

ROOTS ⁱⁿ RESEARCH

2020 REPORT | THE STURGE-WEBER FOUNDATION



**The Sturge-Weber Foundation
ROOTS IN RESEARCH**

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ROOTS in RESEARCH

The Sturge-Weber Foundation's 2020 Research Report

On the Cover: Living blood vessels inside a microfluidic chip containing the genetic mutation (green) responsible for Sturge-Weber syndrome (Credit: Colette Bichsel from Bischoff Lab)

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Million Miles for Sturge-Weber Syndrome	Back Cover

Port Wine Birthmarks (PWB) on the skin are developmental abnormalities in blood vessel formation (capillary malformations) that are more extensive and darker than the pink capillary birthmarks often seen at the nape of a baby's neck. Sturge-Weber syndrome (SWS) is a rare congenital condition usually consisting of a facial port wine birthmark, glaucoma, and seizures, (although not all of these symptoms may be exhibited).

SWF POLICY STATEMENT:

In implementing the purpose of The Sturge-Weber Foundation to improve the quality of life for individuals with SWS and their families, the Foundation will act as a clearinghouse of information, provide emotional support and facilitate research on PWB and SWS.

The Foundation will seek information regarding management and treatment techniques and suggestions concerning education and emotional support and will facilitate the dissemination of appropriate information. If, in facilitating research on PWB, SWS and KT, the Foundation provides financial or other support to a particular research project, the Foundation will base its decision upon need, the Foundation's financial resources and medical advice.

The SWF is a member of:
the Brain Vascular Malformation Consortium (BVMC)
American Brain Coalition (ABC)
The Coalition of Skin Diseases (CSD)
The Association for Research in Vision and Ophthalmology (ARVO)



Seed Money and You: The Rippling Impact

I want to share with you the rippling impact seed money and you have had around the world and how it has gotten us where we are today with a gene discovery and more exciting discoveries to come! Say it fast...34 years of comprehensive personalized services, support and research funding!

Seed money...you know the kind of money where you gather a small amount to either fund your child's college fund, maybe save to buy your first home or in the case of the SWF save it up to bring families from around the country to the first International Conference or to fund research. I hear many times from individuals, well I only have \$25, I wish it could be more! The following will give you a better understanding of the SWF operational and strategic plan over the last 34 years.

It is because of your dedication and donations with EVERY dollar you have donated or raised counting that there has been a united front making a VERY huge impact over the years. I marvel at those who hit the send button from Australia, South Africa, Omaha, NE and thousands of other homes around the world... all seeking support and direction for themselves or their loved one. Let me give you a few examples of how the SWF Routes to A Cure have evolved over the years to illustrate my point.

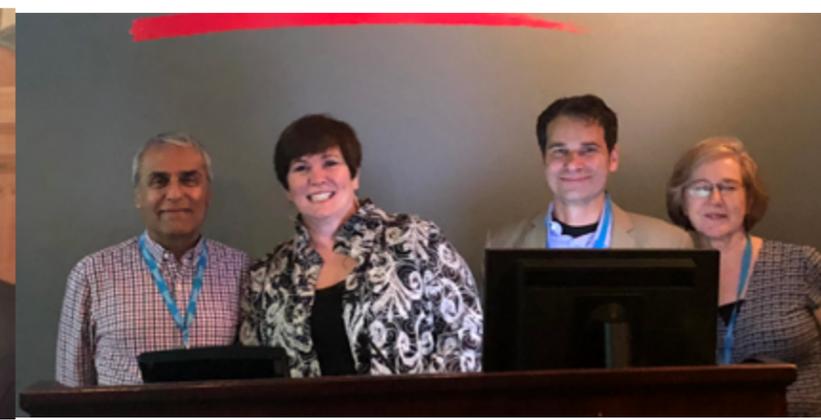
In this special edition of Roots in Research, there are 4 sections illustrating a "rippling impact".

- **Part 1: The Rippling Impact of Networking**
- **Part 2: The Rippling Impact of Collaboration and Research**
- **Part 3: The Rippling Impact of Investing in Infrastructure**
- **Part 4: The Future Harvest**

Following these sections are reports from the SWF Clinical Care Centers, researchers who have received grant money from SWF, newly awarded grants to researchers, upcoming clinical trials and so much more!

**Yesterday,
today and for the future.**

**The rippling impact
of your time,
talent and donations
proportionately impacts
the world around us!**



Network and Support

I remember the very first mama who was like me (Do you remember yours?). I thought I was the only one with a child with SWS and a birthmark on her face before I had that conversation with that mama. I had NO idea how to help her or navigate the world in which I was then living in and would for a lifetime. I have been hesitant over the years when visiting with another mom or dad about SWS to say those words...a lifetime. Truth is though the impact of a birthmark or a SWS diagnosis IS for a lifetime. Some of us dodge the proverbial bullet and the medical issues are slight if any but the reality is we are inevitably changed due to the rippling impact the diagnosis has on our world and on those around us.

Seed money scraped together by families hosting a special event or given in hope for a better world for their loved one or someone they know has had a profound impact on the SWF's ability to bring y'all together face to face to share your journey. It has given all of us a community to offer encouragement and hope and share tidbits on coping, medication administration and well just life...you know "my kids driving me crazy or SOOOOO EXCITED she walked last week!" The SWF carefully saved and invested your seed money to host conferences, educational forums, sponsor events and more so your world would become a lil less scary, more informed and more confident in handling anything SWS or a birthmark would throw your way.

"Friend" Raisers and Awareness

Along the way, Melanie Wood and Kathy Keffer led early fundraising events in their local community hosting softball tournaments, galas and "firehall" dances which kept donations flowing to replenish the coffers and to build a corpus of

funds for the next patient conference and research seed grants. Families and individual's sent in donations and held garage sales and more to improve the quality of life and care for diagnosed individuals. Pamela McIntyre and Jessica Melo liked to run so the Falmouth Road Race began and raised over \$1 million dollars in donations over 10 years! Mark and Kelly Kenney and Meg O'Leary loved football and Thanksgiving and voila. The Turkey Bowl! The Saden's Rock for A Cure! The Willard's Halloweenfest, and the Speer's Myla's Mission Walk. Todd and Jackie Brown loved horse racing and golf so together with Dr. David Brown and Dick Droesch we had our first racing horse named Sturge-Weber and golf tournament!

These long-term events have had a HUGE impact on our ability to keep the SWF viable for the next family and next research investigator in need of funds. They have enabled those of us in medical or financial constraints to take time out before we too can honor those living with SWS, KT or a birthmark and host our own "give back and hand up" special events. Routes To A Cure Walks and Online donation pages make it easier than ever!

