AAP Section on

HEMATOLOGY/ONCOLOGY

Newsletter

Fall 2022

Chair's Update

Cynthia Wetmore, MD, PhD, FAAP

Dear Colleagues,

Greetings to all! I hope many of you are enjoying the crisp(er) air and fall colors for those who see changing seasons out their windows. To those who may have been impacted by floods, fires and storms – please reach out to colleagues and let us know if there is anything we can do to help you. With the changing climate I think that we are all aware of the fragility of our natural resources and I hope that you are able to take a moment to appreciate the beauty around you, and greet at least one person whom you do not know with a smile today.

We, as the Section on Hematology/Oncology have much to celebrate with more of us returning to normal routines of life with COVID. We celebrated Sickle Cell and Childhood Cancer Awareness in September and the return of the academic calendar. The FDA has granted emergency use authorization for effective COVID-19 vaccines for children under 5 years of age, and as we enter the season for influenza, please encourage your families with young children to receive the available vaccines to help protect against these respiratory infections.

I would like to direct your attention to the Special Feature Contribution on the ASPHO website that provides an excellent overview of how the Supreme Court Decision in ***Roe v. Wade*** (1973) and ***Planned Parenthood of Southeastern Pa. v. Casey*** (1992) as it may affect how we prescribe medications and care for our patients (http://aspho.org/knowledge-center/advocacy-brief/september-2022-advocacy-brief).

We would like to share some highlights on the transition of SOHO Executive Committee members this fall:

Executive Committee:

1. A warm Thank You to Carl Allen, MD, FAAP who has completed his 6-year term on the executive committee as of October 31, 2022. We also appreciate his support and participation within SOHO as the chair of the communication subcommittee. We are pleased to announce that Dr. Laura Rooms will serve as the next communications subcommittee chair beginning on November 1, 2022. Dr Rooms is a Clinical Assistant Professor in the Department of Pediatrics and Section of Hematology/Oncology at the University of Oklahoma Health Sciences Center.
2. Warm welcome to Suvankar Majumdar, MD, FAAP who was elected to the executive committee, beginning his term on November 1, 2022. Dr Majumdar is Chief of Hematology at Children's National Hospital in Washington DC.
3. In August, an inaugural meeting of the SOHO Trainee Subcommittee was co-chaired by SOHO Training Fellow Liaisons, Drs Irtiza Sheikh and Ann Marie Mojica. You can view the roster here and the position description here. They are in the process of identifying some short and long-term goals, including opportunities for fellows to participate in mentored reviews. Thank you to all who have volunteered to participate and watch for future opportunities!

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INSIDE THIS ISSUE

American Academy of Pediatrics
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Policy:

The American Academy of Pediatrics provides guidance on when and how to evaluate for bleeding disorders in children who have bruising or bleeding that is concerning for abuse, in two reports published in the October 2022 *Pediatrics*. A clinical report, "Evaluation for Bleeding Disorders in Suspected Child Abuse," observes that many bleeding disorders are rare but that in some instances, bleeding disorders can present in a manner similar to child abuse. An accompanying technical report, "Evaluating for Suspected Child Abuse: Conditions That Predispose to Bleeding," provides data supporting recommendations that distinguish abusive from accidental bruising and that characterize bruising in children with congenital bleeding disorders. These reports were a collaborative effort between the SOHO, the AAP Council on Child Abuse and Neglect and the American Society of Pediatric Hematology/Oncology. Congratulations to co-authors, James Anderst, MD, MSCI, FAAP (COCAN), Shannon Carpenter, MD, MS, FAAP (SOHO), Thomas Abshire, MD and Emily Killough, MD, FAAP (COCAN).

Advocacy:

1. The AAP recently endorsed and signed on to a letter from the Alliance for Children's Cancer (ACC) in support of the Clinical Trial Coverage Act (8546). Under the Affordable Care Act (ACA), private health plans are required to cover the routine costs associated with clinical trials conducted at in-network academic institutions. However, this requirement does not extend to the costs of routine care associated with clinical trials conducted at out of network institutions. This bipartisan Act would require health insurers to cover routine care costs provided by out of network clinicians. Routine care costs of clinical trial participation include the non-experimental costs of treating a patient who is participating in a clinical trial, such as the cost of lab tests, supportive care, or physician office visits. Such costs are part of the standard care and would be incurred regardless of whether a patient participates in a clinical trial. This Act would address this coverage gap for commercially covered children with cancer and ensure broader access to clinical trials for young people. Thank you to Dr David Dickens who serves as the AAP/SOHO representative to the ACC.
2. This past May, the AAP also signed on to letters from the American Society of Hematology to the Senate Finance Committee and the House Energy and Commerce Committee in support of the Sickle Cell Disease Comprehensive Care Act (H.R. 6216). The legislation outlines important steps toward addressing the needs of the SCD community by authorizing the Centers for Medicare and Medicaid Services (CMS) to develop a demonstration program for Medicaid beneficiaries to improve access to comprehensive outpatient care for individuals with SCD.
3. On September 15th the AAP has joined with Children's Cancer Cause and other partners, in holding an FDA-approved Externally-Led Patient-Focused Drug Development (EL-PFDD) meeting on *Reducing Cardiac Late Effects in Pediatric Cancer Survivors*. In total, over 150 people participated in the livestreamed event and was an opportunity for survivors and caregivers to educate representatives of the Food and Drug Administration (FDA), academic researchers, health care providers, and pharmaceutical companies about their personal experiences managing the impact of cardiac late effects on daily living and long-term health. The PFDD Program was created by the FDA several years ago as a mechanism to gather information more systematically from patients and survivors about their conditions, available therapies, and what matters most to them in balancing risks and benefits. This information helps inform FDA's drug development decision making process. As a follow-up outcome from the meeting, Children's Cancer Cause will submit a Voice of the Patient report to the FDA in January 2023.

Thank you to Drs Nino Rainusso (SOHO) and Thomas Ryan (Section on Cardiology and Cardiac Surgery) for serving as the AAP representatives and assisting with the planning of this important meeting.

Thank you also to Dr Mary Jane Hogan and the SOHO Education Subcommittee for their efforts to provide pediatric hematology/oncology programming for the AAP's National Conference and articles for parents via the AAP's HealthyChildren.org site. An update on these activities is found within the newsletter as well.

Thank you for your comments, thoughts and engagement and I wish you all a happy and healthful holiday season and the remainder of 2022!

With my best regards,
Cynthia Wetmore, MD, PhD, FAAP
Chairperson, Section on Hematology/Oncology
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Training Fellow Liaison Column:

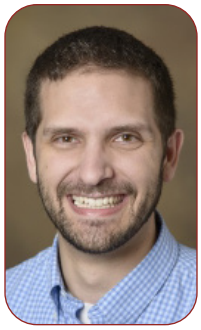
Super Fellowship: Miles to Go before I Sleep

Ann Marie Mojica, MD, FAAP
Pediatric Hematology/Oncology Clinical Fellow
The University of Utah, Primary Children's Hospital

and

Irtiza Sheikh, DO, FAAP
Pediatric Hematology/Oncology Clinical Fellow
University of Texas MD Anderson Cancer Center

"Super-fellowships" or advanced training in pediatric hematology-oncology have become increasingly popular ways for candidates to obtain training in highly specialized fields and distinguish themselves for post-training career opportunities. Following the completion of a categorical pediatric hematology-oncology fellowship, individuals have additional opportunities to train in fields such as stem cell transplant, neuro-oncology, classical hematology, and histiocytosis/lymphoma, among others. These training programs, usually encompassing one year and in some cases, two to three years, are offered by pediatric hematology-oncology fellowship programs across the country. While the concept of super-fellowships is not new, many questions linger in regard to the preparation, application process, support, time commitment, and financial ramifications that go into pursuing additional training. Here, we present three individuals in various stages of their career or training who offer their insight in pursuing an advanced fellowship in pediatric hematology-oncology, discuss their experience while in-training, and elucidate opportunities after completion of a super-fellowship. We hope that the perspectives provided by the following individuals answer common questions in regard to the pursuit of super-fellowships and provide a glimpse of life at the end of the training tunnel!



Trevor Memmott, MD, FAAP
Pediatric Hematology/Oncology Fellow, PGY-5
University of Utah/Primary Children's Hospital, Salt Lake City, UT

1. Why did you choose to pursue a super fellowship?

I came into medicine knowing I would become a Hematologist/Oncologist. After participating in St. Baldrick's fundraising events and working with this special pediatric population during medical school, I refined my choice to Pediatric Hematology/Oncology. As I have progressed through my training in Pediatrics and now Pediatric Hematology/Oncology, I have had amazing opportunities to connect with patients with central nervous system (CNS) tumors, including the child of a close family friend. These experiences form the foundation of my decision to pursue a Pediatric Neuro-Oncology fellowship.

An additional motivation is the fact that there are not enough Pediatric Neuro-Oncologists in this field, and the need is growing. In September 2022, the Central Brain Tumor Registry of the United States (CBTRUS) reported that brain and other CNS tumors are the most common solid tumor, most common cancer, and the most common cause of cancer related death in children 0-19 years of age. This report is disheartening, but it is a compelling call for Pediatric Oncology trainees to step up and meet this health crisis in our country head-on. For me, choosing this fellowship is a calling. I find joy working with these patients and their families. I find fulfillment helping them navigate their journey with all its ups and downs. By working with them, I have the unparalleled opportunity to practice the art of medicine in a space where healing is always possible, even though cure may not be. The privilege to be a physician and healer for these special children and their families elevates my thinking, my way of living, and my professional pursuits. It drives me to push scientific boundaries in my research efforts at the Huntsman Cancer Institute and Primary Children's Hospital. It strengthens me to be "all in" during both moments of celebration and moments of heartbreak, which are far too common among patients with CNS tumors.

