PERSPECTIVES
NEWSLETTER OF THE NORTHERN CALIFORNIA THALASSEMIA CENTER

UCSF Benioff Children's Hospital Oakland

Spring 2020

Pregnancy and Motherhood: The Experience of Four Women with Thalassemia

By Meghan Foe
Guest Editor

When I was a thirteen, I attended a thalassemia conference where there was a lecture about thalassemia and fertility. At the time, I did not understand much about what was being said – there was a lot of scientific talk about low hormone levels and the possibility of freezing eggs. But I do remember coming away with a distinct feeling that pregnancy for young women like me, who have severe forms of thalassemia, would be difficult and unlikely. I did not think much about this at the time; someone had taught me enough about feminism to persuade me that I probably would have a productive and interesting life regardless of whether or not I had biological babies. But when I began working at BCHO and met women with thalassemia who had biological children, I realized there was much more to the story of having thalassemia and becoming pregnant than I had initially thought. And when I learned that other young women like me had doubts and questions about their own ability to have children, it was clear that a story about having thalassemia and having biological children – from the perspective of the women themselves – needed to be written.

I interviewed four women with thalassemia, all of whom received frequent blood transfusions. Two had beta thalassemia major, and two had E/Beta thalassemia. Their ages ranged from mid-twenties to early forties. Their children's ages ranged from infants to pre-teens, and one woman was pregnant with her first child at the time of our interview.

Beliefs about Pregnancy

Like me, all but one of the women I interviewed expressed that their expectations about pregnancy had been low. These low expectations stemmed from the symptoms and complications they were experiencing, such as having irregular periods or having an enlarged spleen. One woman recalled getting blatant misinformation from her previous providers about her ability to have children. "I remember going to the doctor, and they were like, you can't have kids," she told me.

This belief likely contributed to the fact that nearly all of the women I spoke to did not discuss the possibility of pregnancy in-depth with their doctors until they were either already pregnant or had reached the time in their life when they decided they wanted to become pregnant. For some of them, pregnancy was simply not something that they themselves were thinking about when they were teens or young adults, let alone something they wanted to speak to their doctors about. But one woman claimed that this wasn't her reason for not bringing up the topic early on. "I don't feel shy or embarrassed in any way," she said. "I am so comfortable with them because they've known me since forever." Her real reason for not bringing it up, she explained, was because she "didn't want to hear negative stuff about it."

Iron Overload, Reproductive Ability, and the Importance of Early Conversations

This is something I discussed with Dr. Titi Singer, a thalassemia physician at BCHO and one of the leading experts in exploring thalassemia and fertility. She explained that it is quite common for the conversation around pregnancy to be difficult. But she maintains that it is extremely important for both patients and providers to have conversations about reproductive health and pregnancy early – in their teens even.

For individuals with thalassemia – particularly those with severe forms like beta thalassemia major – this urgency stems from the recognition that the iron overload that comes from frequent, lifelong blood transfusions can affect their reproductive ability. Iron can deposit

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in the pituitary gland, a small organ in the brain which is responsible for stimulating or producing reproductive hormones in our body. These hormones, such as LH, FSH, estrogen, and testosterone, are essential to our ability to reproduce. While iron in the pituitary can be removed if patients are diligent and aggressive with their iron chelation therapy, decades of iron accumulation will eventually make the pituitary shrink – something which is irreversible. For women, iron can also deposit in the ovarian tissue, causing damage to the eggs.

This is not just something that women need to be careful of. Men, who are equally responsible for reproduction, may have pituitary shrinkage too. Iron can also accumulate in other male reproductive organs, making them less fertile. Thus, it is of great importance that young people who have even the slightest chance of wanting to have biological children in the future maintain low iron levels and monitor their endocrine function.

Taking the First Steps: Assessing Fertility

The first step to planning for pregnancy for women with thalassemia is often a referral to a fertility specialist to assess "fertility potential" – in other words, the body's ability to reproduce without assistance. For the women I interviewed, the fertility specialist ordered blood tests of their hormone levels and ultrasounds to check the number of eggs or follicles they had. "It was just like any other couple who goes through fertility help would go through," explained one woman.

Fertility Treatments for Women with Thalassemia

Two of the women I interviewed became pregnant without any medical assistance. Both women had E/beta thalassemia, an intermediate form of thalassemia that usually requires fewer blood transfusions. This is quite common according to Dr. Singer. Nearly all women with intermediate forms of thalassemia like E/beta thalassemia can become spontaneously pregnant. In contrast, 70-80% of women with beta thalassemia major will need some kind of intervention to become pregnant.

Yet this is not any reason to lose hope, Dr. Singer insists. Women with thalassemia who produce very low levels of hormones, do not get regular periods, and have only a few follicles can become pregnant with medical assistance. There are two main possibilities: for women with adequate follicle counts, they may require stimulation with reproductive hormones; for women with lower follicle counts, in vitro fertilization (IVF) – where an egg or multiple eggs are taken from the woman's ovary, fertilized with sperm outside of the body, and transplanted back into the woman's ovary – is likely necessary. Both of the women with beta thalas-semia major whom I interviewed only needed hormone stimulation to become pregnant.

Staying Healthy During Pregnancy

Once the women became pregnant, the focus turned to ensuring that they and the pregnancy remained healthy. They underwent a series of tests, much like the annual testing done for comprehensive thalassemia care: the T2*, SQUID, DXA, ECHO, and glucose tolerance tests are done to monitor for cardiac iron, liver iron, bone density, heart function, and risk for diabetes, respectively. Cardiac tests are especially important, as pregnancy is a significant strain on the heart. As a result, experts often would not recommend pregnancy for women who have very high levels of iron in their heart — or who are at risk for heart failure — until they can reverse the damage.

This is especially important since physicians often recommend that women stop their iron chelation therapy during the pregnancy. Women with very high iron overload may stay on Desferal — the only iron chelation therapy whose molecule is so large that it cannot pass from the mother to the fetus through the placenta. Many women may also need more blood transfusions than usual during pregnancy.

In addition to the heightened level of thalassemia care necessary during pregnancy, the women were followed by obstetrician/gynecologists (OB/GYNs). All of the women I interviewed were followed by high-risk OB/GYNs or perinatologists, due to their medical histories. The women reported that the medical appointments could get overwhelming. "The OB/GYN is every week or two, and then I have another extra appointment with them to make sure [the baby] is okay since I have thalassemia, and then my blood transfusion here," one woman described. "It's just like constant appointments."

