CUSHING'S NEWSLETTER

...AND HYPERCORTISOLISM?

A PATIENT-FOCUSED PUBLICATION BY THE CUSHING'S SUPPORT & RESEARCH FOUNDATION

2024 *offered biannually* Vol. 01

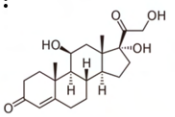
CSRF

INSIDE THIS ISSUE

Have you heard about **hypercortisolism**? You might already know there are many names for various forms of high cortisol - endogenous, exogenous, subclinical, pseudo, cyclical, non-neoplastic, MACS, and the list goes on. Our healthcare providers are not all in complete agreement on definitions, and we're seeing a growing trend of non-endocrinologists recognizing "hypercortisolism" more commonly than "Cushing's".

If all forms of Cushing's exist under the broad umbrella term "hypercortisolism", and if our non-endocrinologist doctors are more familiar with that term, is it time to devise a new strategy for more timely diagnosis with the doctors we see much more often than an overscheduled specialist we might not get in with for months?

Is it also time to change the name of this newsletter??



Leslie and Gretchen take a break at IceBar during the European Congress of Endocrinology in Stockholm, Sweden, May 2024

There is so much to share with you!

If you're new to this publication, welcome! We hope it will be a great resource for you, please let us know if you'd like to receive future issues. This newsletter has been a cherished offering from CSRF for almost 30 years, and its writers are passionate about curating relevant, interesting, helpful content. Readers love sharing it and using it as reference material. We feel motivated when we hear that a patient got a copy from their doctor when they were just beginning testing. I think we all wish we'd had an instant peer community the moment we heard the word Cushing's; the next best thing is to create that for others now, and that drives every program, project, and print resource we offer.

If you've been a reader for awhile, you may be wondering if you missed a couple of issues. We've grown so much in the past five years, most of those with the smallest team ever. I hated putting this newsletter on pause and hope that it's back on track for regular distribution. To make that more efficient, we are revising our publication schedule and updating the "personality" of our offerings, and we hope you will approve.

>This publication will be distributed two times per year. Members will receive the digital version early, as we send the issue to the printer. A few weeks later when print copies are mailed out, we will also post it on social media and the website.

>We will begin publishing a shorter digital monthly newsletter starting end of August 2024 that will be emailed to members and posted on social media and our website. This communication is intended to share the latest news, registry build updates, and upcoming events.

Finally, what do you think about a name change for this publication? It's been "cushing's newsletter" for decades, and started out as a 2-4 page compilation in the late 1990s. Should we incorporate "hypercortisolism" into the title, to broaden our audience? Is there a better word than "newsletter"? Maybe something else? Email me and let me know what you think!

Sincerely,
Leslie Edwin, President
leslie@csrf.net

Gretchen during active Cushing's, and recently while in remission.

Welcome Gretchen Jordan, Our New Associate Director

We were thrilled to develop a professional relationship with Gretchen in early 2023 as we discussed projects with our Patient Advisory Committee, and we lucked out when we were able to officially bring her on as Associate Director by summertime.

A message from Gretchen:

I am honored and excited to announce that I have accepted the position of Associate Director with CSRF! This role holds a special place in my heart, as I myself am a Cushing's Disease patient with Grave's Disease and Thyroid Eye Disease. It is not just a job for me; it is a personal passion.

After growing up in South Dakota I have spent over two decades in Minneapolis, Minnesota. My career journey brings a diverse range of experiences to this job. It began in the world of sports, working with a minor league baseball team, then transitioning to an advertising agency, and eventually finding my way back to sports with the MN Timberwolves and Lynx basketball teams. Those were days of long hours and thrilling adventures, and I cherished every moment of it! To broaden my horizons, I moved on to 15 years of assisting Fortune 500 companies navigate their global supply chain complexities by implementing software solutions.

In 2020, my battle with Cushing's Disease intensified, forcing me to make the difficult decision to step away from my career. I had been grappling with symptoms for eight long years before finally receiving a diagnosis and undergoing successful pituitary tumor surgery. Little did I know that my journey was far from over. The road to recovery turned out to be an unfamiliar and challenging one, compounded by

a lack of proper post-operative care and support. With only two weeks of steroid treatment prescribed, I unknowingly experienced an adrenal crisis, enduring months of suffering at home without realizing that I should have sought emergency medical attention. Adrenal crisis was not a term I was familiar with until after the fact.

Despite the hardships, I am forever grateful for the life I have led, and I now recognize how all the paths and skills I acquired along the way have uniquely prepared me for this new adventure in my career. I eagerly look forward to collaborating with physicians, patients, and others in our community to raise awareness about Cushing's, reduce the time to diagnosis, and provide vital support to patients during their postoperative journey. Together, we can make a difference and empower both doctors and patients in the fight against Cushing's.

Leslie and Gretchen at the 2024 European Congress of Endocrinology Meeting with Dr. Andreea Bojoga from Romania.