2. Was the fellowship supported by employers with time, money or encouragement?

I am very fortunate to have amazing clinical mentors who helped me solidify this decision to pursue a Pediatric Neuro-Oncology

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fellowship. They encourage me to be the primary oncologist in many Neuro-Oncology cases and help me not spread myself too thin, which has been fantastic for my learning and growth. They have also let me take the lead in meaningful scholarly projects within the Neuro-Oncology community, which has helped me contribute to the field and to patients.

I also have meaningful relationships with clinical mentors in other subspecialties at my institution, such as Radiation Oncology, Neurosurgery, Palliative Care, and Physical Medicine and Rehabilitation. These teams know of my goal to become a Pediatric Neuro-Oncologist and already treat me like a full member of the Pediatric Neuro-Oncology team. My decision to pursue a Pediatric Neuro-Oncology fellowship is reinforced as we work on collaborative inter-departmental quality improvement projects and developing institutional guidelines to optimize care for our Pediatric Neuro-Oncology patients.

In addition to clinical mentor support and encouragement, my research mentor at the Huntsman Cancer Institute plays a pivotal role in facilitating my interests in translational medicine and targeted therapies. He provides funding support, grant-writing support, hours of one-on-one mentoring, and networking opportunities with national experts in our area of research. This has reinforced my desire to be a physician scientist who can take a clinical concept to the lab and then translate it effectively and efficiently back to the clinic to bring better treatment options to Pediatric Neuro-Oncology patients.

3. Was it worth the time and effort?

Since I have not yet begun, I can only speak to the time and effort leading up to this decision, but I would say it has been 100% worth it. I am confident that my Pediatric Neuro-Oncology fellowship training will help me further refine my research interests within the Pediatric Neuro-Oncology community, will strengthen my clinical skills and knowledge necessary to care for these children, and will serve as a springboard to a successful and fulfilling career in this wonderful field.

Eman Abdelghani, MD, FAAP
Pediatric Hemostasis Thrombosis Fellow
Nationwide Children's Hospital, Columbus, OH

1. Why did you choose to pursue this "super fellowship"?

My passion for hemostatic and thrombotic diseases in children started during residency. I pursued a hematology/oncology away elective rotation during residency where I was exposed to a wide variety of classical hematological diseases including coagulation disorders in children. I also learned about the possibility of doing an additional year of advanced fellowship to further subspecialize and gain experience in hemostasis and thrombosis and thus started thinking about it. I subsequently pursued a hematology/oncology/BMT fellowship at Nationwide Children's Hospital. Like any other pediatric hematology/oncology fellowship, the first year was mostly clinical. My interest in hemostasis/thrombosis continued to grow. In my second year of fellowship, I chose to conduct my research in Dr. Bryce Kerlin's lab to learn more about the basics of coagulation. Therefore, I joined an ongoing project to study the role of direct oral anticoagulants in nephrotic syndrome in an experimental animal model. I also co-led a project to better understand the role of antithrombin in nephrotic syndrome-associated hypercoagulopathy. Despite learning a lot about hemostatic and thrombotic diseases in my categorical fellowship, I didn't feel I had enough experience to start my career in this field. I made an effort to attend comprehensive bleeding disorder clinic and stroke clinic during 3rd year of fellowship but still didn't think it was enough. I decided to pursue The Joan Fellowship in Pediatric Hemostasis–Thrombosis to gain a more foundational understanding of coagulation disorders in children to 1) enhance my knowledge and experience in this field in order to make myself a better physician for this patient population, and 2) make myself more marketable as I start looking for jobs following fellowship. I am currently a 4th year hemostasis and thrombosis fellow at Nationwide Children's Hospital.

2. What support did you get while making this decision?

I am employed as a fellow at Nationwide Children's Hospital and I continue to have access to all fellow resources. I had sincere encouragement from my mentors and program director, who felt this program would profoundly support my professional development.

3. Was it worth the time and effort?

I am 3 months into this one-year long advanced fellowship program, with plans to graduate next summer. I love this fellowship so far, and I find it incredibly useful in building my knowledge in this field. I am excited to see what the next 9 months bring. This additional year of training will also afford me more time to finish my basic research project and hopefully have another publication by the end of the year. While also using this time to search for a job, I have noticed the interest this extra year of training has garnered amongst potential

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future employers, and, I have definitely felt very competitive. My interest and skills in hemostasis and thrombosis definitely help me standout in a highly competitive job market. Thus far, I am glad to have made this decision and it has been worth the time and effort to working towards my future career goals.

Nitya Gulati, MBBS, FAAP
Assistant Professor,Pediatric Hematology/Oncology
Texas Children's Hospital/Baylor College of Medicine, Houston, TX

1. Why did you choose to obtain the degree?

I am a pediatric oncologist at Texas Children's Cancer and Hematology Center (TXCH), Baylor College of Medicine (BCM). I completed my pediatric hematology/oncology fellowship at the joint program between New York-Presbyterian Hospital/Weill Cornell Medical Center (NYPH-WCMC) and Memorial Sloan-Kettering Cancer Center (MSKCC). In 2018, I pursued a pediatric histiocytosis and lymphoma fellowship at Texas Children's Hospital/Baylor College of Medicine (TXCH/BCM). How I ended up here was in part careful planning and in part serendipity.

During the last two years of my general pediatric hematology/oncology fellowship, I devoted my clinical time to following patients in the leukemia/lymphoma clinic, narrowing my focus on relapsed/refractory high-risk hematologic malignancies. In addition, I focused my lab research efforts on epigenetic mechanisms in the pathogenesis of B-cell lymphoma, for which I was awarded a St. Baldrick's Foundation Fellowship Grant in 2017. On the clinical research side, I was working on a multi-institutional clinical project describing our experience using brentuximab and bendamustine as salvage therapy for patients with high-risk relapsed Hodgkin lymphoma. As I thought about my next steps and considered job opportunities, I had three options.1) Continue my lab research for another year; 2) Look for a faculty position; 3) Pursue an advanced fellowship. While I enjoyed research, I knew I was never going to be the Principal investigator (PI) of a lab. Instead, my long-term career goal was to establish myself as a clinical researcher specializing in the study of pediatric hematologic malignancies with a focus on lymphomas. Additionally, as I looked for academic clinical jobs, I quickly realized that faculty positions for someone straight out of fellowship were few and far between. Most big academic centers were looking for junior faculty with at least 2-3 years of experience. In addition, they wanted someone with independent grant funding or someone who had a well-developed clinical niche and expertise. The exception was subspecialties with a fourth-year fellowship, such as neuro-oncology or bone marrow transplant. As I started looking for 4th-year fellowship positions, I knew that Texas Children's Hospital had a well-established advanced fellowship track. To my utter surprise and delight, they had a 'Lymphoma and Histiocytosis' fellowship.

The Lymphoma/Histiocytosis fellowship at TXCH/BCM allowed me to immerse myself in the clinical setting and closely follow patients with lymphomas and histiocytosis to become adept at management with both conventional and novel upfront and salvage therapies. In addition, I became part of a team that boasts of leaders and world-renowned experts in lymphoma and histiocytic disorders. This rare community of physicians and scientists understands more about the biology of histiocytosis and rare lymphomas than anyone in the world and is pushing the envelope in terms of novel therapies.

2. What support did you get while making this decision?

It was not an easy decision to leave a funded position at my alma mater. The thought of moving to a new place and having to learn and become proficient in a new system in a short period was very daunting, especially since I wasn't sure if the position would evolve into something beyond the one year of fellowship. However, my mentors at MSKCC/NYPH-WCMC and the St. Baldricks foundation were very supportive of my decision. In fact, with their support and the support of my mentors at TXCH/BCM, I could transfer my St. Baldricks fellowship grant to TXCH/BCM.

3. Was it worth the time and effort?

The 4th year provided me the space and time to better cement and reflect on what I wanted from my career. Training at a new institute helped me question the norm and open my mind to new and novel ways of approaching a diagnosis, not to mention the skill set it gave me in managing disease pathologies that very few people know about, such as Langerhans cell histiocytosis, non-LCH histiocytic disorders, hemophagocytic lymphohistiocytosis, post-transplant lymphoproliferative disorders, and primary immunodeficiency disorders. My training has opened up several job prospects at some of the best institutions, which would not have been possible without this fellowship. I now have mentors who are leaders in the field from both MSKCC-WCMC and TXCH/BCM. They have given me several publications and leadership opportunities in national and international organizations. On a more personal note, I have developed deep, meaningful friendships at work that go beyond professional ties.

