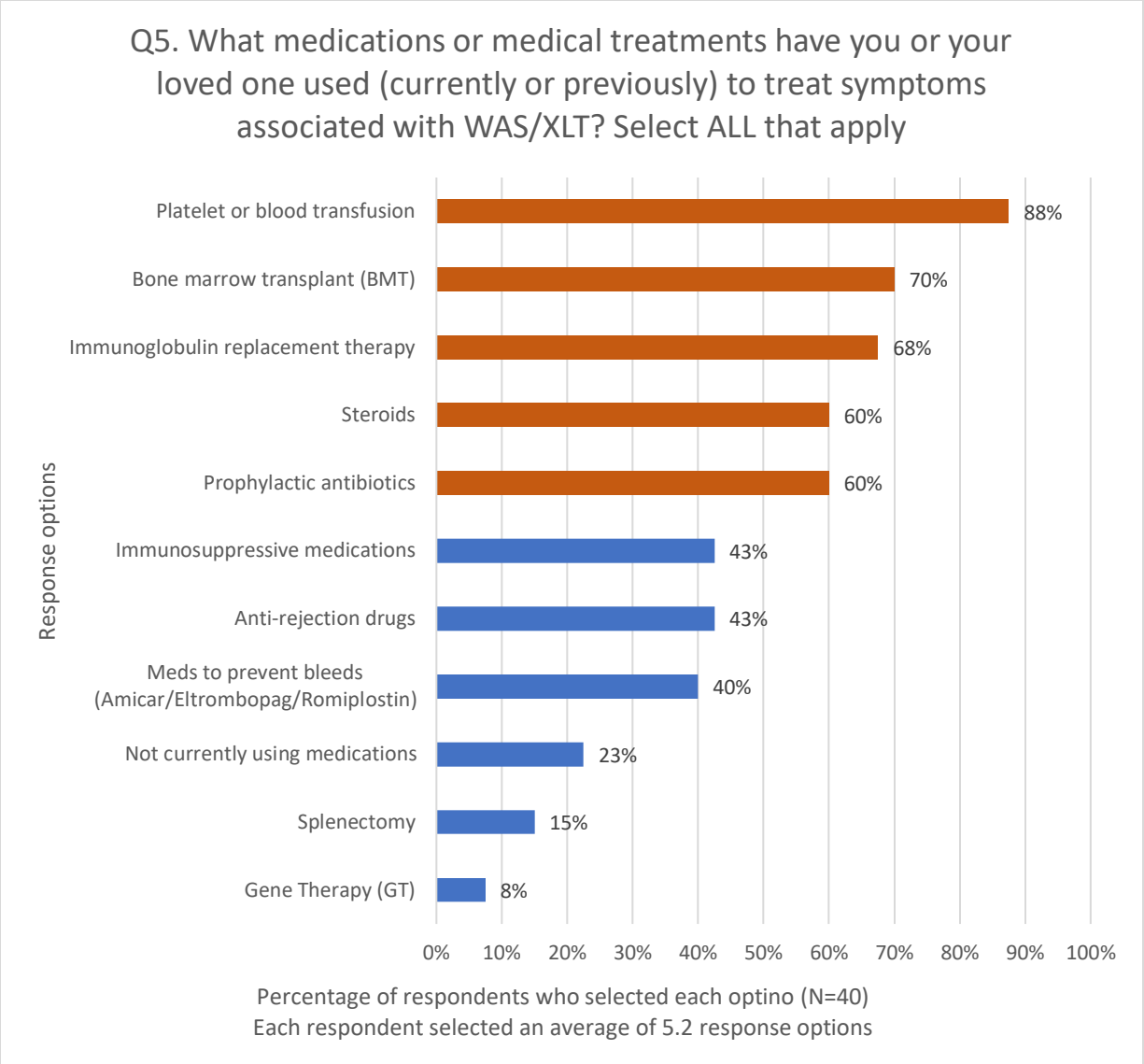
Poll responses selected by more than 50% of poll respondents are shown in **orange**.