Join one of our remaining worldwide Zoom support calls in 2024:

Saturday, September 7, 11:00am EST

Wednesday, October 16, 7:00pm EST

Saturday, November 23, 11:00am EST

Wednesday, December 18, 7:00pm EST

To RSVP:

surveymonkey.com/r/2024CSRFsupportcalls

Or scan this QR code for the link:

We want to meet you!

Over the last couple of years we have begun to set up patient dinners in cities where we travel for conferences. In 2024 so far we have met folks in Boston, Chicago, and Nashville, and we're headed to Washington DC in October and Palo Alto, CA in November. If you live in one of those two cities and would like to know more about these dinners or you're ready to RSVP now, we can't wait to meet you! Let us know here:

surveymonkey.com/r/2024patientdinners

Have You Seen a Hidden Disabilities Sunflower?

by Gretchen Jordan

The "HD Sunflower" was launched in 2016 and aims to support people living with "invisible" disabilities by raising awareness, training business personnel, and sharing stories to foster a more inclusive and understanding society. HD Sunflower recognizes that many disabilities, health conditions, and chronic illnesses are not immediately apparent to others. This can lead to misunderstandings and skepticism about the legitimacy of a person's need for support, especially if they do not "look like they have a disability." Individuals can obtain a special lanyard when they arrive at any of a large and growing global network of airports and businesses (retail, universities, theme parks, government agencies, financial institutions, healthcare, etc.) who are choosing to support the mission to give visibility to their patrons and customers who might need some extra help.

Cushing's syndrome patients, for example, may have one or more "hidden" challenges - increased need for water, weak muscles, and impaired stress management are just a few. We don't always have an unusual physical appearance to strangers. Whether in active Cushing's or recovering from it with weakness or some form of adrenal insufficiency, our community might find a little extra help to be comforting and possibly even necessary.

The sunflower symbol on the distinct green lanyard is a visual cue to trained employees that the person wearing it has a hidden disability. The sunflower was chosen for its universal recognition and its association with happiness, positivity, strength, growth, and confidence.

Hidden Disabilities also hosts a podcast series called Sunflower Conversations which highlights various hidden disabilities. I recently recorded one of these conversations with them about the critical functions of cortisol and the often-overlooked symptoms of Cushing's Syndrome, emphasizing the need for greater awareness and early diagnosis. We also discussed the pituitary gland's functions and its role in our overall health.

We appreciate Hidden Disabilities' mission to support those with hidden conditions and thank them for asking us to contribute to their resources for Cushing's.

Learn more about Hidden Disabilities by visiting https://hdsunflower.com/ or scan the QR code below:

Hidden Disabilities Sunflower Podcast
conversations.hiddendisabilitiesstore.com

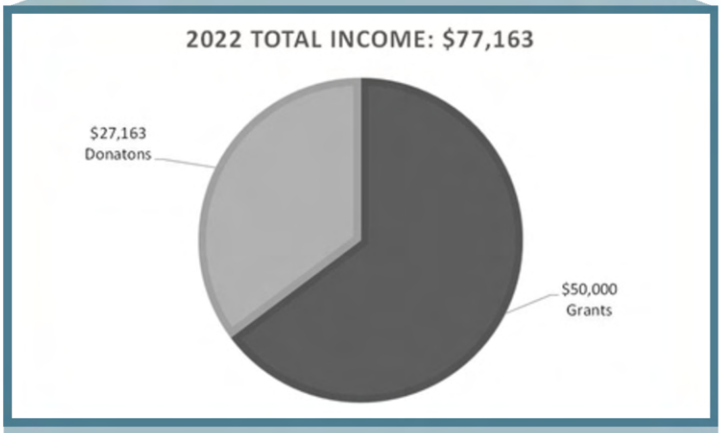
Sunflower Conversations YouTube Channel
@hiddendisabilitiessunflower

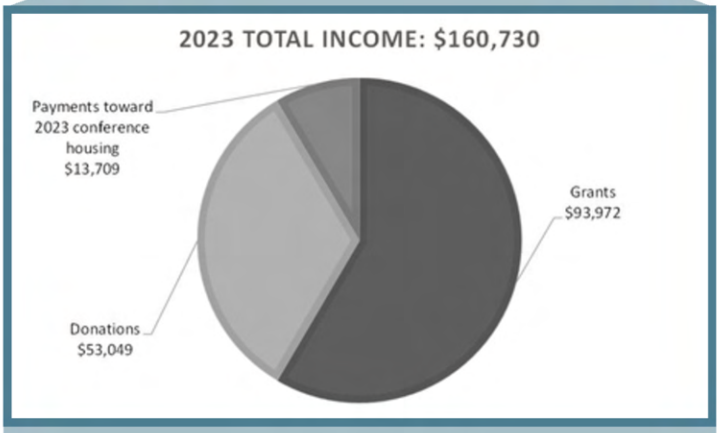
CSRF FINANCES: FY 2022 & 2023

In 2022 we were emerging from the pandemic and slowly starting to attend conferences again. We had two paid staff and minimal overhead because to this day, all Directors and employees work from home. 2022 also saw us chartering our Corporate Council whose membership fee is considered an unrestricted grant. Good stewardship of funds allows us to have operating expenses that do not exceed that income, so in 2022 we were also able to begin saying that all donations go straight to our programming and advocacy.