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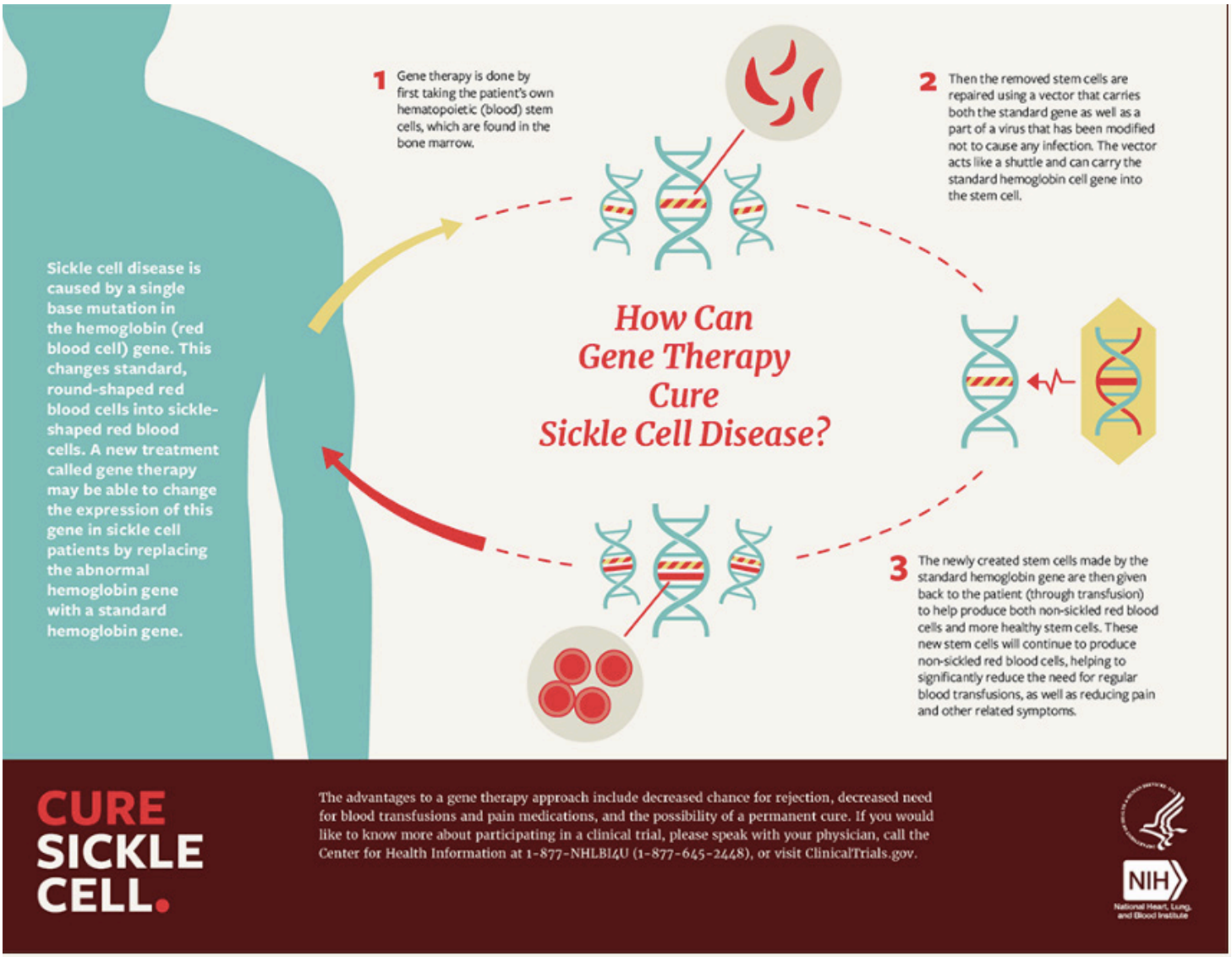
In summary, in this highly competitive job market, I sincerely believe that this additional year gave me a solid foundation and the platform to maximize my impact on the lives of children with cancer as a collaborative clinician-scientist focused on histiocytosis, lymphoma, and lymphoproliferative disorders.

Featured Clinical Topic: Sickle Cell Disease: The State of Gene Therapy

Lewis L. Hsu, MD, PhD, FAAP, Professor of Pediatric Hematology-Oncology
Sri Lakshmi Jamalapur, MD, FAAP, Assistant Professor of Pediatrics

Overview of Gene Therapy in Sickle Cell Disease:



Source: Cure Sickle Cell - https://curesickle.org/genetic-therapies. *This site, developed by National Institutes of Health/National Heart, Lung and Blood Institute, has many resources for patients and providers.*

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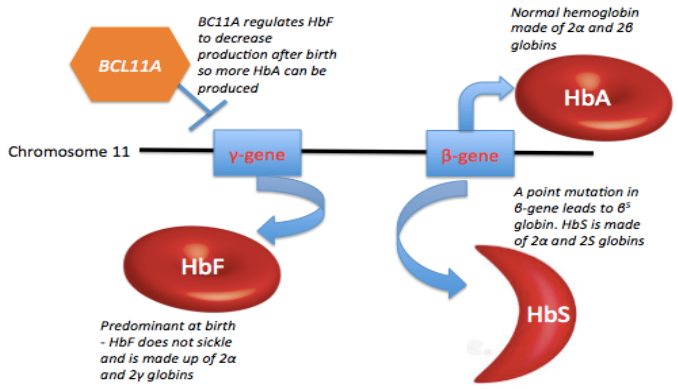
Briefly, hemoglobin is made up of four globins (proteins). At birth, the predominant hemoglobin is fetal (HbF), which is made of two α-globins (four alleles located on chromosome 16) and two γ-globins (two alleles located on chromosome 11). Shortly after birth, with the expression of gene *BCL11A*, the body decreases the amount of HbF produced and replaces it with normal adult hemoglobin (HbA). HbA is made of two α-globins and two β-globins (two alleles located downstream from the gene that encodes for the γ-globin of HbF).



Sickle cell disease (SCD) is one of the first genetic disorders we learned in biology and medical school, and at the forefront of molecular biology, SCD now is one of the most active areas of progress in gene therapy. SCD is clinically characterized by severe recurrent episodes of pain, organ damage and premature death. Despite being first described in 1910, progress in implementing research-proven interventions and towards a universal cure have been slow. SCD is due to abnormal hemoglobin. A single point mutation in the β-globin gene results in the production of sickle hemoglobin, HbS – an abnormal hemoglobin that polymerizes into a sickle/ 'C' shape during times of stress, such as hypoxemia, dehydration, or acidosis. Fetal hemoglobin, HbF, can reduce or possibly eliminate HbS polymerization, if there are sufficient quantities of HbF within the red blood cell.

Current therapies for SCD focus on symptom management, preventative or disease modifying – the latter of which only had one medication available until 2017. Curative options include blood and marrow transplantation (BMT). This involves replacing HbS with more normal HbA, thereby decreasing the amount of sickling. The best outcomes reported for individuals with SCD who undergo BMT are in those who are younger and have a matched sibling donor. Unfortunately, this limits the donor pool and risks of BMT include graft rejection and/or graft-versus-host disease (GvHD), delayed immune reconstitution, infertility and secondary malignancy.

Gene therapy has long been proposed as a potential cure for SCD. It is autologous and thereby avoids some of the inherent risks seen in BMT. Gene therapy alters the underlying genetic components to promote antisickling.

Broadly, there are four mechanisms by which genes can be interrupted:

1) Gene addition – using a viral vector (ex: lentiviral vector) system wherein genes are transferred into the genome; this delivers a globin gene that does not sickle into the stem cells. HbS is not altered therefore, both HbS and the newly introduced non-sickling hemoglobin is produced.
2) Gene editing – removal/replacement of DNA sequences causing permanent change to reduce percent of HbS by allowing increased production of hemoglobin with antisickling properties (such as HbF). This method involves targeting specific genes (such as the BC11A gene – which negatively regulates HbF). This method uses a guide and an enzyme that can cause double stranded breaks to change the DNA sequence; usually to induce an increase in HbF (by turning off the regulation of HbF)
3) Gene silencing – uses the regulation of gene expression in a cell to prevent the expression/production of certain proteins – it is similar to gene editing in that it increases HbF, however it does so by relying on a viral vector delivery (as see in gene addition)
4) Gene correction – aims to eliminate HbS production by directly removing the mutation while simultaneously delivering the corrected DNA sequence template

Regardless of type of gene therapy employed, the process generally involves intensive screening, stem cell collection (stem cells get processed ex-vivo), chemotherapy to prepare patient for transplant, transplant and finally post-transplant follow up. Figure 1.

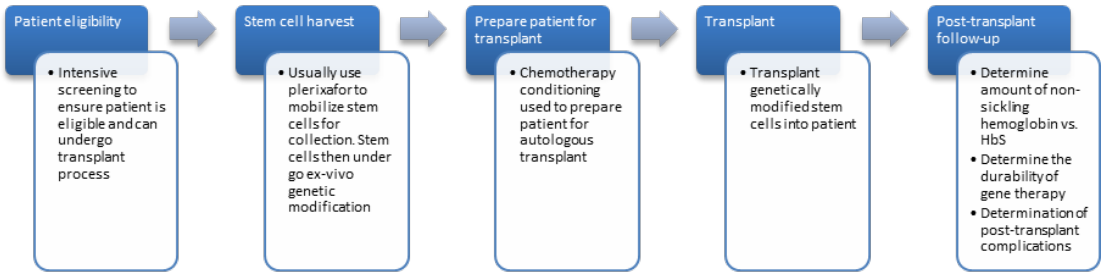


Figure 1: General process of gene therapy

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The main risks of gene therapy are probably the side effects of myeloablative chemotherapy, including infertility and secondary malignancy. Two patients in a SCD gene therapy clinical trial developed acute myelogenous leukemia. Studies determined that the vector used in the gene therapy itself was not associated with the malignancy, but the etiology for the AML remains unclear. Furthermore, the long-term risks of gene therapy are still unknown.