So many more of you volunteer at education conferences, on Capitol Hill, and thankfully there are not enough pages to list everyone but I am personally grateful and humbled. The Board of Director's over the years donated countless hours to ensure the SWF maintained fiscal and governance accountability. Lauris Partizian and Valerie Lano volunteered for years when the SWF desperately needed administrative help but didn't have the funds for staff. Ian Hubling was our first webmaster. His technological ability made it possible for the world to become much smaller and for you to

(continued on page 18)

It all started innocently enough much as the roots of the Foundation did...a little spark of knowing what needed to happen! So, after about a year of answering people's snail mail and phone calls I figured well let's try and get these people together. I got an article in The Denver Post on Sturge-Weber syndrome, Kaelin and the fledgling Sturge-Weber Foundation.

While Kaelin was napping, I was sitting at my Amoco donated desk (that I still use today) in my unfinished basement in my oh so elegant office attire of sweatpants and t shirt when a telephone call came in..."Hello, this is Betty Ford's secretary and she'd like to honor you..." Uh Yeah Right...click! A minute later it rang again..." Please don't hang up!" And the rest is history...the Sturge-Weber Foundation Research Fund was established with the First Lady Betty Ford Award donation for tenacity in the face of adversity and this small "seed grant" of \$5,000 which was to be the corpus of research funding.

\$5,000 First Lady Betty Ford Award

The Former First Lady Betty Ford was being honored by the Beaver Creek Hyatt and she wanted to share the event with those who had tenacity in the face of adversity. Jim and Sarah Brady were the national honorees and Kirk and I were the Colorado honorees. HUGE gala and cocktails at the Ford's home and many new contacts made to help along the way. The most important moment though was when we were surprised with the \$5,000 award check. Our annual budget was \$2,500!!! The further we reach out...the closer we become!!!! Just go for it you never know what will happen and we need an ARMY of Warriors like you and President and Mrs. Ford to maintain the momentum until there are no more children born with SWS!

Volunteers and \$30,000 Seed Research Grant

The years flew by while Kaelin stabilized her glaucoma and seizures and the Foundation had an Access database registry of 400 cases of diagnosed SWS. The office moved from my home to a small office with a part time administrative assistant, Marsha Dingbaum (who still donates today!) to help juggle the workload. Two young mother's working around naptime and school schedules to connect with other people impacted by a diagnosis and in need of support.

Volunteers

Drs. Bill Weston, Joe Morelli and Allan Eisenbaum provided expert medical advice and propagated awareness on TV and in print. Dr. Eva Sujansky and colleagues published medical journal articles based on the information I had recorded during support telephone calls from the 400 families. Back then patient advocates were not being recognized as authors on papers or I would have another 2 papers to my credit! Dr. Richard Finkel put flyers on SWS and the SWF in the bags of doctors attending the Child Neurology Society annual meeting inviting them to a meeting to discuss plans for clinical studies. Drs Steve Roach, John Bodensteiner and Harry Chugani took the reins and we were off! They amassed a Medical Advisory Board to write articles, give lectures, review research grant proposals and extend the "SWS experts" around the country.

Today we have thousands of healthcare providers in our database and young clinicians being trained around the country and abroad to care for our patients. Of course, as if that wasn't enough they decided we needed to publish the first SWS textbook in forty years and with Alberta Edwards able guidance we did. The second edition is still available to order online and the third edition will be forthcoming!



\$30,000 Seed Grant

Dr Bernie Maria received the first research grant. Seed money to make an impact on our understanding of SWS. All your generous donations were carefully saved and spent which enabled us to bring more hands to the fight to foster more awareness, clinical studies and attend medical conferences to engage more clinical and research care providers and investigators. The seed grant also let the medical community know that the SWF and our supporters were serious about making strides in our understanding and ultimate goal to find the cause.

\$50,000 A Center of Excellence to Clinical Care Network

The next phase of organizational growth brought a move to New Jersey and the addition of more staff to handle communication, patient and caregiver networks and “friend” raising special events. It became apparent the SWF needed to expand the knowledge base and established targeted endeavors to shape research. The SWF awarded a \$50,000 seed grant to establish a Center of Excellence (COE) at Johns Hopkins Hospital with Dr Anne Comi directing that initial center. The initial SWF COE proved to be a good working model and we appreciate Dr. Comi for her dedication and have continued to work with her well after she chose to become an independent and self-funded center. As the SWF membership grew and evolved, we recognized the need to minimize daily life disruptions and the financial burden for families having to travel across country in some cases. We began to expand the now Clinical Care Network (CCN) facilities across the country at key universities and hospitals committed to excellence in care and research. Today there are over 26 CCN facilities and a burgeoning cadre of young professionals.

\$25,000 Data Needs A Registry

Those first 11x17 papers that I recorded vital statistical data collected from patient reported information was transferred to an Access database with the growth of new software programs. We maintained this data in Access for many years and expanded what we recorded based on the influx of reports by patients. Little did we know we had a “registry”. Today registries are numerous, online and cover a variety of data collected. The registry requires \$25,000 annually to maintain, data mine and engage patient participation. My dad used to say, “From little acorns grow mighty oaks” no truer words have been spoken! Your vigilance in sharing the natural history of SWS in your life along with thousands of others diagnosed has shaped our understanding of the course of the disease and treatment.

The corpus of data collected over the years has been used as documentation in many medical journal articles educating a new generation of caregivers and researchers. The profound impact of gathering data, sharing the statistical data while engaging clinicians and researchers has opened up new fields of study and enlightened families and caregivers alike. THANKYOU!

\$40,000 NIH CSO and Multi-Million dollar BVMC

The rippling impact of being responsible stewards of the compounding donations gave us the ability to fund the SWF’s first Chief Scientific Officer (CSO) who was a former program officer at the National Institutes of Health (NIH). This investment provided strategic leadership and established the first strategic research plan to guide us in setting goals and action items. Our CSO’s knowledge of the NIH grants and review committees positioned us to submit for
(continued on page 18)



So, the truth is the SWF actually started in a spare bedroom in our first home. Kaelin took her naps and I answered “snail mail” or made phone calls to physician’s requesting their help. Thanks to donated Amoco office furniture of a desk, file cabinet, office chair and electric typewriter I was able to move the office to our downstairs unfinished basement when files and supplies outgrew the bedroom space. I was so caught up in ensuring we had enough money from trickling in donations to deliver support via the mail and a phone line and to develop a healthcare provider resource list that it never crossed my mind or Kirk’s to reimburse us for the use of electricity or increased long distance phone bill (yes we actually had to pay for long distance charges in the dark ages!).

Families were in need and while donations were slowly coming in after incorporation in September 1987 there weren’t enough donations to cover mailings, newsletter printing etc AND pay the utilities let alone to pay for my time. There were increasing days when I had to meet doctors or give interviews when Kaelin wasn’t napping. With a HUGE plethora of medical bills and doctor visits to pay for we couldn’t afford to pay for babysitters AND utilities too. I finally relented and took a “salary” equal only to the babysitting costs and burgeoning telephone bills required to conduct the SWF business.

There were more and more people learning of the SWF via their doctors and slowly the case files grew (yes only paper back then) and donations did too! The Board of Directors approved the hire of a part time administrative assistant and office space. H U G E leap of faith for the organization and me personally as I had to leave Kaelin a few days a week with her preschool teacher, Sue Furia, so I could keep up with inquiries and demands. I always wanted to be a stay at home mom but clearly God had other plans!