In 2023 we held an international, multi-day conference, and a good portion of our budget is related to that activity. That was also the year that we added new non-endocrine conferences to our schedule. We were in excellent shape to offer Gretchen a position in 2023 as well, one of our best moves to date!

Thank you!





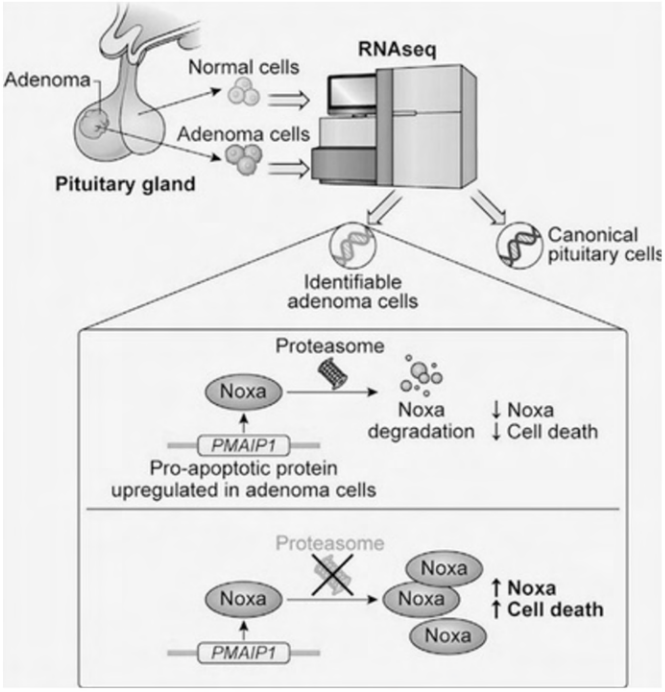
New Knowledge of Pituitary Tumor Cell Behavior: The National Institute of Neurological Disorders and Stroke (NINDS) lab on the Bethesda Campus of the US National Institutes of Health (NIH) pinpoints driver of pituitary adenomas causing Cushing's disease.

by Sonia Feau, Contributing Author & Patient, featuring an interview with **Dr. Prashant Chittiboina**, Neurosurgeon at NIH

The small size of the pituitary gland belies its important role as master regulator of many of the hormones that our body needs to function properly. Tumors on the pituitary can occur in up to 10% of the general population. These tumors - called adenomas - are benign, in that they do not cause cancer. However, they can substantially disrupt the normal functions of the pituitary gland, with big consequences. Cushing's disease is one such consequence. In this disease, the pituitary adenoma causes too much cortisol (a stress hormone) to be made, leading to a plethora of systemic complications and physical changes. While treatments exist, the effects of ongoing cortisol overproduction cannot be fully reversed. The best way to treat Cushing's disease would be to stop the overproduction of cortisol at the source, by eliminating the pituitary adenoma.

Dr. Prashant Chittiboina, an investigator in the Neurosurgery Unit for Pituitary and Inheritable Diseases at NIH, studies the basic biology of pituitary adenomas in order to identify new ways to eliminate those that cannot be removed surgically. In a recently published study (scan the QR code or visit the url listed at the end of the article), his team collected cells from the adenomas and adjacent normal tissue of 34 patients during surgery. They created an atlas of normal and abnormal pituitary cell types, and used this information to reveal a molecular signature unique to the adenoma cells.

They showed that this molecular signature includes a trip-wire protein (noxa) that should be toxic to the adenoma cells.



Graphical Abstract from the article.

However, adenoma cells were able to destroy this protein and protect their survival. Using a new mouse cell model, Dr. Chittiboina's group showed that a drug already approved for other conditions can override the adenoma's destructive abilities and allow this trip-wire protein to accumulate in adenoma cells. This study paves a smooth road to testing such treatments for Cushing's disease in human patients.

Dr. Chittiboina, this is the first time that such cutting-edge technology has been used to understand pituitary adenomas, what motivated you to conduct this research on Cushing's disease?

Dr. C: We are at the front edge of using such technology to understand pituitary tumors. However, it is our surgical techniques, innovative pairwise analysis and long-term follow-up of patients that makes this study special. In other words, the technology is interesting but it is our clinical approach that led to these discoveries.

What were the most surprising or interesting findings from your research?

Dr. C: There are a few. First is that we were able to see how excess cortisol in the blood was suppressing growth hormone secretion in the pituitary gland. Low growth hormone is a particularly vexing problem in people with Cushing's syndrome. The second was that a majority of the tumor cells weren't very 'cancer-like'. Only a small sub-population seemed to be cancer-like. This means, that once the typical tumor cells form, they calm down. Last was how these cells were evading the trip-wire mechanism.