Though gene therapy seems promising, further studies are needed to evaluate the efficacy of gene therapy – determining how much new hemoglobin is produced. Other studies needed are to determine gene therapy duration, complications of gene therapy and to evaluate what symptoms/complications of SCD improve with this process (can it prevent vaso-occlusive crises or end-stage renal disease – common complications of SCD?).

As of September 2022, there are approximately 7 active and upcoming gene therapy studies in SCD. Though there are no current FDA approved gene therapies for SCD, in August 2022 the FDA approved gene therapy for the treatment of adult and pediatric patients with transfusion dependent β-thalassemia – another type of hemoglobinopathy. In light of this, we can anticipate that there may be FDA approval for SCD gene therapy in the near future.

Study Name	Type of gene therapy	Editing Tool	Vector Type	Genetic Target	Protein product
LentiGlobin	Gene addition	N/A	BB305 LVV	N/A	HbA^{T87Q}
DREPAGLOBE	Gene addition	N/A	DROBE 1 LVV	N/A	βAS3
CLIMB	Gene editing	CRISPR-Cas9 RNP	N/A	*BCL11A* gene	HbF
PRECIZN-1	Gene editing	Zinc finger	N/A	*BCL11A* gene	HbF
Genetic silencing of *BCL11A*	Gene silencing	ShRNA	BCH-BB694 LVV (encodes a microRNA-adapted shRNA)	*BCL11A* mRNA	HbF
MOMENTUM	Gene addition	N/A	yG16D LVV	N/A	HbF^{G16D}
CEDAR	Gene correction	HiFI CRISPR-Cas9 RNP	Nonintegrating AAV6 donor DNA repair template	Sickle mutation (specifically the point mutation to change adenosine to thymine	HbA

Table 1: *Current and upcoming studies of gene therapy in SCD. N/A – not applicable; LVV – lentiviral vector; HbAT87Q – Hb with a single mutation conferring most of the antisickling effect of γ-globin; βAS3 – an antisickling β-globin containing 3 amino acid substitutions in the wild-type HBB; HbFG16D – modified HbF that increases affinity to α-globin to outcompete sickle mutated β-globin; AAV6 – Adeno-Associated Virus serotype 6.*

As more studies establish the efficacy of gene therapy, shared-decision making should be utilized between patients, families and providers when discussing any treatment option for patients with SCD. Specifically, emphasis should still be made between the benefits, risks and 'unknown' aspects of each treatment option. Exciting research is also bringing new medication options for care without gene therapy. However, these scientific advances are juxtaposed with continuing inequities in SCD care, which led to a recent call to action (NASEM 2020 sickle cell blueprint for action): barriers to care, stigma, negative attitudes and uneven knowledge.

In conclusion, gene therapy holds promise as a curative option for SCD, though additional information related to remediation of organ-related SCD complications, long term efficacy, durability and complications of gene therapy need to be further studied.

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2. Abraham AA, Tisdale JF. Gene therapy for sickle cell disease: moving from the bench to the bedside. Blood. 2021 Sep 16;138(11):932-941.
3. National Academies of Sciences, Engineering, and Medicine. Addressing Sickle Cell Disease: A Strategic Plan and Blueprint for Action. Washington, D.C.: National Academies Press, 2020.
4. The Cure SCD Initiative website has many resources on gene therapy for providers and patients, including stories, scientific and health services research. https://curesickle.org/

Workforce & Training Perspective: Evaluation and Evolution of the Pediatric Hematology-Oncology Fellowship Recruitment Process

Priti Tewari MD, FAAP
Associate Professor, Pediatrics
Pediatric Hematology Oncology and Advanced Fellowship Program Director
Children's Cancer Hospital at The University of Texas at MD Anderson Cancer Center

March 2020. As many parts of the world paused and shut down, medical systems rapidly transformed to work harder than ever putting our own health at risk to stand up to our calling: care for and provide compassion towards patients, their families, and each other. Medical students, residents, and fellows paused from their day-to-day educational rotations to join the frontlines as well. As educators, we caught our breath and rapidly learned how to be innovative in teaching, providing didactics, and safely and responsibly staying connected especially with our trainees.

Naturally, as the months passed, we found ourselves watching COVID-19 peaks and dips in various areas of the nation as the ERAS® application process opened in 2020.

Programs rapidly scurried to redesign fellowship recruitment. Zoom rooms? Google meet? Breakout rooms? How many interviewees per day? Mail recruitment materials? Recorded tours or live smartphone tours?

As a program in Houston, Texas (HTX) we had to adapt and innovate our approach. I added a slide describing our one-of-a-kind Texas Medical Center in our 'Highlights of our Program Presentation', included links with online videos to local popular neighborhoods, and encouraged those (which seemed like many) who had never even been to Houston to chat with folks throughout the day about our city, and their life in Houston when they are not at work. Naturally, applicants had to also rapidly prepare and adapt to the virtual process.

Amongst configuring/reconfiguring schedules, off-camera breaks, and closed trainee meets ups, our program used an interdisciplinary approach with interviews including Pediatric hematology-oncology faculty, fellows, and advanced practice providers. Evaluations were collected from our program interviewers, and after a long on-screen season rank lists were discussed, created, and submitted. Interestingly, evaluations and candidate discussions at the rank list meeting seemed to highlight many similar themes and uniformity among our interdisciplinary team members. The program adjustments had paid off and the December 2020 Match was a huge success.

As our matched incoming class of trainees arrived to work on July 1, 2021, masked, they rapidly settled into their new city with their colleagues, our patients, and our program. Following this essentially forced 'emergency' recruitment system and near social experiment for recruitment, the class of 2024 fellows were a phenomenal fit for our program.

In December 2021 as vaccinations became available the same workforce who left the safety of their homes during the drastic pandemic start now were first to line up to get vaccinated to help protect their families, their patients, each other, and themselves.

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As the next recruitment approached COVID-19 variants emerged, with new spikes, and sustained uncertainty, we continued protective measures with masks (at times shields as well) and another virtual interview season. This time recruitment was very similar except much smoother with my proudly perfected share screen skills. We also anticipated potential issues so rapid backup plans were created if there were tech malfunctions. The second recruitment season was also re-designed with valuable feedback from the prior year's candidates (including those first-year recruits) which primarily included: considering shortening the interview day due to online fatigue.

This second time around I intentionally collected one specific data point during the interview by asking 'Have you ever been to Houston?'. Exactly 50% had never landed in HTX. End Results: bright, optimistic, and spectacular fellows matched and entered our program on July 1, 2022. Most importantly, those entirely virtually recruited candidates have been thriving and phenomenal matches to our program and enjoying their city of choice as well.

Currently, as many have become vaccinated, children returning to school, and continuing trends of decreasing serious morbidity and mortality risks from COVID-19 infection, in-person national academic meetings are resuming, masks are disappearing, institutional travel precautions lifting, and we entered our 3rd recruitment season since March 2020.

All program directors have our experiences, insight, and input. While only a few years have passed since March 2020, many years have passed since our fellowship match started, and so much has changed since the old normal[1]. Exactly how should we move forward? Was the old system still logical? Was it frozen in a previous decade? In a busy clinical world where physician well-being is heavily compromised, was it the best possible system for trainee/program time efficiency[2,3]? Above all was it fair, and equitable? Was it inclusive to the trainee who simply could not apply to certain programs because they couldn't financially afford to or did not have time for an extensive interview process?

Potential limitations of the virtual-only process include loss of connection; inability to show candidates new and beautiful patient rooms and towers; difficulty assessing candidates in further depth, specifically really getting to know someone who was no longer present live in 3D for a dinner the night prior, or for a day of touring our faculty offices and facilities[4].

On the other hand, how much time and money are saved by a program, and more importantly the applicants? Our applicants are primarily Pediatrics residents juggling time and coordinating call schedules as they schedule interviews in between calls and heavy clinical responsibilities. Saving up to $5,000 may likely be a substantial amount of money for a resident balancing expenses, preparing for a potential move, and additional training years[5-7]. Does cost preclude applicants from applying to programs otherwise, was the financial burden of in-person interviews an overlooked inequity? What are environmental considerations, and should that be a responsibility that we take accountability for as well[5,8]?

Although nothing is currently published specifically in our subspecialty, a survey by our pediatric anesthesia colleagues following the 2021 season highlighted that virtual interview applicants felt they were able to learn about salary and benefits, available academic opportunities, available clinical opportunities, clinical schedule of the fellowship, mentorship opportunities, clinical experience and training of the fellowship, and expected work-life balance during the fellowship. Applicants reported saving $3,000-$5,000 using the virtual process and programs reported savings up to $5,000[6].

A 2020–2021 cycle survey by Orthopedic programs identified 42.2% of applicants applied to more programs due to the virtual process, 66.7% of applicants accepted more interviews due to the virtual format, and 67% of respondents did not feel the virtual interview format negatively affected their match process. The survey also noted 84% of applicants reported saving over $2,000. Programs reported interviewing more applicants compared to previous in-person years and about half of the program directors and applicants reported they would use a virtual format in the future[9].