Seeing multiple physicians who specialized in different things presented additional communication barriers, too, especially since many of the OB/GYN providers did not know much about thalassemia. "The prenatal doctors were always looking stuff up about thal," one woman recalled. "They would be like, 'well yeah, we should be worried about this' but not really know what applied to me or didn't apply to me."

Another woman described being nervous about planning for a blood transfusion after delivery. "I was really nervous about the process of them getting the right blood and getting it washed," she said. "It seemed a little bit more confusing to them for some reason. But finally

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they got it right." It helped, all of the women stated, that their hematologists were very involved in the pregnancy and often communicating with their OB/GYNs about their medical needs.

Genetic Inheritance of Thalassemia

Individuals with thalassemia who want to have biological children face the risk that their child may have thalassemia if their reproductive partner has the trait or the disease, as well. Every woman I interviewed remember their hematologist talking to them about their child's chance of having thalassemia during their pregnancy.

Yet perspectives about preventing thalassemia varied greatly among the women I interviewed. Two of the women learned early on that their partners did not have thalassemia trait, so there was no chance that their child could have a severe form of thalassemia.

Another woman, who was pregnant at the time of our interview, ex-pressed fear about her child having thalassemia. "I didn't know if they would end up having what I have," she said. But insurance would not cover the test to see if her partner had thalassemia trait, and the prenatal diagnosis test was also costly. She took it all in stride though, stating, "I guess we just have to wait until after she gets here!"

In contrast, however, the last woman I interviewed had very little concern about the risk of her children having thalassemia during her pregnancies. "If they for some reason happen to have thalassemia, I think I am going to be okay," she said. Her views towards thalassemia were informed by her own abilities and quality of life, "I can walk, drive, have a job, I don't need a lot of help, so I think the boys are going to be both pretty fine."

Building a Support System

All of the women stressed the importance of having a strong support system around them during their pregnancies – something that is important regardless of whether someone has thalassemia or not. For these women specifically, the significance of having a medical support system was invaluable. "It was important to get a care team together…to talk about stuff they think is important for you to be aware of, to talk to you and each other about it," one woman described.

Family and friends were another important source of support. However, many of the women described a temptation to keep their pregnancies secret – even after the first trimester, when the majority of prospective parents begin to share the news. "I didn't tell anyone right away, because I was worried about the baby with all the risk factors," one woman explained. Another woman described how – even when both she and her husband knew she was pregnant -- she was cautious to show her excitement about the pregnancy to him. "I kept it internally, but like slim chances so let's not show him," she said.

A "More or Less Normal" Experience

Despite their worry, all of the women described feeling like their pregnancies were "more or less normal." One woman described feeling even better than usual. "I loved pregnancy," one woman exclaimed, "it was probably the most happiest, joyful – maybe the second most happiest time in my life. I always said, if I could concoct whatever hormone mixture and levels I had, I'd make it rich."

All of the women who were working when they became pregnant continued to work throughout the pregnancy. "I waited until my water broke during my first pregnancy," one woman exclaimed. "I was just like, 'I guess the baby's ready to come, I'm not going to work anymore!'"

Of the three women who had already gone through delivery when I had interviewed them, two underwent C-sections and one did not. C-sections are more common among women with thalassemia, usually because these women tend to be smaller and have smaller pelvises. It is recommended that women prepare to receive a blood transfusion following childbirth. Women with thalassemia also may be at higher risk for forming blood clots and getting infections – particularly if they have had their spleen removed. Thus, doctors often recommend that they take blood thinners like aspirin and antibiotics after delivery.

Being a Parent with Thalassemia

I was curious about how these women talked to their children about thalassemia. Did they hide parts of their health care from their children, or did they show it to their children from an early age? The three women who already had children told me that they prioritized making thalassemia as normal as possible for their children. "I always talk about it like brushing your teeth," one woman described. "You always have to brush your teeth, keep them healthy, right? Same thing." Another woman told me about how her son is good at recognizing her physical limitations. "He will be like, 'oh we should do something that's not that hard,' or if they're looking for chaperones on a field trip, [he'd ask] 'Are you going to feel good that day? Would you be able to walk for that long?'"

One woman told me that having children has made her more open about having thalassemia, not just to her own children – who are still too young to understand thalassemia – but to others in her life. "My whole life, I've been told to keep it a secret," she told me, "there's been shame associated with it." Her desire to be more open comes in part from the recognition that she will one day have to tell her children about her thalassemia. Plus, she wants her openness to be a lesson for her children. "I want to be a good role model for them, teach them not to be ashamed of themselves, their family, any quote-unquote "flaws," she said. "I want to teach them to be honest."

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THE ASPHO 2019 DISTINGUISHED CAREER AWARD GOES TO DR. ELLIOTT P. VICHINSKY

By Caroline Hastings, MD

Dr. Elliott P. Vichinsky has been awarded the 2019 American Society of Pediatric Hematology Oncology Distinguished Career Award . This award is presented to individuals in our field who have made critical contributions in the areas of patient care, research, education, and advocacy. Elliott has been, and continues to be, one of the most influential and powerful contributors to care in hematology. His academic accomplishments have single-handedly changed the paradigm of patient care in sickle cell disease (SCD) and thalassemia, and he is recognized as one of the premier translational research scientists in hemoglobinopathies in the world.

He has been the division chief of hematology oncology at Children's Hospital Oakland since 1985, and more recently assumed the position of Chief of Hematology at UCSF Benioff Children's Hospitals (Oakland and San Francisco). Elliott embodies the concept of great leadership. He is strong, tenacious, courageous, and unintimidated. He believes in his visions and ideas and most importantly in his faculty. This trust inspired generations of physicians to achieve their goals while retaining a sense of purpose and self-preservation.

Elliott's career continued to burgeon with his success and passion, reflected in his over 300 peer-reviewed publications and over 75 books, chapters, and reviews. In Oakland, he has been fully committed to the medical care of children in this community. He created the first outpatient infusion center, convinced the state of California to create a newborn hemoglobinopathy screening program, and built the Hemoglobin Reference Laboratory (now a national and international resource). He recruited faculty to rebuild the bone marrow transplant program with a focus on hematologic disorders, and indeed the first patient transplanted had 4-gene deletion alpha-thalassemia. For many years, he personally provided care for all patients with genetic blood diseases regardless of age. Over time, he developed a multidisciplinary program to provide unprecedented seamless transition of care to adult providers in the same facility.