How might your findings impact the way we understand or treat Cushing's disease in the future?

Dr. C: This was a key study for my group. This study has laid the groundwork and a path for my group to continue investigating all other pituitary adenomas. Specifically for Cushing's disease, we now have a much better understanding of how tumors form at the cellular level.

Bortezomib, the drug that you used in your study, is FDA approved to treat multiple myeloma and mantle cell lymphoma, do you think it could be repurposed for Cushing disease? Any plan on doing a clinical trial on patients that cannot be surgically cured?

Dr. C: Yes! Stay tuned. We have at least three promising ways to address Cushing's disease with drugs. We hope to start a 'basket trial' that allows us to quickly test the promise of these and other drugs at the NIH.

What future research do you think is needed to build on these findings and their potential applications?

Dr. C: We still need to understand how the tumors form in the first place. If most tumors do not carry genetic mutations, what then initiates the tumors? That is a question that is keeping me up at night.

If you would like to read the full article, scan the QR code or search online for the article **Pituitary adenomas evade apoptosis via noxa deregulation in Cushing's disease.**

Reference:
David T Asuzu et al., Pituitary adenomas evade apoptosis via noxa deregulation in Cushing's disease, Cell Rep. 2022 Aug 23;40(8):111223

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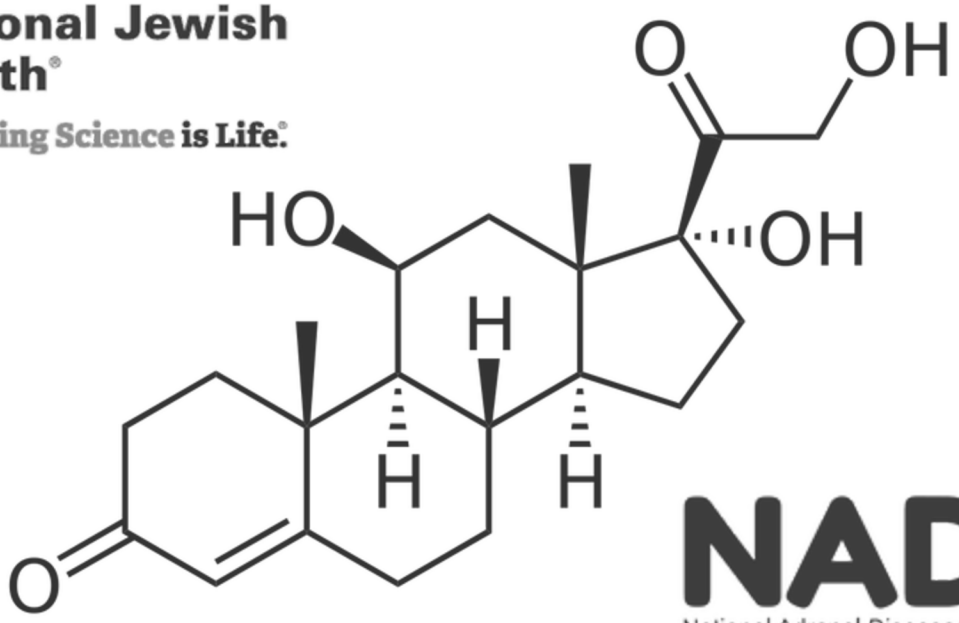


NADF
National Adrenal Diseases Foundation

First-Of-Its-Kind Cortisol & Function Study: A Patient's Report On Adrenal Insufficiency Research

by Bill Dodge, Contributing Author & Patient, featuring an interview with **Dr. Elizabeth Anne Regan,** Physician Researcher at National Jewish Health, Principal Investigator on myAI Registry, NADF Board Member

The idea that an adrenalectomy or a pituitary tumor surgery is "the cure" for Cushing's comes with a big caveat. Yes, surgery can stop the overproduction of cortisol. But with pituitary-related Cushing's or an autoimmune disease that can slowly impair adrenal function, it usually takes careful fine-tuning with steroid therapy to regain normal cortisol production. For those who have both adrenals removed, adrenal insufficiency is permanent and a daily steroid regime is life-sustaining. At a past NIH Patient Day, Dr. Constantine Stratakis, one of the world's top Cushing's researchers, offered his succinct breakdown: "For Cushing's patients with pituitary tumors, adrenal insufficiency (AI) is temporary, and usually lasts for up to 12-18 months. For patients with single adrenocortical tumors, AI also lasts for about 18 months, on average. However, patients that have had a bilateral adrenalectomy (BLA) face a life-long need for cortisol replacement. AI [also known as Addison's Disease] can lead to acute hypoglycemia, hypotension, or severe electrolyte abnormalities that can cause death in a few minutes."