Applicant perceptions in urologic oncology, where reported costs to applicants are even higher, showed 63% of respondents would prefer a virtual format in the future. Benefits include lower cost and reduced time away from residency with the most notable weakness being the inability to observe the culture of the program[7].

Many of our leading academic associations provided helpful guidance and statements regarding how to proceed going into the 2022-2023 recruitment season. The American Association of Medical Colleges (AAMC) provided 5 key recommendations (supported by the American Medical Association, National Resident Matching Program, Educational Commission for Foreign Medical Graduates, Council of Medical Specialty Societies/Organization of Program Director Associations) for the 2022-23 cycle (Table 1) including tips and resources for best practices[10].

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As Pediatric Hematologists-Oncologists we must pause, evaluate the process and be open to embracing evolution. A key component and step, as highlighted by AAMC recommendation #5, we need to collaborate, collect, and evaluate our field's data[10]. Recognizing until then we are mostly sharing opinions and anecdotes loaded with personal/potential biases.

Pediatricians and pediatric hematologist oncologists are inherent leaders and natural advocates who embraced the virtual interview process as a necessary safety measure following March 2020. The last 2 recruitments have certainly taught us that virtual recruitment is a feasible process[11]. The COVID-19 pandemic shifting our system hopefully results in a forced evaluation and evolution of a decades-old process. Just as the medical community has led and supported the world thru the pandemic, our medical community needs to come together, collect and evaluate data; and evolve and accept best recruitment processes in our current world. We also need to build in reflective practices moving forward so we are not waiting for another world pandemic to drive us to change.

Table 1. AAMC Guidance for 2022-23 Recruitment[10]

AAMC Interview Guidance for 2022-2023 Residency Cycle	
Recommendation #1	Programs should conduct virtual interviews for all applicants (including local applicants) for the 2022-23 cycle.
Recommendation #2	Hybrid interviewing within the same program is strongly discouraged for the 2022-23 cycle.
Recommendation #3	Programs should share their interviewing plans with applicants clearly and early, preferably when application requirements are released.
Recommendation #4	Programs should prepare for the interview cycle by reviewing resources on anti-bias practices, best practices in creating and implementing virtual interviews, and creating tools for recruiting in a virtual context.
Recommendation #5	Organizations should commit to collaborative research to explore key aspects and outcomes of in-person and virtual interviews.

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Call for Nominations:
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We are seeking AAP members with an interest and enthusiasm in education to assist with the development, ongoing maintenance, and innovation of this important educational program.

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Featured AAP Section Newsletter Articles:

Are You Ready? How to Practice and Survive After a Disaster

Dennis Cooley, MD, FAAP
(AAP Board of Directors District 6 Chairperson)

Dennis Cooley is a past AAP President of the Kansas Chapter. In 2019, he was elected as Chair of District 6 and began serving on the AAP Board of Directors. From 2010 to 2018 Dr Cooley served on the AAP's Committee on Federal Government Affairs and was Chair of the AAP's Subcommittee on Access from 2016-2018.

Disaster preparedness for our practices may not be considered a high priority. Disasters are not everyday occurrences and other practice problems are more pressing. But we think nothing of getting insurance for our homes and cars on the off chance some rare event might occur. We should think of disaster preparedness and planning the same way- as a form of insurance that every practice and office should have in place.

As pediatricians we have many roles that we can play during disasters. Community planning, front line surveillance and volunteer medical care to name a few. In addition, our offices can be used as walk-in clinics or in some instances special care facilities. But our most important role is to maintain the function of our practice.

Maintaining a functioning practice in the time of a disaster serves the greater good of the community by doing what we do best- taking care of the needs of children. We are the experts. In addition, there are also other reasons to maintain our practices- personal reasons. Our families, our staff, and of course our patients all rely upon us for financial, medical, and emotional support.

Disasters that affect our practices can come in many forms. Too often we think of disasters in terms of only large, major occurrences. But in reality, most disasters occur on a smaller scale. For example, a building fire or power outage will have many of the same problems as the tornado that destroys large sections of your community. But one key principle to remember is that all disasters are local. Don't expect immediate help from your state or the federal governments. You need to consider how you will manage over the first few days or possibly longer. To be successful you must be proactive and not reactive. Just as you must obtain insurance before and not after an event you must prepare your office before these rare events occur and not just hope things will work out afterwards.

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Disaster planning involves an all-hazards approach and when planning for your office response this should be followed. But all-hazards doesn't mean that every practice plan is identical. While basic planning frameworks can and should be used, each office is unique, requiring special thought and considerations when developing the plan.

First and foremost, in any disaster plan should be the safety of staff and patients. Planning with drills helps staff know evacuation routes and safety protocols. Building damage can be mitigated by knowing where shut off valves are located. Generators may help you stay in your office providing limited care. But you still should look at alternate practice sites in the event your building is so damaged you cannot use it. Above all, get signed agreements with other facilities if you plan to use them in your disaster plans.

Make a list of important or expensive equipment. Maintain a place of storage that will provide maximum safety. For example, if you are in a flood plain the basement is probably not a good choice. Also maintain information on repair or replacement and know how to readily access it.

Determine what basic supplies you will need to manage over the first few days or weeks. How can you assure that these supplies will be available? One option is a 'go box' stocked with supplies that allow you to provide basic care to your patients. Again, it must be readily available so choose where you store it wisely.

In any disaster the first and most frequent breakdown is in the area of communications. Think about three questions when developing the communications section of your plan. Who will I need to communicate with? What information needs to be shared? How am I going to accomplish this?

Special mention should be made about vaccines. Vaccines are probably the single most expensive item in our inventories. Hundreds of thousands of dollars are involved. A separate vaccine recovery plan needs to be made. This is a requirement by the CDC if you do VFC. In my experience power outages are not uncommon. A word of warning- generators sometimes fail! Be prepared in these instances. Also, be sure to read the fine print on your vaccine insurance policy. Some may cover only 'acts of god' and not accidental losses due to a staff member.

It makes sense that during a disaster when your practice capabilities are limited your income most likely will suffer. Develop a relationship with a financial institution that will allow you to get a rapid line of credit should the need arise.

As physicians we forget to take care of ourselves. We are not immune to the stress of disasters. We too will be worried about our families in addition to the responsibilities we have to our patients and staff. In the immediate post disaster period we can suffer fatigue and physical and emotional strain. Self-care is not being selfish. Start by making sure you have your family's personal disaster plan in place. Consider making pre-arrangements to get relief from your practice responsibilities for brief periods of time during the recovery stages. Also look to your state AAP chapter. Many of them have plans set to assist their members during disaster situations. I think the hardest thing we have to do as physicians is ask for help.

Disasters are not uncommon. Hopefully, you will never experience one of these events. But the benefits of having a well thought out disaster preparedness plan in place if your practice suffers a disaster are well worth the efforts. A proper plan takes time and thought to develop. The AAP has a number of resources to guide you in developing such a plan. Two of these *Preparedness Checklist for Pediatric Practices and Pediatric Preparedness Resource Kit* can be found online at https://www.aap.org/en/patient-care/disasters-and-children/professional-resources-for-disaster-preparedness/.

* This article was reprinted with permission from the Section on Administration and Practice Management (SOAPM) spring 2019 newsletter.

Are You Ready for An In-Office Disaster?

Jeanne Marconi, MD, FAAP

(Former SOAPM Executive Committee Member)

Jeanne Marconi is a pediatrician President, managing partner, and Medical Director at The Center for Advanced Pediatrics, a multi-specialty pediatric practice in Norwalk, CT.

At the 2018 AAP NCE SOAPM Section H addressed many ways disasters can affect the children we see; our communities and even ourselves as disaster can have a direct hit on us as well. Following in the motto of the Boy Scouts, "Be prepared for a day when the unexpected happens". From the natural to the supernatural we heard it all. As I focused on the disasters that can affect you in your own here please find some of the highlights.

In office disasters come in many forms natural, external and internal. Natural can include those caused by hurricanes, external can be violence (mass casualty), community outbreaks (measles, flu), hazardous spills and fire. Internal can be administrative and facility related. Administrative can include embezzlement, sudden death of a key employee, an unexpected leave of a key player, HIPPA breach, internet or EHR access issue. Facility disasters may include internal floods, AMBER alert from your office, no electricity etc. Are you ready for all of these in your practice? Have you spent any time on a disaster plan? Do you have a plan of action if you could not work out of your office tomorrow? If not, please take this opportunity to seriously consider what you need to prepare and do to be sure you are as ready as possible for any of these unexpected disruptions.

First, be sure you and your office are well protected by insurance. General liability, business interruption, key man plans, cyber coverage; vaccine loss coverage, errors and omissions and the list goes on. Be sure you are in control of your inventory and property, have a list. Stay tuned as SOAPM is planning a webinar on all the insurances you should consider.

Second, create a communications plan. Have contacts handy and not in your old- fashioned rolodex. Landlords, vendors, staff, insurance agents, utilities, clean-up services, meet and hire an insurance adjuster just in case you need one. All of this will save so much time and stress.
Know what you might do if you cannot see patients in your space. If you do not have another office contemplate who you might call for assistance, the hospital, a colleague etc.

Know how to connect with your patients to keep them informed. Social media, email, local radio and cable companies.

Ensure safety of staff and do not touch or clean-up anything until your personal adjuster tells you to. Take photos and time and date them.