Elliott's accomplishments are of global proportions, affecting care for children and adults with genetic disease and advancing the field of clinical and translational research. Elliott has led the field in all major clinical issues that undermine health, well-being, and longevity in patients with SCD. He conceptualized the studies to improve our understanding of the pathophysiology of the disease and determine whether the interventions impacted patient lives. His groundbreaking discoveries with his colleagues have changed the lives of affected individuals for generations to come.

Elliott's contributions extend internationally with his work in global education of clinician researchers in under-resourced countries as well as leadership in clinical trials in thalassemia with colleagues in the United Kingdom and Canada. For years, Elliott has held an international symposium with presentations by global leaders in the field, inviting physicians and scientists from Africa, India, and the Middle East to promote high-level discussions and collaborations.

Elliott is far more than his CV, publications, grants, and titles. He is fearless—a necessary and often overlooked prerequisite for being an effective leader. He is internally driven to do the right thing, even when it will likely be met with controversy or inherent risk. He has challenged (and still does) local health care administration and the community to address care of adults with SCD, and has given his voice to national radio to bring attention to this major disparity in access to expert care. He created a unique model of providing care throughout the lifespan of individuals with hemoglobinopathies, a novel approach that is now becoming recognized as an obligation for providers and health systems to become someday the "standard of care."

Elliott is an example of the best of academic medicine. He has mentored hundreds of students and peers and acknowledges them for what he has learned from them too. He has raised a generation of talented and thoughtful trainees who value their contributions to the health and well-being of their patients. He is a consummate physician, my life mentor, and dear friend.

PREGNANCY

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This is not the only way children changed these women's relationship to thalassemia. All of the women discussed feeling more inclined to take care of themselves – despite how difficult it could be sometimes to balance their needs with those of their children. "Nobody could ever prepare me for how consuming a child can be, emotionally, physically, every ounce of yourself," one woman said. But she was practical in her outlook, "If you start to neglect yourself, then nobody wins in that situation. Everybody loses."

This sentiment was echoed by another woman, who was pregnant at the time of our interview. She described how her outlook towards her thalassemia treatments have changed. "I used to be like, I am not going to drive all the way to get a blood transfusion. But since I got pregnant, I was like, okay it's for my daughter so I am going to come." She smiled, "She makes everything worth it."

INTERVIEW WITH DR. WADE KOYONO

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Following the Lead of Patients and Families

A large part of Dr. Kyono's moral conviction about offering in utero transfusions comes from an understanding of the challenges faced by many of his patients' families. "Many of these families have lost a lot of children before they realize what the problem was," he told me, "and for a lot of them, they'll do anything to have that child."

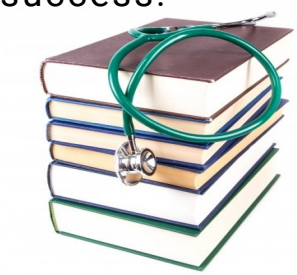
Given these circumstances, he believes strongly that families should be able to decide for themselves whether to pursue in utero treatments, if their pregnancy is diagnosed with alpha thalassemia major. This is especially true, he believes, if the parents are able to truly understand what the outcomes look like. "Some parents might not mind their baby being transfused maybe, because their child will be practically normal," he stated.

Centering patient experiences and needs is an integral part of Dr. Kyono's vision. In addition to the importance of elevating patient stories in his outreach and education to providers, patients and families are extremely valuable in providing support and reassurance to those who have newly received similar diagnoses. "It's been really nice for this new patient to see Elianna, because they can see what happened and how well Elianna's been doing. It's made them feel comfortable about what's happened and what's going on," he said.

Dr. Kyono hopes to elevate patient stories and support on a larger scale. "We really want to start an alpha thal support group, so that they can connect with other parents and talk to them about going through the intrauterine transfusions and delivery."

As much as Dr. Kyono talks about what he hopes to provide the alpha thalassemia major community, there is a recognition that it is truly a two-way street – that behind it all, patients are driving the changes we are seeing systemically. "The patients are the bottom line of all of this," he insists, "how they're doing and how they appreciate what's going on – that's a type of advocacy that pushes us forward."

Meghan Foe and Lisa Du have left BCHO for medical school. We wish them much success!



USING MAGNETS TO QUANTIFY LIVER IRON CONCENTRATION

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The Future of Iron Quantification with Magnetic Susceptibility

In December 2018, the Biomagnetometer Program in Hamburg, Germany shut down its SQUID-Ferritometer due to low patient volume, high program cost and staff retirement. While this end of an era is sad, it highlights the urgency for low costs alternatives to helium-based technology. To help the field of biosusceptometry move forward, BCHO is moving forward with the FDA application for the SQUID. Our goal is to establish the SQUID as a predicate device for devices that quantify iron with biosusceptometry. This move will make the FDA process faster and less expensive for device developers. As leaders in the field, we are in a position to facilitate the development of novel technology. Our vision is to help develop biosusceptometry techniques to be used in conjunction with MRI techniques to provide the best care for patients around the world.

2019 THALASSEMIA CARE WALK

By Seema Khadim

Before 2019, I had never arranged a Care Walk before. It all began when my daughter and husband introduced me to Meghan, the thalassemia outreach coordinator at BCHO. We talked about awareness, how important it is and how there is a large number of population unaware of this disease. Not many people know about the inheritance of this genetic disease.

Meghan and I decided that we would arrange for a Care Walk to raise awareness about thalassemia in my community. The Care Walks are an initiative started by the Cooley's Anemia Foundation, which is a national organization that raises awareness and seeks to improve the lives of patients with thalassemia.

We discussed many ways that would could make the walk a fun event for patients, families and friends – an event where patients can get together and interact with one another, and where families would get a chance to talk and everyone can have a little fun.

Our Care Walk took place on a Saturday April 27th 2019. On the day of the Care Walk, we all arrived at the park. Members of our family and community helped us set up everything. People started coming in and the weather was great. We all walked a mile and everyone came for lunch after. The sight of everyone chatting over lunch and kids having fun together on the swings and slides, running around, and sipping lemonade was beautiful.