For many of us with different kinds of AI, it can take time to manage dosing well and to understand how cortisol replacement therapy responds to our different needs and lifestyles. Oral steroid medications only provide a baseline. They don't replicate the body's natural way of adjusting cortisol levels to address physical or emotional stress or to help regulate our circadian rhythm. Given the side effects of prolonged

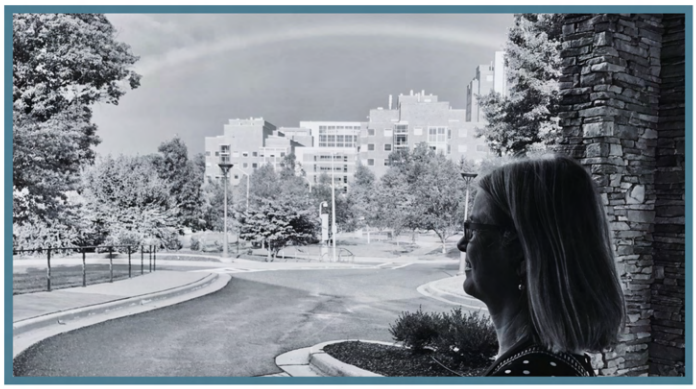
steroid use, the lowest effective daily dose is what doctors usually recommend, but up-dosing is often necessary. An emergency kit with a syringe and 100mg dose of hydrocortisone is crucial for dealing with medical emergencies. Among the different situations that may bring on an adrenal crisis are severe fatigue, low blood pressure, fever or infection, nausea, diarrhea, extreme physical exertion, or even a stressful emotional or social situation. A swift response is vital since irreversible complications can result from a crisis. Each year, roughly 8% of AI patients have an adrenal crisis. AI also increases the risk of death from cardiovascular disease, infections and cancer.

Five years ago, I was diagnosed with primary bilateral macronodular adrenal hyperplasia (PBMAH), one of the rarer forms of Cushing's Syndrome that can be linked to a mutation of the ARMC5 gene and that accounts for less than 1% of endogenous cases (originating inside the body). PBMAH produced 10 tumors on each of my adrenal glands. I nearly blacked out from a drop in blood pressure and was too disoriented to do anything for myself during the one emergency that I've experienced since my BLA. I learned that self-injecting in an emergency is not a realistic option.

Fortunately, mine is one of the many types of adrenal insufficiency that Dr. Elizabeth A. Regan, a physician researcher, professor and former orthopedic surgeon at National Jewish Health (NJH) in Denver, is committing her energy to addressing. Her clinical study (she's the principal investigator) is focused on the absorption and metabolization of oral hydrocortisone and how cortisol replacement therapy relates to patients' physical function, vital signs, health symptoms and other clinical findings. With funding from the NJH and the National Adrenal Diseases Foundation (NADF), this first-of-its-kind study in America is part of the *my*AI Registry for Adrenal Insufficiency *a*t the NJH. Founded in 2019 by Dr. Regan, the goal of this unique Registry is to further patient-centered research and to kickstart more funding for good-quality AI studies that will lead to better care in the future.

After learning about Dr. Regan's work through our CSRF newsletter, I decided to apply for the 60-patient study and was accepted. The consent form explained that the main clinical procedure would involve six blood collections and six saliva samples done in timed intervals, over six hours. The first baseline collection would be done before one's first hydrocortisone dose in the morning. With a patient's consent, these collections would also be used to provide samples of DNA, proteins, RNA, and metabolites for future analysis. The study's current focus is on hydrocortisone, not prednisone or dexamethasone. Prospective subjects need to have been on a regular hydrocortisone dosage for at least three months. Regular fludrocortisone use is acceptable.

One option in the consent form, to receive some of the lab results for a small fee, was immediately appealing. Like many post-surgery Cushing's patients with AI, my own hydrocortisone regime can include moments in the day of extreme fatigue, irritability and a variety of other symptoms. A practical goal for me was to be able to share some of the study's lab results with my endocrinologist back in San Diego with the hope of understanding, and possibly mitigating, the peaks and troughs in my daily dosing. I was also grateful for the chance to play any small part in advancing AI research and to turn my own chronic health condition into some positive energy directed at achieving better care.



Bill's wife walks out with a special sign in the sky years ago when leaving the NIH campus after his treatment

My wife and I flew to Denver in late September of 2022. Adjusting to the high altitude and getting to the hospital at 6:30 in the morning without my first daily dose of hydrocortisone and without any food or drink, other than water, was a challenge.

Dr. Regan's study coordinator, Julia, met me at the hospital doors and guided me through every step of the day's protocol, making the clinic as comfortable and anxiety-free as possible. Before each blood and saliva collection, she asked the same series of questions. Are you feeling tired? Any nausea, dizziness, headache, salt craving, weakness or tiredness, confusion, brain fog, difficulty thinking, shaking, sweating, palpitations, cold or hot sensations? And then my favorite question related to AI symptoms: Any unstable emotions? After collecting this data, Julia took my blood pressure reading and pulse and then had me do a 30-second sitting-to-standing exercise. Once the blood draw was over, I was allowed to take my morning hydrocortisone and other medications, including my fludrocortisone. Then she quickly led me to the hospital cafeteria for a free breakfast, aware my cortisol levels could be next to zero.