Keep your financials up to date. Productivity, P/L statements become critical in any of these disasters.

Know all your logins to all your accounts and have and maintain an updated vendor list.

Make your bank a friend. Keep a line of credit for just in case scenarios. If you cannot see patients, you cannot bill or pay your bills. This is where business interruption insurance is CRITICAL especially if you do not have a fortress of available funds.

Assign a disaster champion. This does not and probably should not be your administrator/office manager or managing partner. This is someone who is a multi-tasker; calm; detail oriented and can easily follow directions. This person will need to know excel and have some knowledge of keeping lists, receipts. Open a disaster account so you can keep all of these things straight. This will be needed for your accountant to process the disaster properly in your books.

Did I say communication? This is an ongoing process and needs to be addressed maybe several times even in one day. All people respond differently in these situations and what you say may not be what they hear.

For those administrative disasters related to a quick departure or for embezzlement be sure there are checks and balances everywhere. Do not develop such strict routines that things can become impermeable to you. Do surprise looks at things and again always have a plan B. Keep a close eye on credit cards and access. Call your credit card companies now and be sure anyone who has one there is a signed communication with the credit card company that this person is only authorized to use them for office use only (please take this seriously).

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After the event, be sure to de-brief and look at processes that you can improve. Be sure to review your disaster plan yearly and update accordingly.

Finally, do not underestimate the effect these events can have not only on you and your family but also on your staff. I can suggest a good debrief meeting perhaps by the hospital chaplain or a therapist you know. Many people do not know how to find closure, and some take longer than others.

I hope this information prompts you to consider a well-structured disaster plan for your practice so you are well prepared for any that may unfortunately come your way.

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The Great Investigator Gap in Sponsored Pediatric Clinical Trials

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The landscape of industry (pharmaceutical or device) sponsored clinical trials in pediatric populations has made enormous gains since regulatory mandates first were introduced in the 1990's. However, the ability to recruit patients into these trials has faced significant challenges thus dampening the progress. A major issue for recruitment is related to the finite number of pediatric research sites interested and capable of conducting these regulatory mandated trials.

In the US, the FDA pediatric regulations have been outlined within the Pediatric Research Equity Act (PREA).[1] This legislation has the aim to progress knowledge and data impacting pediatric clinical care through incentives and mandates for conducting pediatric clinical trials following approval of an IND in an adult population. Since this legislation was first introduced in the 1990's, mandates have expanded into pediatric oncology (FDA Reauthorization Act of 2017 (FDARA)[2] and device work (2007 Pediatric Medical Device Safety and Improvement Act).[3] This has led to more pediatric clinical trials and data which offer insights and care decision support resulting in a positive impact to pediatric medicine and patients.

Various researchers have published on the challenges related to recruitment for pediatric clinical trial work. Per a 2018 publication from Hwang et al, nearly 2/3 of pediatric IND trials between 2007 and 2014 were discontinued or had not reached enrollment targets within 6 years of starting.4 This poses a significant hardship for sponsors, investigators, and most importantly the patients and families participating or looking to the research community and IND/device trials to develop new care options.

Publications and reported metrics have noted several reasons for not meeting enrollment goals.[5] While it is true that pediatric, indication specific populations are limited and even considered rare by some; the 2020 US census showed approximately 22% of the population was less than 18 years of age.[6] This offers perspective to set our expectations and grow our potential to improve how we conduct and meet the recruitment for PREA mandated trials. We will always experience a more limited and shifting pool of pediatric patients but there is the opportunity to expand access to clinical trial work to reach more of the pediatric population.

Having worked in the pediatric clinical trial space for over 15 years, at both a site and now from a contract research organization (CRO) perspective, there is a supply and demand issue at play that is greatly impacting the ability of these trials to enroll and produce meaningful data and expanded choices for pediatric medicine. While there has been needed and successful growth of pediatric investigational new drug trials (demand), there has not been the same growth in developing new investigators and sites with access to a more diverse and broader pediatric population (supply).

The large academic pediatric centers are arguably the best centers for complex indications or advanced therapies where multiple sub-specialists and diagnostic capabilities are required. However, problems arise due to a funnel effect limiting the number of trials an investigator can support both from a recruitment/patient pool perspective but also a resource perspective. Factors affecting the resource

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funnel include clinical care and academic responsibilities and access to trial coordinators. Many of these centers are also involved with government and consortium work which may be prioritized creating further barriers to successful recruitment and completion of industry sponsored trials. When these known centers are unable to recruit or reject a study due to resourcing, competition, or lack of patient population the trial often has to extend timelines (at best) or abandon the trial (worst case), as there are only a finite number of experienced sites and investigators with no good mechanism in place to develop new sites and investigators. This leaves valuable research questions unanswered and data unpublished, the exact opposite intention of the regulations.

Within the industry sponsored clinical trial space, CROs and sponsor companies often seek participation from the same investigators and sites, predominantly large academic pediatric centers in urban areas. As noted, these centers house diverse sub-specialty pediatricians, diagnostic capabilities, research experience, and access to known pediatric patient populations. While these centers have conducted quality clinical trial work for decades, and will remain a key entity for research projects, they cannot fill the overwhelming need for pediatric patient enrollment in the expanding clinical trial space. This begs the question for how to increase access to and improve the diversity of pediatric patients recruited into clinical trials while also helping to fix the supply and demand issue currently being experienced.

The pandemic has further exacerbated issues in conducting pediatric clinical trials as we have seen impacts on human resources at the known sites across all research roles, from loss/aging/retirement of pediatrician researchers, nurse study coordinators, administrative or support staff, and the institutional review boards. Even prior to the pandemic, one article noted the impending problem of aging medical researchers and a lack of younger investigators.[7] This leaves us with an even greater risk of delaying or stalling out important work to further advance pediatric clinical care. Those of us working in this space cannot expect the human resource and recruitment problem to fix itself.

A solution, to help address this supply and demand issue affecting recruitment, is to educate, encourage and support more sites and clinicians to become investigators and opt into sponsored clinical trial work. The urban corridor houses a finite amount of the pediatric population, leaving a portion hidden from or inaccessible to clinical trial work simply due to their location and/or utilization of an academic or known pediatric research center. There remains a subset of mandated clinical trial work that could be conducted outside of the large, known research centers and the urban corridor. Finding hospitals and clinics with pediatricians and support from their administration to learn and invest resources towards regulatory mandated, industry sponsored research has been difficult, but is a viable mechanism to help this supply and demand issue.

There is no doubt that key stakeholders, including clinicians, pharmaceutical companies, and CROs, need to work together to help develop the next generation of investigators. There is a need for a shift in how clinical research is factored into the clinical care of pediatric patients. We need more pediatric investigators and sites to offer and conduct clinical trials to build knowledge and access more treatment options proven through good research. This includes private practices and general pediatrician clinics, local/smaller community or non-academic hospitals with pediatricians or pediatric units, as well as partnerships with Integrated Research Organizations (IROs).

The first step is educating clinicians. Programs that support and educate on government regulations and industry sponsored clinical trial work during residency and fellowship training can help enable and build a new generation of researchers. Additionally, CROs and pharmaceutical or device companies are needed to support selection of green sites and investigators recognizing that this involves some risk and added support is required to mitigate this risk. Advanced planning is required for this, and collaboration needs to occur well before a clinical trial begins. Clinical trials should be a conversation that is normalized and apart of clinical care but we first must empower and educate pediatricians to feel confident about participation for themselves and their patients. Structures and tools that support new pediatrician investigators may also come in the form of partnerships with larger academic centers, CROs, or IROs that provide smaller hospitals or private clinics access to education, mentoring, and create a pathway to enter and thrive within the industry sponsored clinical trial space.

We have a clear gap where there is a large amount of pediatric clinical trial work to be done and very finite resources to successfully recruit, collect data, and effect pediatric labeling or the sharing of results, so critical to scientific progress. There is a true need to build a new generation of pediatric investigators and sites that capture a more diverse patient pool and allow for trials to successfully enroll in reasonable timelines to impact clinical care.

This article is a call to action for all SOATT members to message, encourage, mentor, and promote the important need for new pediatric investigators. Consider what you can do at your own hospital, clinic, or company as a mentor to help develop future researchers and sites. Although the pandemic has had many negative impacts to our lives one major success story is the work researchers have done. Our

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communities are aware of and talking about industry sponsored clinical trials more than ever and now is the right time to encourage the next generation of investigators. The intention is that this article generates further discussion and willingness of how each of us within SOATT can assist development of sites and investigators to ensure new medicines and innovations are properly and efficiently researched in pediatric patients.