Since I have a daughter, cousins, a niece, and a nephew with beta thalassemia major, I can relate to and understand the challenges the patients and families face. Patients and families in other countries have very little knowledge about thalassemia, its management, and its inheritance. Thus, such walks can spread awareness throughout the country and hopefully around the globe as well.

Overall, the Care Walk was a great experience. It was incredibly valuable in spreading awareness about thalassemia and in allowing patients to have a good time with other patients and families. If one person from every other community organizes such Care Walks, imagine the number of people who will learn about thalassemia and thalassemia management. That way, we can all play a part in improving the lives of people with thalassemia.

Q & A WITH KELSEY MILLER

Kelsey Miller is the new study coordinator II working at HEDCO. She works with Dr. Marcela Weyhmiller and Lisa Calvelli in the SQUID program and coordinates many of the administrative aspects of the Iron Overload Clinic. Welcome, Kelsey!

Tell us a little about yourself.

I have lived in the Bay Area since 2012, when I came for my Master's of Public Health program at Cal Berkeley. I grew up mostly in Michigan, and went to the University of South Carolina for my bachelor's degree. After working some odd jobs in Idaho and Arizona, I was really excited to focus on human health as a career after my Master's degree, which focused on Infectious Disease and Vaccinology.

How long have you been working at HEDCO?

I started in mid-January, but am lucky to have known the team here for longer through my work at CHORI.

What is your role as a study coordinator?

My role at HEDCO is to be a part of the Iron Overload program, primarily running the SQUID testing and assisting with the administrative side of running the clinic.

What did you do before working at HEDCO?

I've worked with the hospital as a part of CHORI for the last 5 years researching meningococcal vaccines, managing flow cytometry instruments, and as an administrator for the research animal program.

What excites you about working with the thalassemia community?

I am very excited to learn more about this patient population, because there is such a rich sense of community that I have been able to already see in my first experiences. The thalassemia community has built an incredible and admirable support system among those impacted by this condition and their providers, and I feel privileged to become a part of this.

What do you like to do outside of work?

I love to both watch and play sports, especially rugby, football, tennis, and golf. But as a new mom, most of my time outside of work is filled with all the fun and frustration of a 1 year old!

Anything else?

Nothing I can think of!

HOW FOURTEEN MILES BECAME FOURTEEN YEARS

By Anamika and Rajesh Arora

Despite living 14 miles away from the Oakland Children's Hospital (now the UCSF Benioff Children's Hospital Oakland), it took our family 14 years to return to a place which was our home for five years. We have made many great memories during this time but have suppressed these feelings and emotions for several years after the passing of our daughter.

Our first daughter, Shivani, was born on December 27, 1998. At that time, like any other parent, my wife and I felt we were on the top of the world. A few days later, as we were rejoicing with family, we got unexpected news that our little princess has a possible genetic blood disease and we need to go in for additional testing. The testing occurred, and we were promptly notified that Shivani has beta thalassemia major. My wife and I had no idea what these words meant but instantly tears started pouring down our faces.

Then Oakland Children's Hospital stepped in with their warm hearts and created a support platform for our entire family. There, we met Dr. Vichinsky, who managed the entire treatment plan for Shivani, and Debbie, who took care of Shivani every other Sunday at the hospital. Many memories were created at this time, one of which was Debbie making sure that every injection Shivani got was painless. Dru Foote provided a motherly touch every single time we talked with her. These interactions strengthened our resolve to find a cure for our daughter.

We went through 8 IVF cycles with pre-genetic testing to have a child who is genetic match with Shivani. We were all excited, as if we had taken care of Shivani's sufferings. The God had another plan; Shivani developed infection during cord blood transplantation at OCH and passed away on Feb 4, 2004.

Time once again stopped for us and infused a lot of hatred and anger in our hearts. We went to Shivani's graveyard every day for the next 6 months, hoping she might come back or talk to us. We couldn't go back to our routine life and didn't return to work for almost a year. We worked hard to wipe off painful memories of the last 5 years from our life being spent at OCH. Slowly, we started to look toward our 2-year-old son. We resolved to live for him and never tell him what happened with his older sister. Life started to get back on its normal track, but that deep pain inside never subsided. Eight years later we got another daughter, Siya who looks exactly like Shivani.

The memories of Shivani and the painful experience which we kept in our hearts started to unfold when our son, Aryan turned 13 and started asking questions about his older sister. Once again, we started talking about Shivani and what she went through in her short life. It was painful in the beginning, and it seemed like the anger still existed. But slowly, the emotions of anger and frustrations started to convert into emotions of gratitude and thankfulness. A certain form of guilt started to develop that OCH and thalassemia community did so much for us, and we turned away from it just because things didn't work out for us.

Aryan continued to explore more and developed a firm belief to do something for kids suffering from thalassemia -- a way for him to live with the sister he never got to play with.

Finally, we made a call and reached out to Dr. Vichinsky and expressed our desire to visit day hospital where Shivani spent a lot of time. We were so happy to see Dr. Vichinsky and Debbie after 14 years; tears would not stop as we walked through the hallways where our daughter lived once. This visit gave our family a purpose -- a determination and a commitment to work with thalassemia community to help, support and spread happiness. This would be our true homage to our daughter Shivani.

LEADING STATEWIDE CHANGES FOR ALPHA THALASSEMIA MAJOR IN HAWAII: AN INTERVIEW WITH DR. WADE KYONO

By Meghan Foe

Before 2017, Dr. Wade Kyono had not seen a patient with alpha thalassemia major in over 10 years. In normal circumstances, this would be considered unusual; alpha thalassemia major is most common among people of Southeast Asian and Filipino descent, communities which are prevalent in Hawaii, where Dr. Kyono is a hematologist-oncologist at the Kapiolani Medical Center for Women and Children. Yet today, Hawaii has become a leader in the field of care for alpha thalassemia major, with a system in place to offer in utero transfusions to every pregnancy diagnosed with alpha thalassemia major across the state. We interviewed Dr. Kyono to find out how this happened.

Historical Practices for Alpha Thalassemia Major

Alpha thalassemia major is a severe type of thalassemia that causes anemia when the fetus is in the womb. If untreated, alpha thalassemia major can lead to hydrops fetalis, where the fetuses may become very sick, or even die. It is becoming increasingly clear, however, that early prenatal diagnosis and treatment of alpha thalassemia major with in utero blood transfusions (IUT) can minimize the damage caused by the fetal anemia and lead to optimal outcomes after birth.