Part Time Administrative Assistant/Office Space/Volunteers

Infrastructure isn’t a “sexy” program to think about or to fund but it is absolutely essential to meet demand for services, awareness, networking and research. Without hands on deck and funding to keep them, the ability to support those in need and the pace of discovery will grind to a glacial pace and or halt. The Board’s approval to hire the administrative assistant and to get the office was key to the SWF’s ability to keep the momentum going and position the organization to eventually fund research.

We had over 400 identified cases of Sturge-Weber when we relocated to official office space. Lots of file cabinets and thankfully another typewriter etc to keep pace with press inquiries, brochure mailings to families and healthcare providers.

We also had the ability to plan our first family conference and all the logistics that entails. Basically, we were really off and running! The Betty Ford Award helped us reach a wider audience and the Anne Landers column answering Anita Messer’s letter doubled our membership overnight.

I remember the call from Ms. Lander’s assistant asking us if we had the ability to answer the letters we would receive. Of course, I eagerly and naively told her yes! Thank goodness for the wisdom of my elders and family! My aunt and uncle Carlene and Bruce Fisher came over and triaged the over 400 letters and new families to welcome making our member total 800! We placed the letters into regional piles around my living room so we could respond with regionally based information. With their help, our volunteers now numbered 6 along with our Board members Don Hanley, Stan Fisher, Pete Ober, Kirk Ball! My daddy always says, “Many hands make light work”.

PART 4 The Future Harvest



Today not for profit startups have a plethora of on-line platforms, software and software integration that make it more efficient and streamlined to communicate. The ease of which an organization can reach out to other not for profits (npo's) for advice is amazing! Back in the dark ages when npo's were really just emerging especially in the rare disease space there were not as many resources to access. We relied on the spirit of generosity to share our collective knowledge of governance, education, patient support etc. Online social media forums have "been there done that" expert parental advice that still needs to be tempered with reminders each case of SWS, KT and birthmark issues are unique and while experiences shared are a great comfort to people the experiences are not your personal journey or your medical matter.

The further we reach out, the closer we become SWF has benefited every day from all the latest technology and social media venues as we tailor fit our responses to your inquiries. New volunteers continue to step up to give back to all of us! Chris and Dana Davis supported the new website which is an internationally respected and vetted resource for patients and caregivers alike. The adjustment from traditional office to a blend of traditional and remote workers who interface with volunteers around the world has put the SWF in a perfect position for rapid response. The tailor fit service, online forums, and vast network of resources ensures you ARE in good hands!

As donations and grants are received, the SWF is able to expand services and programs with knowledgeable staff and volunteers working together to foster the vision and mission. I know what I know and I know what I don't know! I have never been afraid to admit I don't know... which is why I search out the world to find the brightest researchers

and clinicians, volunteers and staff to forge new inroads and plant new seeds of thought and hope.

Healthcare Providers and Investigators

Yesterday's scientists and clinicians are training a new front line of investigators. They are utilizing technology and our very increased understanding of SWS, KT and birthmarks since the dark ages of 1986 to improve the quality of care and increase the pace of discovery. Lisa's Research Fellowship funded by the Peltier's, a \$200,000 donation, has fostered excitement for young investigators and increased collaborations. Fellowship recipients then apply to the National Institutes of Health (NIH) for larger grant awards.

With over 26 SWF Clinical Care Network (CCN) facilities, individuals and parents no longer have to trek across country from one coast to the other like I did with Kaelin in 1987. They can rest assured that these CCN facilities have dedicated and knowledgeable staff who will provide the best care and collaborate with researchers around the world. The blend of national facilities with various areas of expertise ensures that collaborations among the CCN and with those from beyond the CCN will keep the SWS clinical and scientific research burgeoning for years to come.

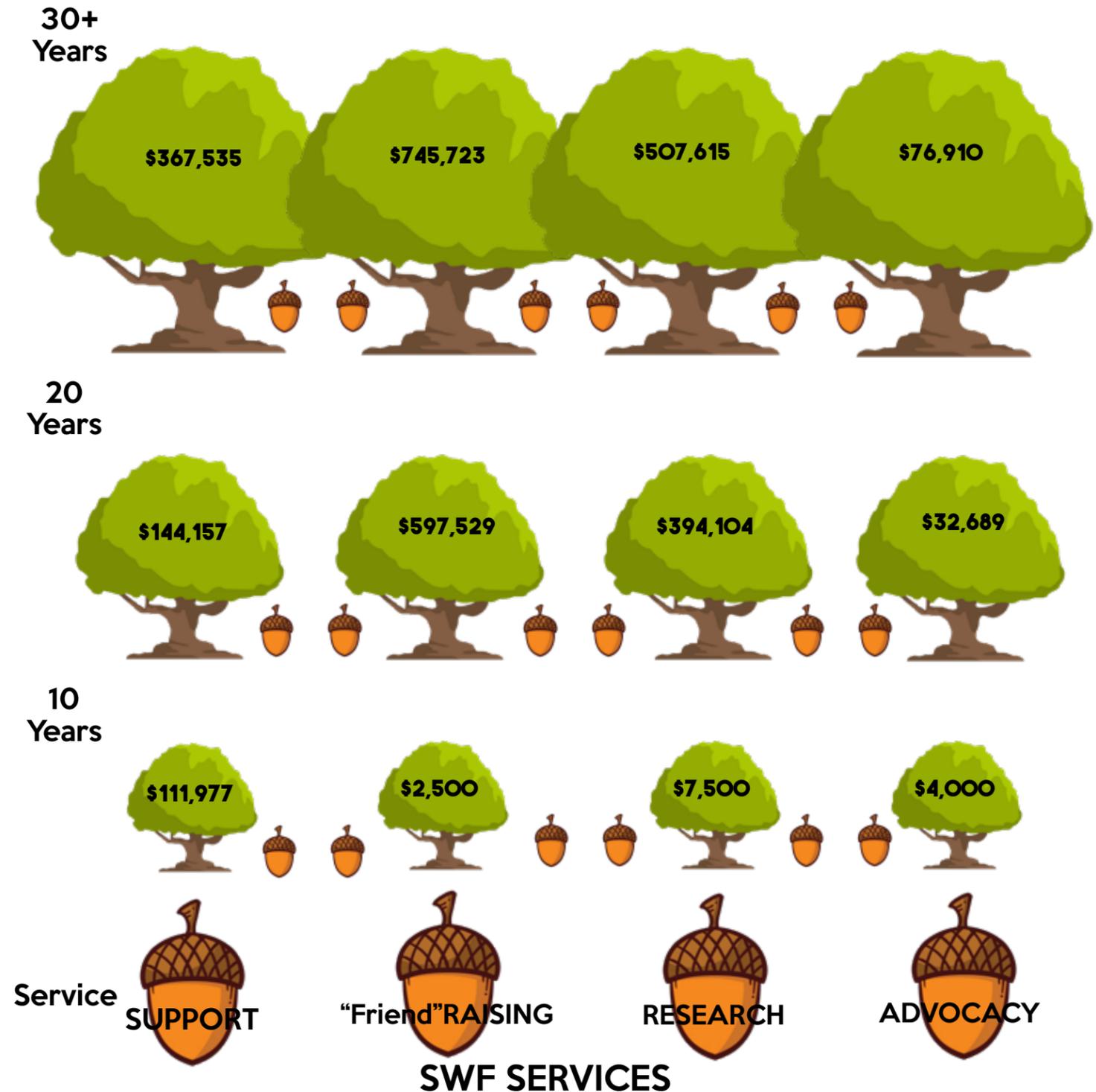
I realize how blessed I've been and how fortunate the SWF has been to have so many dedicated volunteers and families as I look back over 34 years of service and support. I live in hope that new families with a diagnosed loved one and individuals living with a diagnosis don't take for granted all that has been planted so far. While we continually harvest the fruits of our labors, we need individuals to step up and nurture the SWF with their time, talents and treasure. Your attention and commitment will ensure that the next