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Hot topics in Hematology and Oncology

Reviewed by: *Laura Rooms, MD, FAAP, Assistant Professor Pediatrics, The Jimmy Everest Center for Cancer and Blood Disorders in Children, University of Oklahoma Health Sciences Center.*

1. **Latoch E, Zubowska M, Młynarski W, Stachowicz-Stencel T, Stefanowicz J, Sławińska D, Kowalczyk J, Skalska-Sadowska J, Wachowiak J, Badowska W, Czajńska-Deptuła A, Dembowska-Bagińska B, Garus K, Skoczeń S, Pobudejska-Pieniążek A, Szczepański T, Machnik K, Panasiuk A, Sęga-Pondel D, Malesza I, Raciborska A, Zielezińska K, Urasiński T, Mizia-Malarz A, Wawrzeńczyk A, Karolczyk G, Kołtan A, Wysocki M, Wołowiec M, Matysiak M, Krawczuk-Rybak M. Late effects of childhood cancer treatment in long-term survivors diagnosed before the age of 3 years - A multicenter, nationwide study.** *Cancer Epidemiol***. 2022 Jul 19;80:102209. doi: 10.1016/j.canep.2022.102209. Epub ahead of print. PMID: 35868173.**

   The treatments used to achieve the high survivorship rates of pediatric cancers comes with consequences to a population that is experiencing "intensive growth and maturation of all organs". The effects of anti-cancer therapy on infants and young children exceed those on older children in adolescents, which in turn predisposes them to more significant morbidity later in life. This article describes a cohort of 561 long-term childhood cancer survivors in Poland, selected from the Polish National Childhood Cancer Survivors Registry that received anti-cancer therapy between the ages of 0-3 years of age. Median follow up time from completion of therapy was 9.85 years.

   Of those enrolled, only 16.8% had normal function of all organs assessed. Four or more dysfunctions were noted in 39.2% of children. Urinary system involvement was most commonly observed at a frequency of 30.8%, followed by 23.6% with circulatory abnormalities, 23.5% with immune dysfunctions, 20.8% with gastrointestinal issues, 19.2% with musculoskeletal conditions and 17.8% with impairment of nervous system function. Endocrine disturbances, including gonadal dysfunction became more prevalent

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as the duration of follow up increased. The strongest link to detrimental effects was noted in patients who received radiotherapy as part of their treatment. Overall incidences of late effects were similar to survivors treated at an older age, with the exception of hearing loss and gonadal dysfunction.

2. **Teachey DT, Devidas M, Wood BL, Chen Z, Hayashi RJ, Hermiston ML, Annett RD, Archer JH, Asselin BL, August KJ, Cho SY, Dunsmore KP, Fisher BT, Freedman JL, Galardy PJ, Harker-Murray P, Horton TM, Jaju AI, Lam A, Messinger YH, Miles RR, Okada M, Patel SI, Schafer ES, Schechter T, Singh N, Steele AC, Sulis ML, Vargas SL, Winter SS, Wood C, Zweidler-McKay P, Bollard CM, Loh ML, Hunger SP, Raetz EA. Children's Oncology Group Trial AALL1231: A Phase III Clinical Trial Testing Bortezomib in Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia and Lymphoma. *J Clin Oncol*. 2022 Jul 1;40(19):2106-2118. doi: 10.1200/JCO.21.02678. Epub 2022 Mar 10. PMID: 35271306; PMCID: PMC9242409.**

   The authors summarize the results of the Children's Oncology Group (COG) Trial AALL1231, a study undertaken to improve outcomes in the pediatric T-ALL population. The study had as a primary objective to improve on survival outcomes by the addition of proteasome inhibitor bortezomib to a modified augmented Berlin-Frankfurt-Munster (aBFM) backbone and a secondary objective to demonstrate safety of eliminating cranial irradiation in standard or intermediate risk patients.

   The study enrolled 847 patients while open, with a 1:1 randomization between the standard arm (no bortezomib) and the experimental arm (8 doses of bortezomib in total, 4 in induction and 4 in delayed intensification). Accrual ended when the previous study AALL0434 demonstrated improved survival rates with nelarabine, given the statistical unfeasibility of isolating the effect of bortezomib with the addition of nelarabine. Data analysis revealed no statistically significant improvement of outcomes in T-ALL patients, although it did demonstrate excellent outcomes even in the absence of cranial radiation. Further, outcomes for T-lymphoblastic lymphoma (T-LL) patients were significantly superior, with 4-year EFS of 86.4% v. 76.5% in the no-bortezomib arm. Toxicity rates and adverse events were similar in both treatment groups. The authors conclude that bortezomib shows promise in treatment of T-lymphoblastic lymphoma, specifically in the ability to eliminate cranial radiation with its high incidence of associated toxicity and late effects, and recommend its incorporation into future T-lymphoblastic lymphoma trials.

3. **Shalabi H, Qin H, Su A, Yates B, Wolters PL, Steinberg SM, Ligon JA, Silbert S, DéDé K, Benzaoui M, Goldberg S, Achar S, Schneider D, Shahani SA, Little L, Foley T, Molina JC, Panch S, Mackall CL, Lee DW, Chien CD, Pouzolles M, Ahlman M, Yuan CM, Wang HW, Wang Y, Inglefield J, Toledo-Tamula MA, Martin S, Highfill SL, Altan-Bonnet G, Stroncek D, Fry TJ, Taylor N, Shah NN. CD19/22 CAR T cells in children and young adults with B-ALL: phase 1 results and development of a novel bicistronic CAR. *Blood*. 2022 Aug 4;140(5):451-463. doi: 10.1182/blood.2022015795. PMID: 35605184.**

   The authors describe the results of a Phase 1 dose-escalation study in children and young adults (CAYA) with relapsed/refractory B-ALL using a bivalent CD19/CD22 CAR T-cell construct. Monovalent CAR constructs, while efficacious, are known to lead to treatment resistance or failure due to leukemic antigen modulation (e.g., the loss of CD-19 antigen expression on the surface of leukemic cells). Through development of a bivalent construct, the authors hoped to minimize the risk of antigen modulation while avoiding the logistical and practical complications that would be associated with the development and infusion of two separate products simultaneously.

   Of 20 patients with B-ALL, all had successful manufacturing of the product. Twelve had relapse after at lease one allogeneic hematopoietic stem cell transplant and fifteen had received either CD-19 or CD-22 directed therapy previously. Three dose levels were utilized, with no responders at DL1 and no maximum tolerated dose achieved, thereby suggesting the DL3 (3 x 10^6 CAR T cells/kg) as appropriate for Phase 2 testing. Of those treated, 12 patients had a complete response, with an additional 4 who achieved marrow MRD negativity but had persistent extramedullary disease.

   The authors do note limitations in the study, including "truncated persistence and suboptimal CD-22 targeting". They also note an unclear understanding of how CAR pretreatment impacts response, especially when targeting the same antigen(s).

Reviewed by: *Eleny Romanos-Sirakis, MD, MS, FAAP, Associate Professor of Pediatrics, Zucker School of Medicine, Director, Pediatric Hematology/Oncology SIUH Northwell Health*

4. **Tehseen S et al. Thrombosis and hemorrhage experiences by hospitalized children with SARS-CoV-2 infection or MIS-C: Results of the PICNIC registry. *Pediatr Blood Cancer*. 2022:69:e29793.**

Continued on Page 19

This international multicentered registry study reviewed information on the clinical manifestations of SARS-CoV-2 and MIS-C for 915 children hospitalized between Feb 1, 2020 and May 31, 2021. 385 (42%) had symptomatic COVID infection, 288 (31.4%) had MIS-C and 242 (26.4%) had an incidental finding of COVID-19. 16 children (1.7%) experienced hemorrhage, 10 children (1%) experienced thrombosis, and 2 (0.2%) had both hemorrhage and thrombosis. Significantly prevalent prothrombotic co-morbidities included respiratory support (p=0.006), congenital heart disease (p=0.007), central venous catheter (p=0.03), obesity (p=0.002), and cytokine storm (p=0.0.12). Co-morbidities noted in children with hemorrhage included age over 10 years (p=0.04), central venous catheter (p=0.03), primary SARS-CoV-2 infection and MIS-C with thrombocytopenia (p=0.001), and cytokine storm (p=0.02). 1.2% (11) patients died, but none of these deaths were attributed to hemorrhage or thrombosis. The rates of thromboses in children are lower than in adults. Dysregulation in hemostasis among hospitalized children with COVID-19 or MIS-C was more common in children with the listed co-morbidities.

5. **Aref S et al. Predictive values of B-reg and serum IL-10 concentration levels for acute ITP progression to chronic phase. *J Pediatr Hematol Oncol*. 2022;44(6):336-341.**

80 children with acute ITP and 40 matched controls were included in this study, which aimed to determine the predictive value of the regulatory B-cell (B-reg) count and interleukin-10 (IL-10) serum level for active ITP patients who progress to chronic ITP. Flow cytometry and ELISA were used to determine regulatory B-cell counts and IL-10, respectively. A significant reduction in regulatory B-cell percentage and a significant increase in serum IL-10 levels was noted children with acute ITP compared to controls (p<0.001). The absolute regulatory B-cell count was significantly lower and the IL-10 was significantly higher in patients with acute ITP who progressed to chronic ITP compared to those who had achieved remission from acute ITP; these values may be a way to predict ITP chronicity.

6. **Kotwal N et al. Spirometric changes after initiation of hydroxyurea in children with sickle cell anemia. *J Pediatr Hematol Oncol*. 2022; 44(6):e923-925.**

This article summarized a retrospective chart review for patients with sickle cell anemia (HbSS and HBS-Beta zero thalassemia) who were referred to pulmonology for respiratory symptoms. Spirometry change between 2 timepoints was compared for patients on HU (n=62) vs those not on HU (control group, n=30). There was a significant increase in forced vital capacity in the HU group as compared to the control group; the control group showed a decline in forced vital capacity (7.2 +/- 17.1 vs -3.4 +/- 18.2; p<0.01). This suggests that HU therapy may assist in preserving lung function over time in children with sickle cell anemia.