Unfortunately, alpha thalassemia major is grossly underdiagnosed prenatally. Even those who are diagnosed are rarely offered IUTs as a treatment option. As a result, there has been a stark underestimation of alpha thalassemia major. As Dr. Kyono describes, "Traditionally – it wasn't really on our radar. We expected that we should be seeing some, but they were all going through the maternal-fetal medicine providers, and when they were found to be hydropic, they were terminated.

A significant part of the issues is a fragmentation in the health care system, where specialties caring for patients during different phases of their life did not communicate. "Our interface with the maternal-fetal medicine program has traditionally been close to nothing," Dr. Kyono explained.

This is not ideal in alpha thalassemia major, since hematologists have knowledge – such as the possibility of survival and good outcomes with in utero transfusions – that could change clinical decision-making on the part of prenatal providers.

Impetus to Change

The circumstances surrounding clinical care for alpha thalassemia major began to change at Kapiolani in 2017, when Dr. Kyono became the primary hematologist for Elianna, the first baby in the world to receive a stem cell transplant while in the womb through a cutting-edge clinical trial at UCSF. Elianna received international attention for her participation in the clinical trial, with her story featured in publications like the New York Times. Yet for Dr. Kyono, Elianna represents another important first: she is the first patient with alpha thalassemia major he has had under his care who has survived to term due to in utero blood transfusions – which she received concurrently with the experimental stem cell treatment.

With Elianna as the touchstone for what was possible for the treatment and survival of patients with alpha thalassemia major, Dr. Kyono began to delve into the infrastructural and educational barriers that had prevented

progress for alpha thalassemia major for so long.

Overcoming Barriers

The first step to overcoming these barriers was to open avenues of communication between different specialties necessary to care for pregnancies affected by alpha thalassemia major. "We did a prenatal/pediatric conference with neonatologists, maternal-fetal medicine people here at Kapiolani," he told me.

Perhaps as important as determining the right physician audience of this education has been refining the content of the messaging. For Dr. Kyono, the approach to his educational messaging emphasizes both the high quality of life that can be achieved with chronic transfusions, as well as the future possibility of curative treatment.

Most effective, however, has been Dr. Kyono's strategy to provide positive imagery that unlinks the association between alpha thalassemia major and devastating outcomes. "I show them pictures of Elianna, who's now a toddler and is cute and running around," he laughed. "It's hard to say no to that, right?"

Improving Alpha Thalassemia Major Care Statewide

Dr. Kyono's work has led to incredible progress in the state of Hawaii in the last year. Several months ago, one of the other large health institutions in Hawaii, Kaiser Permanente, had a patient whose pregnancy had a prenatal diagnosis of alpha thalassemia major. The team at Kaiser spoke with Dr. Kyono and the team at the UCSF Fetal Treatment Center. They ended up providing in utero transfusions to the baby, while Dr. Kyono prepared to do post-natal transfusions for the baby. It was the knowledge of post-natal treatment possibilities that persuaded the prenatal providers at Kaiser. As Dr. Kyono explains, "they realized that – [alpha thalassemia major] is just like [beta] thal major in terms of transfusions, so they felt comfortable doing the intrauterine transfusions."

Health care in Hawaii is uniquely centralized, where only a few health centers provide specialty care to the entire state. As a result, the growing awareness about offering in utero therapy to patients with alpha thalassemia major at Kaiser and Kapiolani has had immense reach within the state. "I think it's developed into a state-wide program type of idea," Dr. Kyono said. "Like between Kaiser and us… OB/GYNs know about alpha thal major and that we can do [in utero transfusions] for them, it will be sure to come through the maternal-fetal medicine and get to us."

Advocating for Change in the Health Care System

It is important to note, however, that the health care system is complicated, and patients and providers are not the only ones involved in making treatment decisions. Dr. Kyono described some of the pushback he got, both from administrators at his hospital and from insurance companies. "Some of the concerns we had to deal with too were about, 'Is this experimental? And is insurance going to pay for it?' I think [the hospital] had even sent out some of the initial in utero transfusions to insurance and they got declined."

Dr. Kyono had to get creative about how he persuaded the insurers to cover in utero transfusion for alpha thalassemia major. He knew that the main problem was that the insurers associated alpha thalassemia major with being lethal diagnosis, so they refused to pay for any procedures associated with it. So instead of asking insurance companies to cover "intrauterine transfusions for alpha thalassemia major," he asked them to cover "intrauterine transfusions for fetal hydrops due to severe anemia." As he explains, "if you sell it as 'transfusions for severe anemia,' there's no problem getting it covered by insurance."

But strategic wording might not be enough to enact change on a large scale. Moving forward, Dr. Kyono suggests that building a strong evidence-base could be the key to navigating insurance barriers for alpha thalassemia major. "Having a set reference list of articles that could be sent out to people…the proper ICD-9 coding for it should be anemia with hydrops, cardiomegaly, heart failure or whatever they're seeing – that's how we should approach the insurance company."

(Continued on page 5)

IRON CHELATION ADHERENCE IN YOUNG ADULTS WITH THALASSEMIA: THE PATIENT PERSPECTIVES

By Meghan Foe

Medication adherence is the term used to describe whether individuals take their medications as instructed. It is extremely important for people with thalassemia to adhere to their iron chelation therapy, which removes toxic iron that can build up from frequent blood transfusions. However, adherence can be challenging, particularly for young adults with thalassemia. In the Summer 2017, I interviewed 10 young adults with thalassemia between 18 and 35 years old, hoping to understand factors that may contribute to their chelation adherence or nonadherence. Here is what they said...

1. Characteristics of chelators, such as side effects or how easy they are to take, are significant factors to chelation adherence…

> *"I dreaded the Exjade, because it tasted so nasty, and the complications, the abdominal pains, I threw up sometimes. That's the reason why when they first came out with it, I couldn't stay on it."*

…but these medication characteristics are not everything.