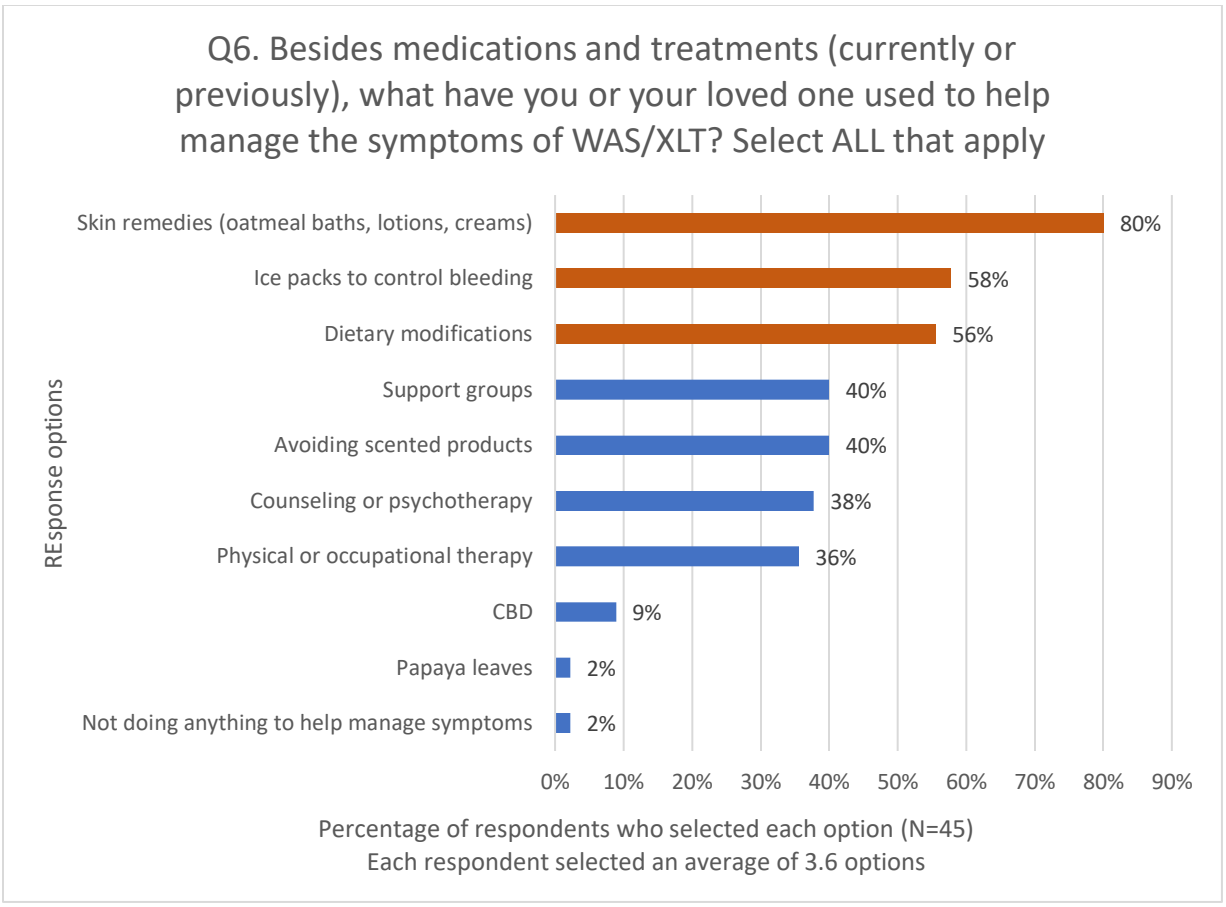


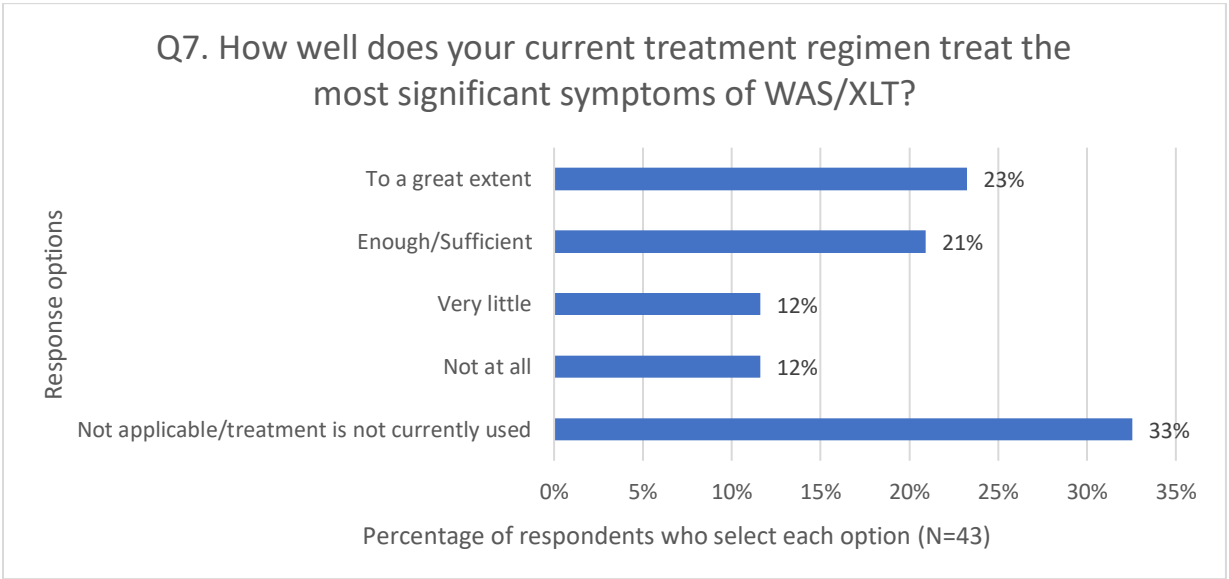

Q2. Select the TOP 3 most troublesome WAS/XLT-related health concerns that you or your loved one have ever had. Select up to 3
Response options
Recurrent viral or bacterial infections
70%
Increased bleeding
64%
Eczema (red patches)
39%
Autoimmune disease (ITP, hemolytic anemia, IBD)
38%
Depression or anxiety
21%
Graft-versus host disease
13%
Food allergies
13%
Lymphoma or leukemia
11%
Bloody diarrhea
11%
Other
4%
Kidney disease (IgA nephropathy, recurrent infections etc.)
2%
0%
10%
20%
30%
40%
50%
60%
70%
80%
Percentage of respondents who selected each option (N=56)