Every hour, the same study questions and procedures were repeated. The highlight of my whole clinical experience was the chance to interview Dr. Regan, an opportunity I discussed with a study assistant before flying to Denver but still wasn't sure would happen. Sure enough, Dr. Regan arrived midway through the testing. She graciously permitted me to record our conversation.

Dr. R: It seems there are many people with AI who report that they are experiencing sudden ups and downs, or "crashes." Our hypothesis in this study is that these ups and downs correlate with your cortisol levels. So that is the essence of what we are trying to measure.

So why aren't endocrinologists doing more testing?

Dr. R: This is really a key question! I have some ideas but no real proof. Doctors depend on several sources for learning about disease. We are taught patterns to recognize disease and "rules" to treat. Each of these can be wrong or outdated. I think that AI is rare enough that few endocrinologists see a lot of cases and so they don't get to see a full spectrum of disease manifestations and that lack of experience gets perpetuated by generations of training (older doctors teach the younger doctors). There are guidelines published by the Endocrine Society that are quite good, but I'm afraid that practicing

Dr. Elizabeth Anne Regan and Bill Dodge

Endocrine Society Guidelines

endocrinologists may not spend a lot of time reading them since it's a rarely encountered disease for which they rely on a limited dataset and memories of what they were taught.

Then there's the big problem that there's just not enough clinical research. And very little of the research has recognized how important it is to get primary information from patients. If a doctor is someone who knows how important it is to learn from their patient, that person will probably make a great endocrinologist and may gradually move away from the rules they were taught to a more mature understanding of the disease and treatment. They will "hear" from patients that they are not feeling well on a current dosing of hydrocortisone and be willing to try adjusting the dose—even without a blood test.

So why aren't endocrinologists using cortisol serum levels for assessing absorption and metabolism of the hormone replacement?

Dr. R: I think that the issue is that they were not taught to do that. There is some literature that seems to say that cortisol levels are not useful, but honestly I find those papers unconvincing. In addition, there is certainly evidence that various groups in Europe do use cortisol levels for drawing conclusions about replacement therapy. Measuring cortisol accurately has been somewhat difficult historically but the current techniques using mass spectrometry appear to be better. The other issue in the US is that physicians say they are concerned that insurance companies won't pay for testing. This may be true now but if we start testing and making clinical decisions based on the results, then it may become a new standard of care. That may happen more readily too if there are more published studies. Even people at the top in the US don't seem to understand this disease. Again, I think that it is because we don't have a patient-centered approach to AI. These patients typically know a lot about their disease and physicians can benefit from listening to them. Some endocrinologists have had training in Europe that has made them more aware of current research but then what happens is that if they land in the US healthcare system, which is different and driven primarily by money and profit, they adopt the usual standard of care of their US colleagues. Fortunately, I know of a number of good endocrinologists who are well informed and do a good job, but I do not see anyone in this country tackling AI research the way Europeans are, nor getting us to new treatments.

What is Mass Spectrometry?

Can you tell me about the numbers involved in the MyAI Registry?

Dr. R: We've got 869 in the Registry as of early October 2023, but it's a moving target. Some people fall out of contact, but we also have steady numbers of people joining as they learn about the Registry. But there's good solid data that I'm starting to analyze on just under 700 people. This makes us one of the biggest projects that's been done in this country as far as I know. Some European countries have done collaborative projects with over 1,000 AI patients in some of their reports but we're creeping up on them. My goal is to get 2,000 people in the Registry. I'm ambitious! [laughter] If there's roughly close to 200,000 people in the US that are affected, and that's a conservative estimate because we miss a lot of disease, I think we should be able to get to 2,000. I don't think we've got the word out yet to the whole community. I'm writing a grant proposal now to grow the Registry. But this is also a political and social problem beyond the science.

Can there be problems with manufacturing and different effectiveness of hydrocortisone?

Dr. R: Yes, people do report differences in how well a particular brand works and I believe that it is likely the case. Manufacturers do not need to demonstrate the "pharmacokinetics" of their product in humans. Also, there are intermittent shortages. We just went through a shortage of Solu-Cortef for emergency injection. The Greenstone hydrocortisone has been difficult to get for almost a year now.

What we're doing here in this study is "pharmacokinetics", which is looking at how your body takes a dose of cortisol and absorbs, distributes, and metabolizes it. The complexity of studying the bioavailability related to different manufacturers of hydrocortisone is beyond the scope of this study. And pharmacists who change manufacturers for a patient's hydrocortisone prescription don't have any data either. They tend to have an opinion that there's no difference.

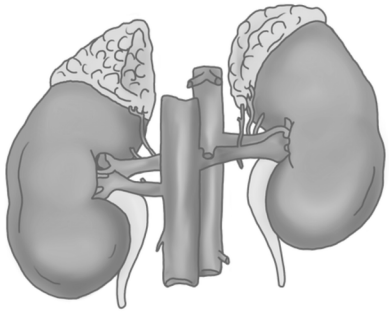
After my BLA, my endocrinologist's response seemed to be 'my job is done.' Why aren't doctors addressing the quality of life with AI?