> *"I would say that I would put [my chelation adherence] at like a bar. And if the bar is filled, I'll take the medication. And basically, like mentality-wise, it fills like 80% in filling the whole bar in taking the medication. And the easiness [of the medication] is the rest."*

2. Controlling iron levels is a central part of the participants' health and well-being, and motivates them to adhere to their iron chelation therapy

> *"I take it because…it's been bringing my iron level down. And I like seeing the progress that I've been making."*

3. Having a competent, comprehensive, and collaborative clinical team is essential to promoting chelation adherence…

> *"[My doctor] made sure that I understood it first, and we worked step by step…And every year we had a goal, and it just gave me something to look forward to."*

…though clinicians with a paternalistic, moralistic approach may be less effective in promoting chelation adherence.

> *"[With regards to chelating] my attitude is that most young people work it out. Like…[clinicians] can moralize with them … you can tell them until you're blue in the face, but if it works in their life at the time, then they'll do it."*

4. If young adults feel like their chelation doesn't take away their autonomy and independent lives, they are more willing they are to adhere.

> *"But I would tell the young people sometimes, like if you have a hot date that night and you don't feel like doing your Desferal then whatever, don't do it, it's really not the end of the world."*

5. Parents are usually highly involved in patients' lives, which can sometimes be helpful in promoting adherence for their kids…

> *"I think it helped for my mom to always be there [to help me chelate]. There was no escape, there was never an option."*

…but parental involvement can sometimes infringe on young adults' view of themselves as independent or autonomous.

> *"I think [having thalassemia] definitely held me back. Like it's not so much the thalassemia, but my mom and dad were really protective of me…And it took a lot on my part to break out of that? And just let myself be my own person."*

6. Feelings of isolation are prevalent for patients with thalassemia…

> *"I don't know if this is because of the disease, but…I feel like I'm not part of, like everybody else. Like there is an alienating aspect of it."*

…but talking to their friends, peers, and others about having thalassemia both decreases isolation and may be related to patients feeling more responsible for their own health.

> *"I didn't really tell my friends…But I started telling them this past year, actually. Because that was when I finally took responsibility for myself. And I finally felt okay having thalassemia. So I like opened up with my best friends."*

7. Integrating chelation into a structured routine promotes adherence, whereas a lack of structure or routine promotes non-adherence

> *"…that's the other secret, is like I don't take my Jadenu on the weekend, because I don't have a schedule on the weekend, and so if I don't have a schedule I don't take it."*

What can clinicians and parents do to make adherence easier?

1. **Collaborate with patients to** set goals in their iron levels and make decisions about their health
2. **Normalize thalassemia and decrease feelings of isolation by** increasing ways to connect patients to each other, empowering them to discuss thalassemia with others, and minimizing the impact of thalassemia on other aspects of their lives
3. **Promote patient agency and autonomy** in their thalassemia care from an early age.

What can patients do to make adherence easier?

1. **Identify regular activities that** you do every day, like brushing your teeth, and try to take your medicine around the same time as those activities.
2. **Track your iron levels** to understand how you're doing with your chelation
3. **Talk to other people with thalassemia.** You can find patients at conferences, social media groups, or through your hematology center. Chances are, if you are feeling a certain way about aspects of having thalassemia, others have felt that way, too!

THE PAST, PRESENT AND FUTURE OF USING MAGNETS TO QUANTIFY LIVER IRON CONCENTRATION

By Marcela Weyhmiller

The SQUID-Ferritometer, or just the SQUID, is a cornerstone of the Thalassemia Program at UCSF Benioff Children's Hospital Oakland. This unique device delivers rapid liver iron concentration (LIC) results. The SQUID's special design allows for non-invasive measurement of young patients providing vital information years earlier than possible with other available techniques to measure LIC.

History of the SQUID

Drs. Elliott Vichinsky and Paul Harmatz lead the effort to bring the SQUID to Oakland in 2002. Constructed by Tristan Technologies, Inc., San Diego, the SQUID was dubbed the "magnetic biopsy" because it largely replace the need to perform liver biopsies at the time considered the gold standard for iron quantification. Patient advocacy groups, including the Cooley's Anemia Foundation and the HEDCO Foundation, donated over one million dollars to establish the Iron Overload Program. These original funds were used for initial operating budget, the construction of the SQUID and the ferrous metal-free HEDCO Health Sciences Building. Today, the Iron Overload Program's team has 25 years of combined experience performing SQUID measurements. The SQUID remains an investigational device and almost 4000 measurements have been performed on more than 1000 patients at risk of iron overload and healthy controls in twenty IRB approved studies. We currently perform about 300 measurements per year.

Iron and Magnetism

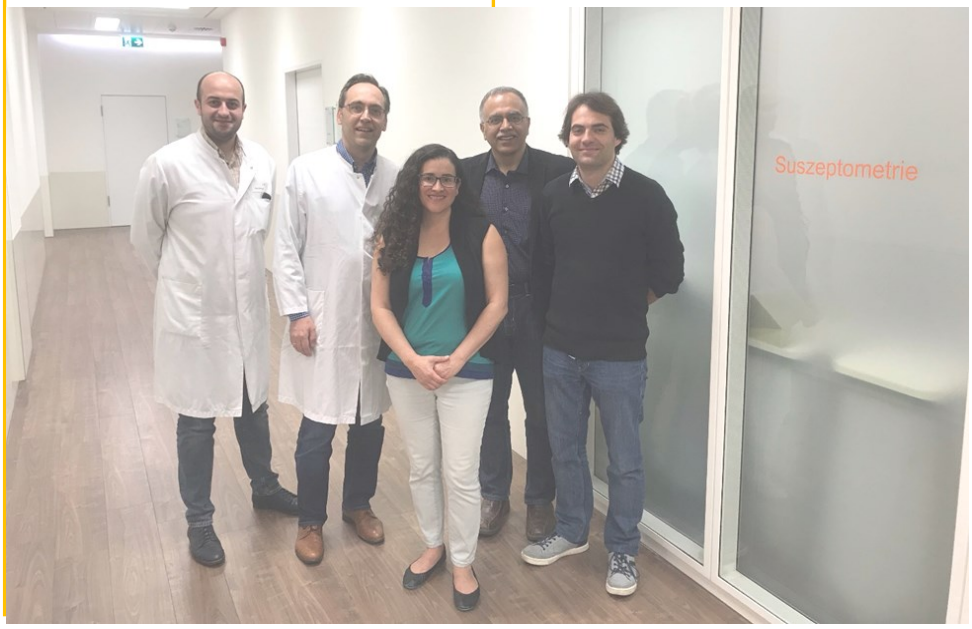
SQUID is an acronym that stands for Superconducting QUantum Interference Device and refers to the super sensitive magnetic detector at the heart of the measurement. SQUIDs are used in fields ranging from physical science to military applications. They are sensitive enough to detect the weak magnetic fields produced by the human body and are used in some niche medical applications focusing on the brain (Magnetoencephalography or MEG) or the stomach (Magnetogastrography).