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The CARE Factor

connect. accept. respect. engage.

BE AWARE OF HOW YOUR CARE MAKES AN IMPACT!



in RESEARCH

SWF RESEARCHER REPORTS AND UPDATES

Sébastien Gauvrit, PhD
\$12,500

Laboratory of Prof. Didier Stainier
Max Planck Institute for Heart and Lung Research



“Investigating Sturge-Weber syndrome vascular defects using zebrafish”

Research BIO and Summary

Dr. Gauvrit is a cardiovascular biologist. His research focuses on understanding the morphogenesis of the vascular system to provide a starting point to move from fundamental to translational research.

Prof. Dr. Stainier investigates questions related to organogenesis, including cell differentiation, tissue morphogenesis, organ homeostasis, and function, as well as organ regeneration to gain an understanding of vertebrate organ development at the single-cell level. Dr. Gauvrit is using the zebrafish as a model to discover and characterize new genes involved in genetic diseases. Dr. Gauvrit's proposal, “Investigating Sturge-Weber syndrome vascular defects using zebrafish,” will generate new genetic tools to model and understand SWS.

Dr. Gauvrit has taken tissue samples and isolated pure endothelial populations from them and expressing GNAQ WT and GNAQ R183Q proteins in established cell lines.

Progress Report

The proposal aims to investigate how somatic mutations in GNAQ lead to vascular defects by generating a zebrafish model for Sturge-Weber syndrome (SWS).

To address this question, I proposed to generate novel genetic tools in zebrafish to model the Sturge-Weber syndrome and visualize the initiation and pathogenesis of the vascular defects.

To model the SWS in zebrafish, I cloned the human ver-

sion of GNAQ and its pathogenic isoform GNAQ R183Q using site-directed mutagenesis. The introduction of the point mutation was confirmed by sequencing. To define its effect during embryonic development, I synthesized mRNA for GNAQ as well as GNAQ R183Q, and I injected it into one-cell stage zebrafish embryos at different doses. At a low dose, 25 pg. GNAQ R183Q mRNA but not GNAQ mRNA leads to developmental defects in zebrafish embryos suggesting the potent effect of the pathogenic isoform in zebrafish.

Then, I introduced GNAQ and GNAQ R183Q into a plasmid containing the *fli1a* promoter expressed by endothelial cells. I fused the coding sequence of GFP to the GNAQ and GNAQ R183Q coding sequence separated by a self-cleaving viral 2A peptide sequence to visualize the transgenic cells.

I tested these constructs (*fli1a*:GNAQ-2A-GFP and *fli1a*:GNAQR183Q-2A-GFP) by injecting it into one-cell stage embryos, but the expression was quite weak. After several troubleshooting approaches and modulation of the concentration without success, I decided to switch my approach to another strategy using the Gal4/UAS system.

The Gal4/UAS system is a dual expression system in which the yeast transcription activator protein Gal4 binds to activate the UAS (Upstream Activation Sequence) enhancer sequence. This system presents several advantages over a simple targeting of endothelial cells. First, it is much more robust in terms of expression, and second, this system allows us to keep the same genetic constructs to express in different Gal4 transgenic lines expressed in different cell types. Indeed, we have several zebrafish lines expressing Gal4 targeting endothelial cells, pericytes, and venous endothelial cells.

We hypothesize that endothelial cells are the main driver of the disease, but an increasing number of publications suggest that vascular malformations could be due to defects in pericytes. Therefore, the UAS strategy is interesting in the long term run to investigate other cell types' implication in the emergence of the SWS.

I tested these constructs (UAS:GNAQ-2A-GFP and UAS:GNAQR183Q-2A-GFP) in the Tg(*fli1a*:Gal4) transgenic line, and as expected, the GFP expression was stronger.

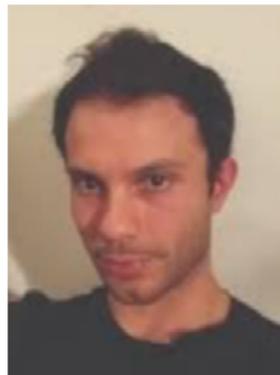
The Sturge-Weber Foundation continues to foster opportunities for researchers through grants and participation in clinical trials.

Researchers are tirelessly searching for answers, testing theories, and running trials to discover better treatments and hopefully, a cure for Sturge-Weber syndrome and other Port-Wine Birthmark related conditions.

I raised the injected embryos for the UAS:GNAQR183Q-2A-GFP construct to adulthood, which took around three months, and I started screening potential founders. I found two fish carrying the transgene, and their progeny present pericardial edema, a classic hallmark of cardiovascular defects in zebrafish embryos.

Now, I am raising more fish carrying the UAS:GN-AQR183Q-2A-GFP transgene from an outcross of our potential founders. I will also perform qPCR on the embryos overexpressing GNAQ R183Q to ensure that they express the human isoform and validate the model. I will then perform FACS sorting to isolate endothelial cells based on the GFP expression to do RNA sequencing.

Davide Zecchin, Crick Institute, London - \$5,000
Genetic Therapy for the Sturge-Weber Mutation



Summary and Progress Report

Dr. Zecchin is an expert in cancer genetics. He recently joined the laboratory of Dr. Veronica Kinsler at The Francis Crick Institute. Dr. Kinsler is an expert in mosaic disorders and GNAQ, which when mutated causes Sturge-Weber syndrome. The lab has done pioneering work in characterizing the development of birthmarks.

1. To culture, immortalise and fully characterize GNAQ-mutant primary patient cells.

During the last six months we have been obtaining skin and brain biopsies from SWS patients and I have established a new pipeline to isolate pure endothelial populations from these lesions. Purified populations are then expanded for further study. Full characterization of cells derived from these biopsies is ongoing. This strategy, now validated, will allow establishment of GNAQ c.548G>A, p.(R183Q) mutant cell lines from SWS patients within the next few months.