Dr. R: Everybody loves the idea of a surgical cure. Surgeons love to do surgery. It's unusual for them to think too hard about long term outcomes. On the other hand, the American Association of Endocrine Surgeons has started to address this problem by putting together more comprehensive patient information. But the long term outcomes and quality of life are also what the endocrinology community are not looking at. We do not have good studies of people across the breadth of AI subtypes. To make progress and figure out how to improve quality of life – which is another way of saying "how well is the dose and timing of my replacement hormone reducing my symptoms?" – we need to have well-designed research studies comparing the results of different treatments. The studies are expensive to do and getting the funding to do them requires that you have a very experienced research team. Our AI world is not quite ready for this kind of well-funded research. But it can get there!

What are some of the challenges dealing with the broad spectrum of AI?

Dr. R: We don't know the natural history of the disease well. With the pre-disease, maybe it's the genetic pre-disposition, maybe the environmental factor, maybe autoimmune disease. There's progression from early symptoms to severe disease and complications. We need to investigate this more because it may hold the clue for how to reverse the disease. The endocrinology world breaks down AI into primary, secondary and tertiary but that really doesn't give us a complete picture, not from my point of view as an epidemiologist.

You, Bill, are primary AI. You lost your adrenal glands from surgery, but you're very different from someone who is primary from an autoimmune attack and loses them slowly. At the point where they're symptomatic, they may still have adrenal function. And actually there are studies that show if you treat the autoimmune disease, the AI may get better. So this disease is very complicated and we cannot group all primary AI or central AI together without at least considering what is going on with the person's physiology and cortisol levels.



The other complexity is that with a disease that typically needs lifetime treatment like AI, to understand treatment outcomes, you need to look at both short-term and long-term outcomes. We need to look at the rates of major complications of AI, which are adrenal crisis and premature death, as well as the complications from treatment. The effects of excess steroid can lead to osteoporosis, atherosclerotic disease and metabolic syndrome. All of those long-term outcomes also exist in the population at baseline and we need to ask whether the long-term treatment with fairly low dose replacement of cortisol increases the risk of those same complications known for high-doses of steroids. Once we understand if that is true then patients should be able to participate in shared decision making with their doctor for what choice they want to make around the competing risks of treatment.

Also, the day-to-day symptoms and function for AI people needs to be better understood. Things like thinking ability and the energy to get stuff done, and feeling good or bad throughout the day. Those impacts of the disease really haven't been recognized or addressed. For example, an important question that's been raised by Dr. Stafford Lightman in the UK is what happens when you don't have any cortisol in your brain overnight? There's potentially something harmful that's going on but we don't have the tools yet to understand it.

I'm curious about your own dosing regime and what works for you?

Dr. R: Well. I do have AI and that is part of why this work is so important to me. As a physician and researcher, I feel more comfortable in adjusting and managing the disease than many people. I also have an endocrinologist who is very supportive of me doing this. What I do is I start with recreating my own baseline circadian rhythm and then when I want to do something extra, I updose. I updose before, preferably, and not after the need. I break my pills up into little pieces and I anticipate one hour for absorption before I'll get an effect. I run about 25-30 mg total daily and I'm doing well. I don't have osteoporosis, my bone density is normal, I don't have high glucose or hemoglobin A1C levels, my BMI is 20 and I've lost weight on the regimen. My regimen seems to be working for me. It is pretty clear that people vary a lot in their absorption and metabolism of cortisol so what works for me is not a formula for everyone.

In thinking about dosing and timing, I also consider the half-life of cortisol in the body which is about 90 minutes and so I expect that three hours after a dose has been absorbed to its max, the steroid's effect starts to wear down. So that means for many people that five hours after your dose of hydrocortisone, you might be slipping. There are a lot of variables and people are different in their absorption and metabolism, but that is my personal thinking. Some people discuss the concept of "duration of action" for steroids like hydrocortisone and prednisone that might be longer and justify twice-a-day dosing. But after looking for supporting research, I don't find much solid evidence that this reflects the true cortisol effects in a deficient person. It was a concept that became popular in the study of people on higher doses of glucocorticoids for things like rheumatoid arthritis.

Natural secretion of cortisol is "pulsatile" on top of the basic circadian secretion. You've got the rhythm that peaks around 8:00 am and then cortisol bottoms out at 11:30 to midnight. Some of the extra pulses seem to be pre-meal. A vast majority of AI patients are on a standard dose of

20mg hydrocortisone daily, which we know is potentially not going to match the normal pattern. One of the questions we ask on the Registry is whether need for cortisol has changed over time: a few say 'yes' but the majority say 'no'. I think you have to consider the context of whether this is a group who are truly tuned-in to their situation and symptoms. We know that patients adapt to conditions and decrease activities that bring symptoms. They don't push because they know they're going to be tired or dizzy. Some folks are walking around with undetectable cortisol. It's been interesting for us to confirm with some of our patients' clinical results that they have zero cortisol levels when we test them. But they seem to be mostly ok, as long as they manage to avoid any stress.