The iron in our body is magnetic! Tissue iron stored in ferritin and hemosiderin has a strong positive response to an external magnetic field and is classified as paramagnetic. Other paramagnetic elements such as cobalt and nickel exist in the body in trace amounts. Iron by far is the most abundant magnetic element especially when stored in body tissues. Biosusceptometry a technique to quantify iron in the body based on susceptibility, a material's intrinsic response to a magnetic field. Magnetic techniques such as the SQUID and Magnetic Resonance Imaging (MRI) are naturally suited to quantify body iron because of this magnetic behavior. Our bodies also respond to applied magnetic field and this response is the basis behind MRI. To accurately quantify iron with biosusceptometry, the signal from the body must be subtracted from the total signal measured. The SQUID solves this problem with the help of the water bag and a correction factor determined from the body mass index (BMI).

Biosuceptometry measures a three-dimensional volume and is best suited for homogenous near-surface tissues that are at least the size of a softball. The SQUID measures an in vivo volume of about 300 cm3 which is about 30,000 times larger than the in vitro tissue sample measured in a biopsy. The liver and spleen are ideal organs to measure with biosusceptometry. However, organs with complex geometry such as the heart or tissues located deep within the body such as the pancreas are not suitable for this technique. A challenge unique to SQUID-based technology is the need for liquid helium which is a non-renewable resource and very expensive.

Non-invasive Methods to Measure Liver Iron Concentration

Because of the narrow market and high costs of operation, the manufacture was not financially motivated to obtain FDA approval for the SQUID. Currently no FDA-approved devices exists that utilize magnetic susceptibility to quantify body iron. This means that the SQUID has no similar or "predicate" device which could re-



duce the cost and time for the FDA application.

Development of MRI techniques for measuring LIC was a major advance in thalassemia. The availability of MRI is still limited outside large medical centers and invasive for young children or those who need general anesthesia. There is an inherent maximum upper limit to the iron concentration measurable by current MRI protocols. As hospitals switch from 1.5 to 3 Tesla MRI scanners, this inherent maximum is shifted to lower iron concentrations. Iron overload remains a critical global issue and many patients with thalassemia still do not have access to MRI. Despite the importance of this issue, no commercially available devices existing that are dedicated to measure body iron concentration. In the United States, the only FDA-approved techniques to quantify body iron are biopsy and FerriScan ® (Resonance Health). There remains an unmet global need for a low cost, accessible, accurate and precise measurement of the hepatic iron concentration.

Development of Novel Devices

Biosuceptometry may be the answer to developing a dedicated, rapid and inexpensive device to assess liver iron concentration. Since no images are generated with this technique the analysis is rapid (on the order of a few minutes) and straightforward making it ideal for high volume. A direct measurement of the iron, there exists no maximum upper limit measurable. Recently, there has been lots of interest in developing new devices based on biosuspectomety. The goal of these new devices is to assess LIC with less expensive technology and, more importantly, forgoing liquid helium. Inherent to this technique are the technical challenges of producing relative motion (or changing magnetic fields) to generate the measurement signal, the need to subtract the signal from the body and most importantly the requirement for accurate patient positioning.

BCHO has become a hub for BLS device development research due to our expertise in iron quantification and biosusceptometry. We received grants from two companies and a one UC Multicampus Research Programs and Initiatives grant to help develop novel biosusceptometers which are less expensive (construction and operational costs), have smaller footprints and are sufficiently robust to operate in a diverse clinical environment. In 2018, we completed two studies on prototype devices that work completely at room temperature and we expect a liquid nitrogen - cooled prototype later in the fall of 2019.

In the summer of 2018, we tested the most recent version of the Room Temperature Susceptometer (RTS) prototype, Insight Magnetics, San Diego. The RTS utilizes similar components as the SQUID - the same locator loop and water bag. Key differences make the device technically simpler and less expensive to construct. Rather than SQUIDs, the sensing using it made from coils of ordinary copper wires. Instead of moving the patient away from the sensor, the RTS utilizes an oscillating magnetic field and periodically moving sensing unit. In our small feasibility study, we compared LIC results between the RTS and the SQUID on 15 participants and saw excellent correlation. In May 2019, Dr. Lal and Marcela visited the group of Sebastian Mueller at the Suszeptometrie Center in Heidelberg, Germany. The Mueller Group has an older version of the RTS, which they have been using to study iron overload in alcoholic liver disease and we learned about their experience with the device.

In the Fall of 2018 we completed a small feasibility study on Biomagnetic Liver Susceptometer based on Piezoelectric Magnetic Sensor (BLS-PM). The BLS-PM was developed from technology developed by the Professor Qiming Zhang at Pennsylvania State University and constructed by Nascent Devices, State College, PA. The novel sensor combines piezoelectric materials - which change shape when exposed to an electric current (or visa versa) and commonly used in ultrasound transducers - with magnetostrictive materials - which change shape when exposed to a changing magnetic field. By sandwiching these two layers together, the sensor can convert the magnetic signal from the liver iron into an electric signal related to the iron concentration. This first generation prototype moved the patient and bed in a constant up and down motion. Unfortunately, this study was prematurely closed due to mechanical failure of the motor and insufficient data was collected to see any trends between the two devices.