In parallel, in order to produce reliable models for testing our gene therapy strategies, a second method for constitutively expressing GNAQ WT or GNAQ R183Q proteins has been undertaken in established cell lines. These cells will be a key second method of assessing the specific targeting of the mutant GNAQ allele by our approaches and to measure their effect at the protein levels.

2. To design and test allele-specific siRNA in an existing GNAQ-mutant cell line (UPMM1).

I have designed siRNAs specifically targeting the GNAQ c.548G>A, p.(R183Q) allele and sparing the wild-type one. Those siRNAs will be soon tested on the recombinant cell models mentioned in point 1, and on the UPMM-1 cell line harbouring the same mutation on GNAQ gene.

3. To design and test allele-specific base editing in UPMM1.

A recent publication described a new method to obtain sequence-specific RNA-editing*. This is based on combining the enzyme adenosine deaminase acting on RNA (ADAR2) with associated ADAR guide RNAs (adRNAs) that include a programmable antisense region complementary to the target RNA. This new technology, differently from Cas13-based methods, lacks expression of bacterial proteins (e.g. Cas13) that can trigger immune-response in immune-competent recipients, and it showed efficacy also *in vivo*. Based on this evidence, we evaluated that implementing this new strategy to edit the GNAQ c.548>A allele could be advantageous. We are currently in contact with Prof. Mali and we will soon obtain from publicly available sources the plasmids codifying for the components of the RNA-editing toolkit to test them on our GNAQ-mutant models.

*Katrekar D et al. *In vivo RNA editing of point mutations via RNA guided adenosine deaminases.* *Nat Methods.* 2019 Mar; 16(3):239-242

4. To select the best candidates from aims 2 and 3 for testing in the primary cell lines, to assess functional and phenotypic rescue in vitro, and to look systematically for off-target effects in the genome.

This part of the project has not yet been reached.

Sarah Wetzel Strong, PhD - \$12,500

Research Scholar
Duke University
Department of Molecular Genetics and Microbiology
Marchuk Lab



SWS Mouse Model

The overarching goal of my project funded by the Catalyst Award from the Sturge-Weber Foundation (SWF) is to develop a mouse model of Sturge-Weber Syndrome (SWS) that allows for the study of the pathology and progression of the vascular lesions associated with SWS, and the factors that influence the pathogenesis of SWS during the embryonic period. To our knowledge, the Marchuk lab has developed the first mouse model allowing for controlled expression of p.R183Q GNAQ from the endogenous gene locus. The biggest advantage of our model over other

systems is that we are able to precisely control at what time during the course of embryonic or postnatal life we want to express p.R183Q GNAQ and in what tissue types at physiological levels, allowing for interrogation of the effect of these variables on phenotypic presentation. In the months immediately prior to shutdowns due to COVID-19, I made great strides in the development of this model, as described below. Fortunately during the shutdown, we were able to

keep a low level of maintenance breeding for these mice, which I have already ramped up the breeding on in eager anticipation of expanding on the findings I have made thus far.

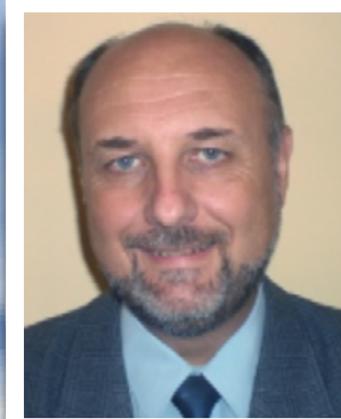
One of the sub-goals for this project is demonstrating that expression of the gene product encoding p.R183Q GNAQ
(continued on page 15)

SWF CLINICAL TRIALS AND CALL FOR PARTICIPANTS

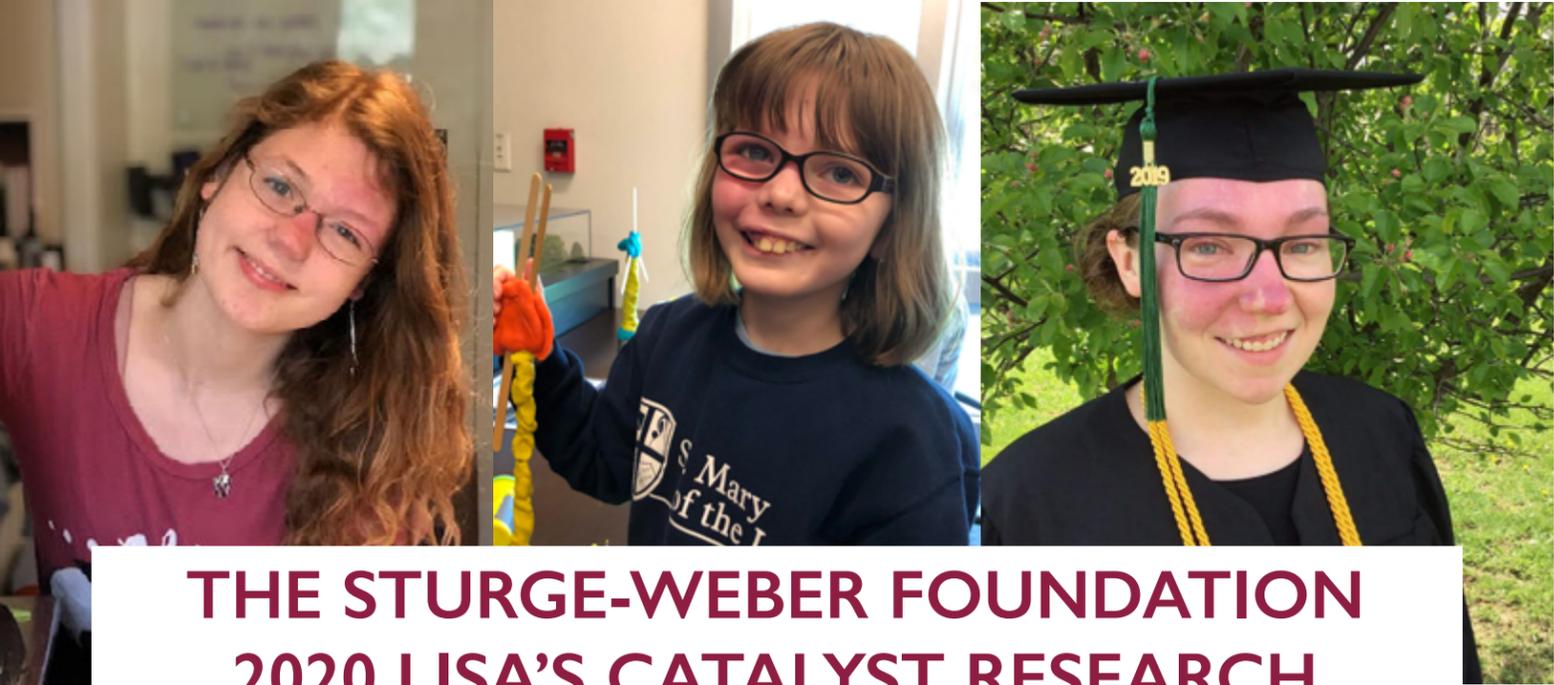
New, NIH-funded imaging and neurocognitive clinical trial at Wayne State University, Children's Hospital of Michigan in Detroit
Principal Investigator: Prof. Csaba Juhasz, MD, PhD