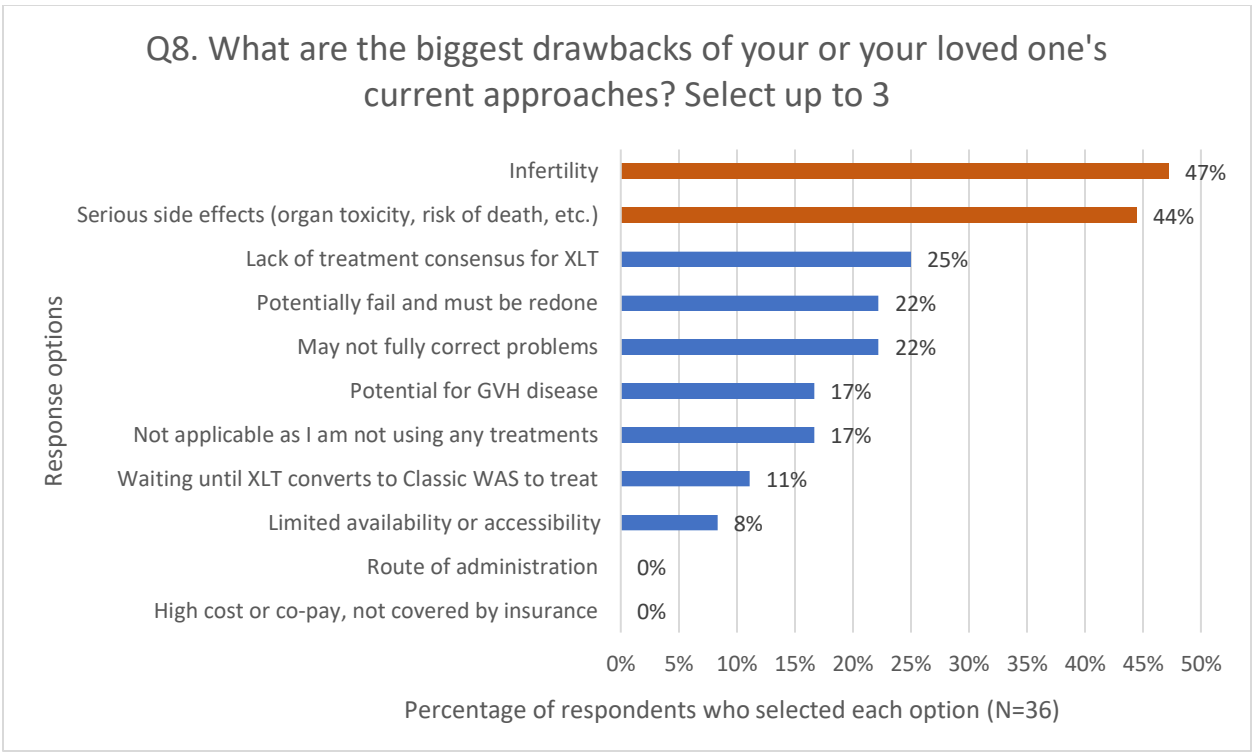

Q3. What worries you most about you or your loved one's condition in the future? Select TOP 3
Response options
Developing cancer, autoimmune disease
61%
Premature death
55%
Mental health issues
33%
BMT or GT failing
33%
Infertility
27%
Severe bleeding issues
24%
Making the wrong decision to transplant/not transplant
18%
XLT converting to Classic WAS
14%
Developing life-threatening infections
12%
Developing graft-vs-host disease (GVHD)
6%
Financial costs and/or job security
4%
That relationships will suffer
2%
0%
10%
20%
30%
40%
50%
60%
70%
Percentage of respondents who selected each option (N=51)