(Continued on Page 5)

Open Thalassemia Research Studies

Title	Abstract
Natural History of Iron Burden and Risk of Organ Injury as Assessed and Predicted by Non-Invasive Measurement Techniques	Longitudinal assessment of whole body iron burden is essential for managing chelation and phlebotomy therapies and may be effective in predicting risk of organ injury. Biomagnetic susceptibility measurement of liver iron concentration using SQUID technology. We will assess iron burden by biosusceptometry and serum ferritin at CHRCO and evaluate the clinical evidence of cardiac, hepatic, endocrine and orthopedic dysfuntion, and relate it to total iron burden as assessed by biosusceptometry and other non-invasive techniques.
Towards the Development of a Noninvasive Prenatal Testing for Beta-Hemoglobinopathies	The goal of this project is to show proof of concept for a non-invasive prenatal test (NIPT) for beta-hemoglobinopathies utilizing a novel DNA probe capture assay and next generation sequencing (NGS). Our preliminary data have shown that our probe capture/NGS system can overcome the challenges implicit in the analysis of cfFDNA for NIPT: low DNA amount. The final proof of principle for this NIPT assay requires blood samples from pregnant couples, confirmed to have mutations in the beta-globin gene. For this work we are collaborating with our Indian colleagues at the Postgraduate Institute of Medical Education and Research, Chandigarh.
A Phase 3 Single Arm Study Evaluating the Efficacy and Safety of Gene Therapy in Subjects with Transfusion-dependent -Thalassemia, who do not have 0/0 Genotype, by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo with a Lentiviral A-T87Q-Globin Vector in Subjects under 50 Years of Age	This gene therapy study is a single-arm, multi-site, single dose, phase 3 study to evaluate the safety and efficacy of autologous hematopoietic stem cell transplantation (HSCT) using LentiGlobin® BB305 Drug Product in patients with β-thalassemia major. Patients must be less than 50 years of age with transfusion dependent β-thalassemia who do not have the β0/β0 mutation and are clinically stable to undergo transplantation but who lack a suitable matched family member donor.
A Phase 3 Single Arm Study Evaluating the Efficacy and Safety of Gene Therapy in Subjects with Transfusion-dependent B -Thalassemia, who have a 0/00 Genotype, by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo with a Lentiviral Globin Vector in Subjects 12 - 50 Years of Age	This gene therapy study is a single-arm, multi-site, single dose, phase 3 study to evaluate the safety and efficacy of autologous hematopoietic stem cell transplantation (HSCT) using LentiGlobin® BB305 Drug Product in patients with transfusion dependent β-thalassemia. Patients must be at least 12 years of age with the β0/β0 mutation and be clinically stable to undergo transplantation but who lack a suitable matched family member donor
A Phase 2, Open-Label, Multicenter Study to Determine the Efficacy, Safety, Pharmacokinetic, and Pharmacodynamics of AG-348 in Adult Subjects with Non-Transfusion-Dependent Thalassemia	This is an open-label multi-center study in patients with non-transfusion-dependent thalassemia, including patient with beta thalassemia and hemoglobin H constant spring disease. Approximately 17 patients will be enrolled at 3 sites in the United States. BCHO will enroll approximately 8 patients. Thalassemia is an inherited blood disease where the body cannot make enough hemoglobin. This produces anemia that can be severe enough to require blood transfusions for survival. Many patients do not require regular transfusions, but are at risk from the effects of severe anemia. The treatment options for such patients are very limited. In this study, we are evaluating whether treatment with AG-348, a new drug that improves the energy metabolism of red blood cells, will lead to improved overall fitness and survival of blood cells. The study will include patients with either beta thalassemia intermedia, or hemoglobin H Constant Spring disease. The primary objectives of this trial are to measure the improvement in hemoglobin level in response to treatment with AG-348. Secondary objectives are to evaluate the safety and pharmacokinetics or AG-348 and to determine the effect of the AG-348 on markers of hemolysis, erythropoeitic activity and iron metabolism.

2019 THALASSEMIA HOLIDAY PARTY by Wendy Murphy, LCSW

We had a great turn out for the patient and family holiday party on Sunday, December 1st. The event occurred again at the Colombo Club. There was delicious food, arts & crafts activities, face painting, caricature artist and a balloon guy! For dessert, we had tasty gelato from the Bonfiglio family (Bacio Gelato) and bundt cakes donated by Nothing Bundt Cakes in Emeryville. In addition, Santa Claus visited us and gave out gifts.

This party was possible through the generous donation of Asset Mark (Investment Services, Concord, CA). Asset mark have been providing financial support to our party for many years and we completely appreciate their generosity. We are also very grateful to the following families for donating toys and gift cards: Bursleys, Fagerlunds, Nguyens and Sirisacks.

SAVE THE DATE FOR 2020

For 2020, the holiday party is scheduled for **Saturday, December 12th** at the Colombo Club at 5321 Claremont Avenue in Oakland. More details to come!

Northern California
Comprehensive Thalassemia Center
747 52nd Street, Oakland, CA 94609

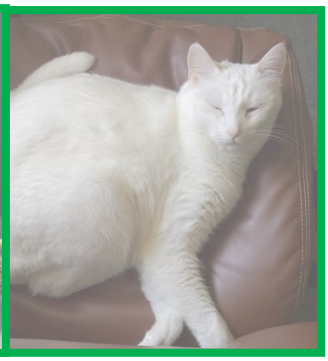
UCSF Benioff Children's Hospital
Oakland

BABIES

Babies come in all shapes and sizes.

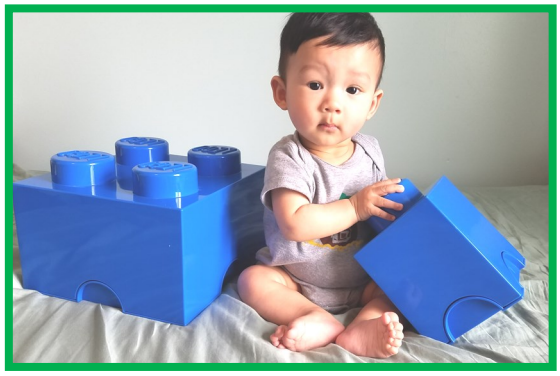
We asked patients in our thalassemia community to submit pictures of the babies who are most precious in their lives. Here's what they came up with!

Chean C. with her babies... Roger C. with his



Jane's favorite people, Pinky and Avery

Zahra Ruparel



(Above)
8 months of Ava!

(Left)
Meghan with her baby, Aleafah Franklin Foe.

Visit us on Facebook:
http://Facebook.com/CHRCOThal

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http://thalassemia.com

Sign up for our e-mail list:
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Perspectives is produced by UCSF Benioff Children's Hospital Oakland.
Editor: Ashutosh Lal, MD. Guest Editor: Meghan Foe. Layout/Production: Meghan Foe, Shanda Robertson
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If you no longer wish to receive our newsletter, please email info@thalassemia.com.