In March, 2020, the National Institutes of Health renewed funding for a 5-year clinical trial to study brain vascular and structural changes in patients with Sturge-Weber syndrome (SWS) at Wayne State University (WSU) and the Children's Hospital of Michigan (CHM) in Detroit. The Principal Investigator of the study is Csaba Juhasz MD, PhD, Professor of Pediatrics and Neurology at WSU/CHM, clinician co-investigators include Dr. Aimee Luat, MD (pediatric neurologist), Dr. Michael Behen (neuropsychologist) at WSU, as well as Dr. Mai-Lan Ho (pediatric neuroradiologist) at Nationwide Children's Hospital. The study procedures include review of previous brain scans (if available), brain magnetic resonance imaging (MRI) scanning with advanced sequences, and detailed neurology and neuropsychology evaluations. Main goals of the study include the validation of a novel, fast MRI approach developed recently at WSU to detect SWS brain abnormalities within minutes; this will allow safe MR imaging without sedation and, in many cases, without contrast injection in the future. In addition, mapping of vascular and neuronal connectivity changes in the brain, that may be missed by routine brain MRI, will be able to predict the type and severity of neurocognitive outcome and provide a more accurate guide for future, targeted treatments. Study results will be discussed with the participants and their family, and a copy of the brain images, their interpretation, and neuropsychology report will be provided.

All study tests are free of charge, and travel costs (including hotel costs if overnight stay is needed for those coming from out of town) are reimbursed. All tests can be completed in a single day visit. Eligible participants are 3 months – 30 years of age with the diagnosis of SWS and those with a facial port-wine birthmark who are at risk for SWS. Participants of previous imaging studies at WSU may be eligible for repeated studies under the new project to evaluate long-term longitudinal changes in the brain. Healthy siblings of SWS patients can also enroll as controls and undergo the same brain imaging. **Those who are interested in study participation can contact directly Dr. Juhasz at Csaba.juhasz@wayne.edu (or call his office at 313-966-5136) for further details and scheduling.**



Dr. Csaba Juhasz



THE STURGE-WEBER FOUNDATION 2020 LISA'S CATALYST RESEARCH GRANT AWARDS

Naïem T Issa, MD PhD-\$30,000

Development of a First-In-Class GNAQ (Gq) Small Molecule Inhibitor

Dr. Issa will test a novel small molecule inhibitor for the Gq protein and its mutant forms which will have significant implications in the field of G protein biology and ultimately for SWS patients. He has a team of experts from Dermatology, Drug Discovery and Pharmacology which brings a diverse depth of expertise to this investigation.



Alex Levin, MD -\$10,000

Delphi for Glaucoma in Sturge-Weber syndrome

Dr. Levin is leading glaucoma experts in a strategic process to identify proper consensus treatment for glaucoma in SWS and to drive further research into the unique aspects of glaucoma in SWS.



SPECIAL THANKS TO THE STURGE-WEBER FOUNDATION INTERNATIONAL RESEARCH NETWORK (SWFIRN)

SWF would like to thank the SWFIRN for its participation and investigation in reviewing the many applications received over the years for the Lisa's Catalyst Research Grant Award. With their expertise, the Foundation has been able to provide much needed funding for groundbreaking research.



Jack Arbiser, MD, PhD-\$10,000

Sturge-Weber syndrome Murine Model

Dr. Arbiser will test the efficacy of a novel small molecule and activators on SWS endothelial cells in this first SWS mouse model. The novel small molecule has previously been effective against uveal melanoma.



ONGOING RESEARCH NEWS

BRAIN VASCULAR MALFORMATION CONSORTIUM (BVMC)

The BVMC is in its third round of funding from the Rare Disease Clinical Research Network (RDCRN). The following Milestone's will immensely propel SWS research.



Project 2: SWS (Lead Investigators: Dr. Jeffrey Loeb and Dr. Doug Marchuk)

- **Milestone #1:** Enroll 50 SWS cases; collect clinical and imaging data, and specimens in enrolled cases; collect clinical and imaging data, and specimens in enrolled cases. Criteria for Success: Enroll at least 43 SWS cases (85% of planned enrollment for Year 2) or cumulative enrollment of 68 cases.
- **Milestone #2:** Communicate regularly with all project recruiting sites. Criteria for success: Continue project group call with all recruiting sites to discuss study logistics, recruitment, and important BVMC or RDCRN updates every other month.
- **Milestone #3:** Develop online dashboard to display and monitor longitudinal clinical data. Criteria for success: Work with DMCC and institutional CTSA to prototype online dashboard display for entering, displaying, and monitoring longitudinal clinical and imaging data.
- **Milestone #4:** Develop and validate quantitative measures from brain imaging. Criteria for success: Analysis of specific quantitative imaging variables will be Size (volume), and standardized location (on a

Sarah Wetzel Strong, PhD - (continued from page 13)

in our mouse model results in the expression of a functional mutant protein product. Since an antibody that specifically detects p.R183Q GNAQ is not commercially available, I have approached this problem by looking for observable phenotypes in animals expressing mutant GNAQ. Happle predicted that the causative mutations for mosaic disorders, including SWS, would be incompatible with life if passed through the germline, which he termed "paradominant inheritance". I have observed a sub-viability of animals expressing one copy of p.R183Q GNAQ in a global mosaic fashion, confirming Happle's hypothesis.

Further verifying Happle's hypothesis, I have found that the animals surviving at birth and during the postnatal period have low levels of mutant GNAQ expression in analysis of the bulk tissue, indicating low levels of mosaicism and not high global expression. In addition to the embryonic lethality associated with global mosaic expression of p.R183Q GNAQ in our model, I have also noticed hyperpigmentation of the brain meninges, indicating that even low levels of expression can drive phenotypic changes. Together, I now have mounting evidence that p.R183Q GNAQ protein product is being produced in these animals, supporting the evidence that mutant transcript is present following

normalized human brain structure) of leptomeningeal angioma, cerebral atrophic changes, calcifications, venous growth (12-24 months)

BIOTECH AND INDUSTRY

The SWF is embarking on a new era of networking and engagement. The stories we've told you in this issue have laid the groundwork for this new era of discovery! The sum of all integral parts short term goals and long-term strategies were and are needed to ensure this new era of discovery will be seamless.

We are behind the scenes working with several Bio tech companies focused on glaucoma, CBD and genetics which will in the near future need to enroll participants. Please look for alerts and the faster we enroll participants the sooner we have more answers! As my daddy says, "From little acorns grow mighty oaks!" and together over the last 34 years we have built a thriving forest!