7. **Askew MA, et al. Pediatric hematology providers' contraceptive practices for female adolescents and young adults with sickle cell disease: a national survey. *Pediatr Blood Cancer*. 2022;69:e29877.**

A 25-question web-based survey regarding pediatric SCD provider contraceptive practices for female AYA patients was distributed to pediatric hematologists across the US. 160 survey responses were included in the analysis. The majority of respondents reported counseling (77.5%) and referring female AYA patients for contraception (90.8%). 41.8% reported prescribing contraception. 54% of trainees provided counseling as compared to 85% of established providers (p<0.001), with a similar trend for prescribing contraception (p=0.05). Key barriers to these practices include inadequate provider training, perceived patient/parent interest, and limited visit time.

Section on Hematology/Oncology Education Subcommittee Update

Mary Jane Hogan, MD, FAAP

Program and Education Subcommittee Chair

Parent Education

One of the goals of the Education Subcommittee is to develop parent articles for the AAP HealthyChildren.org website. Physicians and parents can also print the articles using the icon at the top or bottom of the page. Thank you to the subcommittee members who have worked on these articles. Most recently, the a new article, "Sickle Cell Trait: FAQs for Parents" was published and the article "Sickle Cell Disease: Information for Parents" was updated. Thank you, to Drs Amber Yates, Zora Rogers and Anthony Villella for their work on these articles.

2022 AAP National Conference

The 2022 AAP National Conference was held in-person in Anaheim, California October 7 – 11, 2022. Thank you to the faculty who presented on the following topics this year:

1. Approaches to Abnormal Uterine Bleeding and Other Bleeding Symptoms – Shannon Carpenter, MD, MS, FAAP
2. Iron Deficiency: AAP Update on Screening, Diagnosis and Treatment – Jacquelyn Powers, MD, MS, FAAP
3. The Role of the General Pediatrician in the Care of Children with Sickle Cell Disease - Neha Bhasin, MD
4. Bruised: Child Abuse or Coagulopathy? - James Anderst, MD, MSCI, FAAP

The proposal process for the 2023 AAP National Conference is now underway. If you have a suggestion regarding a topic that we might consider, please sent the topic/title with a brief paragraph describing the what the session would address to me at maryjane.hogan@yale.edu and Suzanne Kirkwood at skirkwood@aap.org by **November 16, 2022**.

Sickle Cell Disease Coalition (SCDC) Update

Zora R. Rogers, MD, FAAP,

Immediate Past Chair, Section on Hematology/Oncology; AAP Representative to the SCDC

The Sickle Cell Disease Coalition (SCDC) was organized by the American Society of Hematology in 2016 to bring together stakeholders in the care of persons with sickle cell disease nationally and internationally. It is composed of public health, research, and provider organizations, patient groups, faith-based organizations, federal agencies, industry representatives, and foundation working on issues of interest to the SCD community. I have been privileged to be involved in the group since its inception and the AAP's liaison representative for the last 6 years.

Meetings are held virtually bimonthly with a previously in-person meeting annually in September (which is Sickle Cell Month). The Coalition is organized into working groups: Access to Care (US), Sickle Cell Trait, Blood Donor (diversity), Global Issues, as well as Research and Clinical Trials. As the AAP representative, I have been on the Steering Committee as well as the Access to Care and Sickle Cell Trait working groups. To date meetings have had a large element of sharing what individual groups are doing and, when geographically possible, inviting attendance from other organizations. SCDC members provided most of the content for the sickle cell transition toolkit (on its website. The group is now evolving and reorganizing, with new statements of purpose, succession plans for leadership, and development of actionable plans for future projects.

As you may have read in prior editions of the SOHO newsletter, the SCDC is just one part of ASH's growing commitment to SCD issues. I would like to make you aware of a new series of podcasts (https://www.hematology.org/about/podcasts-and-apps) that debuted in March and will run through Fall 2022: "Bringing Sickle Cell Disease to Life." It is hosted by Wally Smith, M.D. of VCU, who was one of the first researchers to emphasize the importance of psychosocial issues in designing and evaluating care of persons with SCD. I recommend listening and making your trainees, particularly residents and medical students, aware of its availability.

SOHO Collaboration Site!

As a member of the AAP Section on Hematology/Oncology (SOHO) you have access to the SOHO Collaboration Web site. This member's only benefit of the SOHO grants each current Section member access to the following:

- Opportunities to get involved in the SOHO leadership committees and policy review groups.
- Information for trainees regarding a career in pediatric hematology/oncology.
- Section publications including the newsletter and AAP News articles.
- Quick access to new and/or existing AAP policies developed by SOHO and practice guidelines of interest to SOHO members.

And much more!

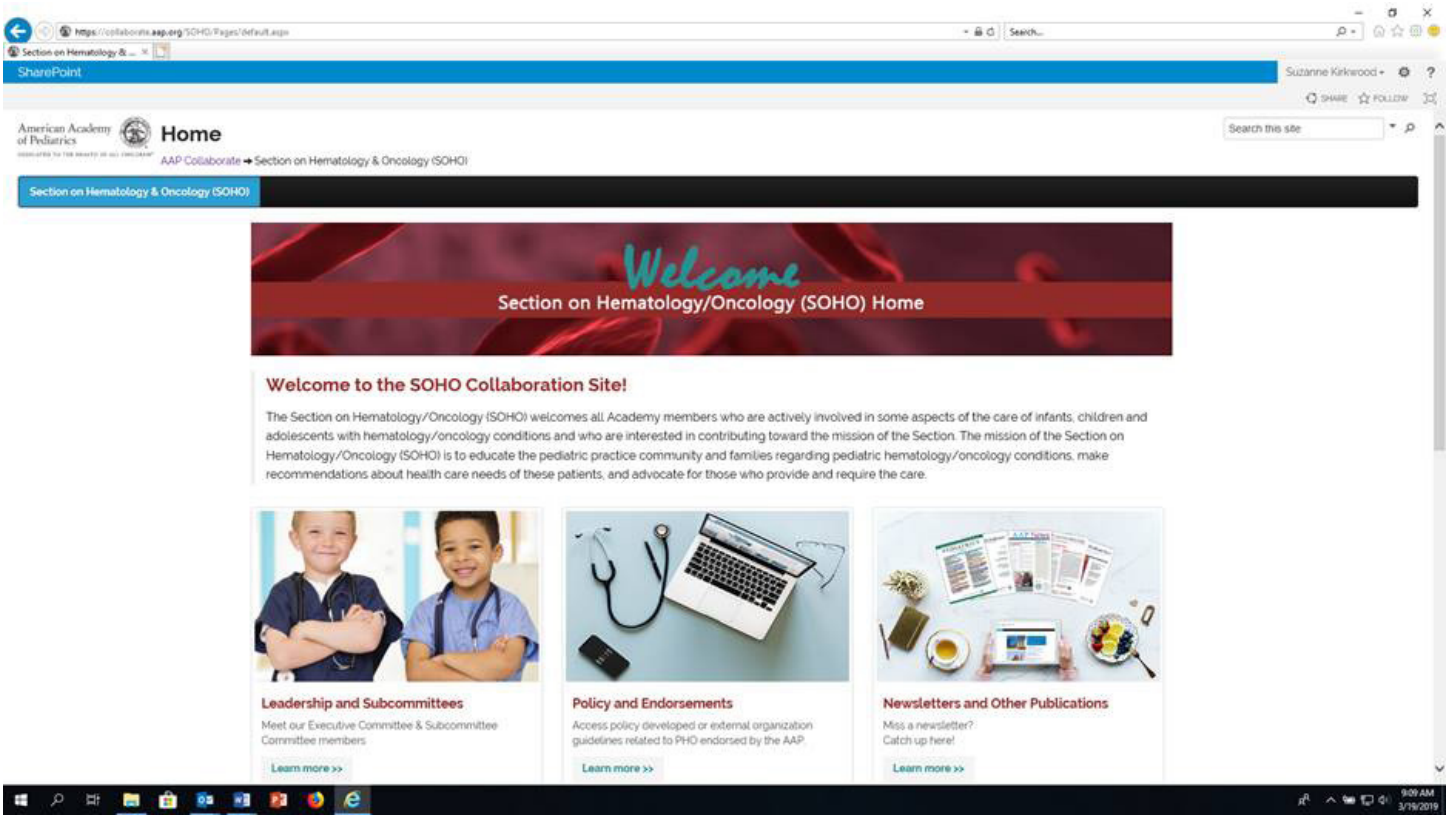
View Access Instructions ***below***. For questions or suggestions regarding the SOHO collaboration site please contact SOHO Staff, Suzanne Kirkwood or the SOHO Chair, Cynthia Wetmore.

Step 1: Visit https://www.aap.org/ and scroll down and click on Collaborate.

Step 2: Log in with your AAP login credentials.

Step 3: Access your Section collaboration site

Step 4: Begin navigating your site. ***Note- You can bookmark your site for future use***



Welcome to Our New SOHO Members

If you know of others who might be interested in joining the Academy and the Section please refer them to the AAP website membership page. Thank you to all who have continued to support the AAP and the Section by renewing their memberships. And welcome to new members of the Academy and the Section!

The Section on Hematology/Oncology Executive Committee

For Upcoming Newsletters . . .

We welcome your input and encourage you to submit ideas or information by email to Carl Allen, MD FAAP at ceallen@txch.org or Suzanne Kirkwood at skirkwood@aap.org for future issues of the newsletter.