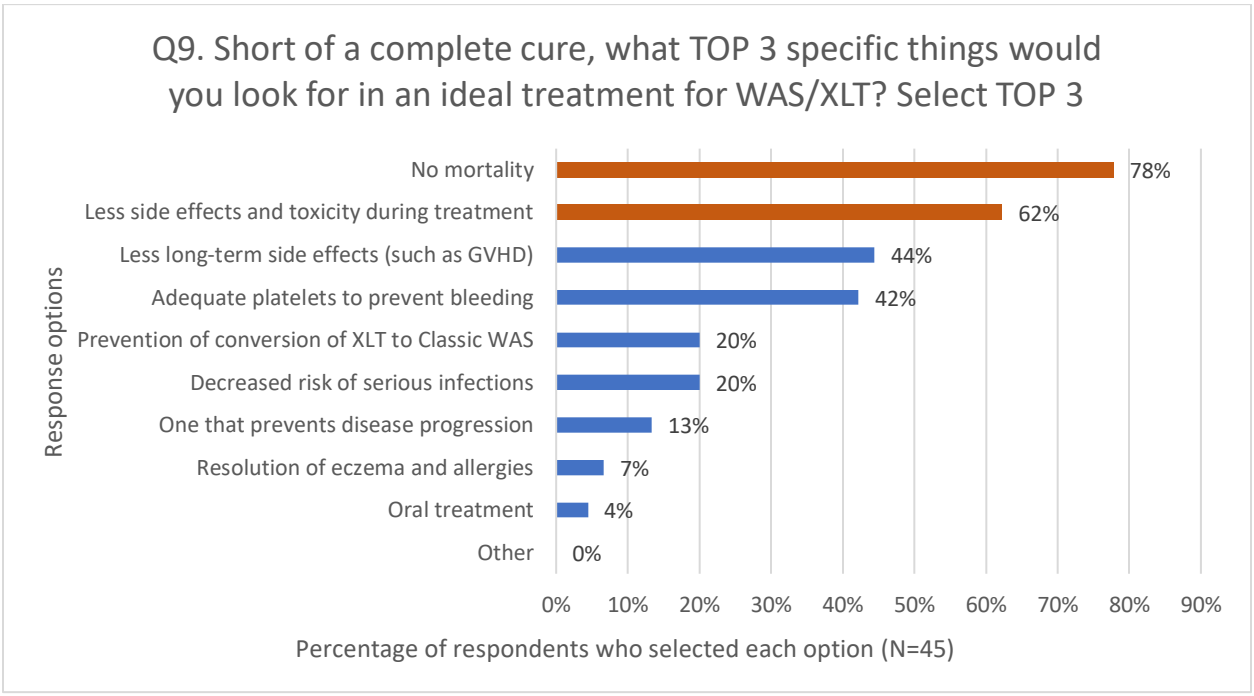

Q4. What specific activities of daily life that are important to you (or your loved one) that you/they are NOT able to do or struggle with due to WAS/XLT? Select TOP 3
Response options
Playing and eating freely with other children
Playing sports, biking, skiing, etc.
Going to school like a healthy child
Family get togethers/socializing
Deciding to have children/Infertility
Balancing work and health
Planning safe vacations
Sleep issues
Eating out (food allergies)
58%
55%
51%
45%
34%
21%
19%
6%
2%
0%
10%
20%
30%
40%
50%
60%
70%
Percentage of respondents who selected each option (N=53)


Q5. What medications or medical treatments have you or your loved one used (currently or previously) to treat symptoms associated with WAS/XLT? Select ALL that apply
Response options
Platelet or blood transfusion
88%
Bone marrow transplant (BMT)
70%
Immunoglobulin replacement therapy
68%
Steroids
60%
Prophylactic antibiotics
60%
Immunosuppressive medications
43%
Anti-rejection drugs
43%
Meds to prevent bleeds (Amicar/Eltrombopag/Romiplostin)
40%
Not currently using medications
23%
Splenectomy
15%
Gene Therapy (GT)
8%
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Percentage of respondents who selected each optino (N=40)
Each respondent selected an average of 5.2 response options


Q6. Besides medications and treatments (currently or previously), what have you or your loved one used to help manage the symptoms of WAS/XLT? Select ALL that apply
REsponse options
Skin remedies (oatmeal baths, lotions, creams)
80%
Ice packs to control bleeding
58%
Dietary modifications
56%
Support groups
40%
Avoiding scented products
40%
Counseling or psychotherapy
38%
Physical or occupational therapy
36%
CBD
9%
Papaya leaves
2%
Not doing anything to help manage symptoms
2%
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
Percentage of respondents who selected each option (N=45)
Each respondent selected an average of 3.6 options


Q7. How well does your current treatment regimen treat the most significant symptoms of WAS/XLT?
Response options
To a great extent
23%
Enough/Sufficient
21%
Very little
12%
Not at all
12%
Not applicable/treatment is not currently used
33%
0%
5%
10%
15%
20%
25%
30%
35%
Percentage of respondents who select each option (N=43)


Q8. What are the biggest drawbacks of your or your loved one's current approaches? Select up to 3
Response options
Infertility 47%
Serious side effects (organ toxicity, risk of death, etc.) 44%
Lack of treatment consensus for XLT 25%
Potentially fail and must be redone 22%
May not fully correct problems 22%
Potential for GVH disease 17%
Not applicable as I am not using any treatments 17%
Waiting until XLT converts to Classic WAS to treat 11%
Limited availability or accessibility 8%
Route of administration 0%
High cost or co-pay, not covered by insurance 0%
0% 5% 10% 15% 20% 25% 30% 35% 40% 45% 50%
Percentage of respondents who selected each option (N=36)


Q9. Short of a complete cure, what TOP 3 specific things would you look for in an ideal treatment for WAS/XLT? Select TOP 3
Response options
No mortality 78%
Less side effects and toxicity during treatment 62%
Less long-term side effects (such as GVHD) 44%
Adequate platelets to prevent bleeding 42%
Prevention of conversion of XLT to Classic WAS 20%
Decreased risk of serious infections 20%
One that prevents disease progression 13%
Resolution of eczema and allergies 7%
Oral treatment 4%
Other 0%
0% 10% 20% 30% 40% 50% 60% 70% 80% 90%
Percentage of respondents who selected each option (N=45)