FEDERAL ADVOCACY

Medicaid Value Based Purchasing Arrangements

Federal Advocacy: SWF Sign Ons

Accelerating Kids' Access to Care Act, HR 5900

Improves access to specialized care for Medicaid beneficiaries. The Haystack sign on letter we signed on to requested policy refinements that ease the burden of accessing the care they need and asked that the legislation, the Accelerating Kids' Access to Care Act, address the need to alleviate access issues for adults as well as children with rare disorders, including rare cancers, requiring treatment from out-of-state specialists through Medicaid.

Cre mediated recombination. Furthermore, I have evidence that expression of p.R183Q GNAQ in mice generates a range of exciting phenotypes meriting further investigation.

A second sub-goal of this project is generating vascular anomalies, a key feature of SWS. Immediately prior to the shutdown due to COVID, I identified several animals expressing p.R183Q GNAQ in a global mosaic fashion that have putative vascular anomalies based on macroscopic inspection. Currently, I am working to determine how expression of p.R183Q GNAQ in these animals affects the structure of the vasculature at the microscopic level (since abnormalities may be present, but not visible macro-scopically at the time point I investigated), and the underlying cause of the vascular anomalies I visualized (eg. hemorrhage, or increased vascular density). Moving forward, I am eager to continue characterizing the samples I have collected thus far, including microscopic characterization of the vasculature. Additionally, I am actively working to generate additional experimental animals to further investigate how expression of p.R183Q GNAQ at different developmental stages and in specific tissue compartments, such as the endothelium, influences vascular development to uncover the key factors for modeling SWS development and pathology in mice.



THE IMPORTANCE OF TISSUE DONATION BARBARA JEAN OSBORN'S STORY

I, Barbara Jean Osborn, was born on February 22, 1937. I was born and was raised up on a farm, life where the medical situation was nothing compared to what it is today!

My reason for bringing this point to the table is due to the fact I was born with, what I now know as Sturge-Weber syndrome (SWS), back then, we knew it as a birthmark. As I grew older and attended school I was not only teased by other students but I was told it was an angel that had kissed me on the face. My mother was always working so there really wasn't anything she could do to help as far as going to doctors. My father was too busy working then going out drinking afterwards.

My older siblings were always there to assist and help until I was old enough to take care of myself. I have had a couple of occasions where my younger sibling and I were sitting at our kitchen table when I was approximately 7 years old and I was told I had a seizure and blacked out and fell onto the floor. There was no convulsing, just a blank stare and I woke

up on the floor. Another time I was told that I was outside playing and became very tired so I went to sit down and I had a blank stare but didn't black out.

Skipping ahead several years to my adulthood, I have found myself in my elder years not becoming very good friends with SWS. In my elder years I have experienced more dramatic symptoms such as: TIA'S (mini strokes), blindness in my right eye, congestive heart failure, kidney disease and several bad cases of pneumonia. I have fought this so far for 83 years. It has not been an easy road.

I would love to dedicate all or part of my tissue to the Sturge-Weber Foundation to research more ways to help the next person or any person that is out there having the same or similar symptoms and fighting like I have had to!

Thank you & God Bless!
Barbara Jean Osborn

PILOT SURVEY OF THE PATIENT EXPERIENCE: LASERS, BIRTHMARKS AND STURGE-WEBER

Conduct, Reviewed and Analyzed by:

Craig Burkhart, MD; Julia Terrell; Karen Ball; Sara Sabeti; Kelly Jo Tacket; Kristen M. Kelly, MD; Burkhart Pediatric and Adolescent Dermatology; The Sturge-Weber Foundation; Department of Dermatology; University of North Carolina at Chapel Hill; Department of Dermatology; University of California Irvine School of Medicine



ABSTRACT

There is limited data on the experience of patients with Sturge-Weber Syndrome (SWS) and/or their parents who seek out laser treatments for their port wine birthmark (PWB). Our study aimed to understand patient perspectives on laser therapy and subsequent behaviors, while focusing on two elements of the Health Belief Model: Perceived Susceptibility and Perceived Benefits. Understanding motivations for treatment can be used to inform patient-centered research and guideline development.

BACKGROUND

- Why do some patients choose to have many laser treatments whereas others choose few laser treatments?
- Sturge-Weber Syndrome (SWS) is a congenital, neurocutaneous disorder classically characterized by two or three of the following: a facial port wine birthmark (PWB), early onset glaucoma, and variable degrees of brain involvement¹
 - The rationale for treating the PWB is to improve color, prevent potential future soft tissue hypertrophy, nodularity, bleeding, or facial disfigurement, and reduce the negative psychological impact²
 - There is wide variability in the number of laser treatments SWS patients undergo.
 - The Health Beliefs Model (HBM) is a widely used framework for understanding the motivations for why people take action to prevent, screen for, and control illness.
 - The HBM has been utilized to create healthcare efforts for many diseases based on how susceptible a population feels to the health problem, whether they believe it is serious, and whether they believe action can reduce the treat at an acceptable cost.

OBJECTIVES

- Pilot an investigation into whether SWF Members' behaviors are guided by their beliefs about lasers based on HBM:
- Perceived Susceptibility:** Beliefs about the chances of getting a condition (i.e. PWB getting worse)
- Perceived Benefits:** Beliefs about the effectiveness of taking action to reduce risk or seriousness (i.e. PWB improving)

METHODS

- The Community Based Participatory Research Framework
- Members and Patients of the Sturge-Weber Foundation designed, piloted, distributed, analyzed, and confirmed accuracy of the interpretation of results
- 31 Question survey mailed to all SWF members assessing:
 - Demographic
 - Disease Severity
 - Laser Experiences
 - Beliefs and Perceptions
- Statistical analysis of data was performed using STATA version 16.4

Demographic Summary

Age	48 years old (Range 8-82)
Race	84% White
Insurance	43% Employer insurance
	17% Medicare
	12% Medicaid
	7% Uninsured
Satisfaction	48% Satisfied with appearance of birthmark

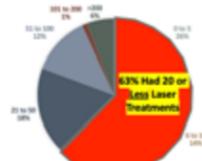
Location of PWB



Location of SWF Survey Respondents



Lifetime Number of Laser treatments



RESULTS

- Perceived benefits of lasers is NOT associated with the number of lifetime treatments (Figure 1)
- Perceived benefits of lasers is NOT associated with spending (Figures 3 and 5)
- Perceived susceptibility is NOT associated with number of lifetime treatments (Figure 2)
- Perceived susceptibility IS associated with spending on travel and medical expenses (Figures 4 and 6)

RESULTS

Fig 1. Perceived Benefits of Lasers and Number of Treatments



Fig 2. Perceived Susceptibility and Number of Treatments

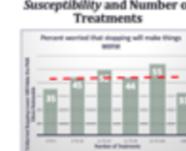


Fig 3. Perceived Benefits of Lasers and Travel Costs

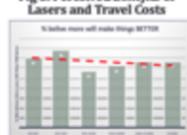


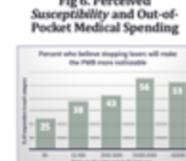
Fig 4. Perceived Susceptibility and Travel Costs



Fig 5. Perceived Benefits of Lasers and Out-of-Pocket Medical Spending



Fig 6. Perceived Susceptibility and Out-of-Pocket Medical Spending



CONCLUSIONS

- In patients with Sturge-Weber Syndrome:
- Fear drives spending on lasers more than hope
 - Fear and hope do NOT play a major role in the number treatments individuals have over a life-time
 - Research should compare outcomes based on patient spending
 - Patients may be helped with guidelines defining who is at risk for complications from PWBs



PSST ... HAVE YOU HEARD YET?

The Sturge-Weber Foundation has a brand new online store! T-shirts, masks, leggings and more are now available for purchase with great designs to help spread awareness for Sturge-Weber syndrome. Great ideas for holiday gifts!

A percentage of every item purchased is given to the Foundation for research. Check it out at ... <https://teespring.com/stores/the-official-swf-store!>

PART 1: Networking (continued)

connect with others who spoke your language or had similar issues...snail mail be GONE! They earned gold tipped wings in heaven!

Never underestimate what a committed few can do for you...OR what more can be accomplished with MORE of you on the front lines in our war on SWS! THANK YOU! YOU make it possible for their earnest pleas to be read, heard and answered...every day the SWF is juggling inquiries from parents and people need direction and connection and ways to cope.

YOU make it possible to maintain a world class cadre of clinicians and scientists to fight on the front lines of our war on SWS and birthmarks! They annually convene to set strategic research goals and funding needs, share ideas for collaborations and case studies, and get energized when they hear the latest reports on progress being made.

YOU make the SWF advocacy and awareness possible because you care and have committed yourself to our cause and uplift a world class army of Warriors that are living a more hopeful life and one focused on a brighter future. Thank YOU!

The world has gotten much smaller since 1987 and the days of "snail mail" and expensive long-distance telephone calls! Pick up your phone and Facetime your newfound SWF friend or shoot them an email or Facebook post for a quick answer to your query! The plethora of resources available and all those networks managed by the SWF have been taken for granted. Increased knowledge requires responsibility and one would hope a desire to share it with

PART 2: Collaboration and Research (continued)

what was in 2008 an emerging mechanism of funding to establish Consortiums. These consortiums consisted of 3 disease groups that shared a similar issue. In our case, it was and is brain vascular malformations (BVMC).

Without your hard earned and generous donations, the SWF would not have been in a financial position to hire an expert to coalesce and collaborate with an amazing team of scientists. Thanks to the NIH, our Sturge-Weber staff and team of researchers, patients participating in research and tissue donation the cause of SWS with the GNAQ gene discovery was made in 2013. A dream come true...for a reason, a season, or a lifetime!

others. We have seen newly diagnosed patients take on amazing leadership roles within the SWF and I'm so proud of them!

The online and social media platforms provide unimaginable resources in need of careful vetting. The SWF takes a leadership role in being the vanguard on your behalf...a trusted resource of knowledge. There is a natural evolution of confidence that occurs after a diagnosis especially with so many resources available. We've seen people come for assistance and families to network with and then they disappear for 10 years only to resurface when another aspect of SWS occurs or their now teenage child is having emotional issues.

The SWF motto "for a reason, a season, or a lifetime" was chosen to reflect the progressive nature of the syndrome as well as for our own emotional involvement in coping with the syndrome. But make no mistake... you do need the SWF for a lifetime! I am hesitant to say that to young parents lest it be perceived as hopeless and a life sentence.

The SWF is needed... to keep advancing the science and clinical care for our loved ones and those who come after us.

The SWF is wanted... to keep bringing families together to create bonds of friendship.

The SWF is required ...to advocate and generate awareness for those who need a wider voice.

The SWF is YOU!!! Stay involved. The further we reach out, the closer we become.

\$50,000 and Another Young Investigator Off and Running

Lisa's Research Award was established in 2015 when the Peltier family stepped up and have every year funded this award which has catapulted our research efforts forward! This award supports young investigators and builds a new generation of Sturge-Weber syndrome key opinion leaders. They have given all of us an immense gift that will have impact long after we are gone. Investing in the future of clinical care and scientific investigations is key to maintaining the momentum! We each are doing our part whether minimal or vast donations they DO increase the pace of discovery and brings us closer together! Why \$50,000? A fellowship pays their salary so they can work with a mentor and investigate their hypothesis which oftentimes leads to

new discoveries and treatments and larger funding from the National Institutes of Health (NIH) to expand the research. It's an investment in our future and theirs!

The Sturge-Weber Foundation International Research Network (SWFIRN) and Patient Engagement Network (PEN), The SWFIRN and PEN met in September 2016 to discuss research needs best practices and to establish strategic research goals. Participants came from around the world to unite and ignite collaborations to drive discovery. This meeting was possible because the National Institutes of Health (NIH) invested in patient participation through the Patient Centered Outcomes Research Initiative (PCORI) which promotes patient input as integral to propagating ethical and effective research. Brian J Fisher, VP of Operations and Corporate Partnerships secured the PCORI \$250,000 grant. This grant also brought industry leaders who

PART 4: The Future Harvest (continued)

generation (until we eradicate SWS, KT and birthmarks) will have just as robust if not more resources and committed collaborators! Together we have created amazing opportunities and accomplished hoped for and even unimaginable goals. Please do even just one thing with who and what you know...Warriors are made not born!

Yesterday, Today and for the Future...the rippling impact of your time, talent and donations proportionately impacts the world around us!

DOUBLING YOUR DONATION

Many employers sponsor matching gift programs to match charitable contributions made by their employees. Gifts from employees', spouses, retirees, even friends, may qualify for a match. Many families, like the Rasmussen's have been able to double their donations and sustain SWF programs and fund future opportunities!

The SWF now has an automated program on its [Matching Gifts Page](#) that will search for your employer and provide the steps to have your donation matched. Now your donation can have an even bigger impact!

Questions? Please contact Maristel Aguilar, maguilar@sturge-weber.org

participated with exciting collaborations between attendees and the SWF currently in development! Regularly scheduled teleconferences keep everyone on task and united so your hope for answers or direction becomes a reality realized through improved quality of care and treatments. Yesterday, Today and for the Future...the rippling impact of your time, talent and donations proportionately impacts the world around us! Stay in touch! Stay involved! You will ALWAYS be needed and matter!

The rippling impact of your participation in research, the registry and financial support has enabled the SWF to seek out around the world the best and brightest clinicians and scientists to jumpstart a career, to launch a SWFIRN for global collaboration, and to fund promising investigations to find the cause of SWS and more!

Warriors are made, not born!

A BIG THANK YOU to our donors of stock and monthly supporters!

Thank you!
**Brett and Rana C.
Stanley and Beverly F.
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Pam and Stan M.
Ann M.
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Anne Y.**



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SAVE THE DATE!
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For Sturge-Weber Syndrome Research

Details and Registration Coming Soon!