How do you see your research funding unfolding in the future? Are you optimistic?

Dr. R: The NADF, which I'm on the board of, is funding this project and bless them for it, but this is a very limited clinical study compared to what you can do with federal funding. So my goal is to move our AI community and its needs into that higher level of funding. It's probably going to take 5-10 years to get there. AI is a common rare disease as opposed to a rare rare disease. A lot of the rare disease funding energy is focused on genetic disease but I think we're more resonant with PCORI (the Patient Centered Outcome Research Institute). Getting into the PCORI funding is where I want us to be. It seems to have a progressive, somewhat nurturing long-term funding approach and it was established under the Affordable Care Act to address the kinds of problems we have with treating AI. What we need to do now is put together a lot of brains to map out the future directions for AI research and improve people's quality of life.

In addition to people with AI, there are two other categories of people who are eligible to enroll in the MyAI Registry: "at-risk" individuals and "controls":

At-risk: Family members, genetically related individuals, people with autoimmune diseases without a diagnosis of AI, those who have taken steroid medications for extended periods of time, and people with ambiguous test results that are suggestive of AI.

Controls: Friends and neighbors who might be kind enough to be part of the research project. You can be an important comparison group since you are without adrenal insufficiency but are otherwise growing and aging alongside the primary group.

Please don't sign up requesting to be contacted unless you fit the qualifications of the Registry!

You can find the Registry on NADF's website by scanning the QR code above or by visiting:

nadf.us/adrenal-insufficiency-study-recruitment.html

You can also help by donating to MyAI Research by scanning here or by visiting:

nadf.us/donate-to-research.html

Elizabeth Anne Regan MD, PhD is a physician researcher at National Jewish Health in the Division of Rheumatology, Department of Medicine, in Denver, Colorado.

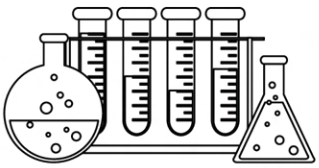
Clinical Trials

For a rare disease, we sure do have a lot of pharmaceutical interest in our community! At its most basic, the purpose of "Cushing's drugs" is to stop excess cortisol and improve or reverse symptoms. Cortisol receptors are everywhere in the body and there are a variety of ways it can be interrupted, depending on the source. These pathways are represented in the drugs currently on the market and also those in trial, and they give patients options. Our data suggests that at least 15-25% of patients will use these drugs at some point in their journey with Cushing's.

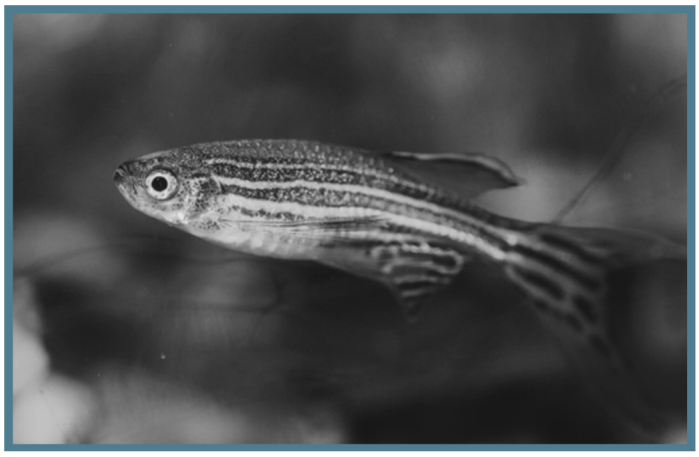
Why would a patient choose a clinical trial instead of prompt treatment? Due to delays in diagnosis, most patients are very sick by the time they have completed confirmatory testing. The idea of getting worse while receiving a placebo could be a deal breaker. Many non-specialist doctors don't know about clinical trials for investigative therapies, and often times trial sites are located in only a few large cities that would require travel and time away from work. That's a lot to overcome, and these companies are motivated to resolve most logistical challenges a potential participant might face. Self-referral is allowed, some positive tests are required.

You can find all sorts of trials at ClinicalTrials.gov by searching Cushing's or Hypercortisolism and checking the box for studies that are "Recruiting". The difference in results between the two also supports our theory that "hypercortisolism" is going to play a big role in the normalization of all forms of Cushing's - it has 79 hits on ClinicalTrials.gov compared to 11 for Cushing's as of the date of this article's writing.

CSRF is on a mission to learn more about the very early stages of drug development for a future article about origins of molecule discovery and what scientists know that drives them to find solutions, especially for a small or rare disease population.



Not all drug trials start with a pharmaceutical company though! We had the honor of meeting Dr. Ning-Ai Liu (Cedars-Sinai in Los Angeles) at the Endocrine Society conference earlier this year, and she sat down with us to talk more about the unique way she developed a laboratory model for a pituitary tumor that enabled her team to discover a medication to study for the treatment of Cushing's Disease.



Little Fish, Big Discovery

Creative thinking leads to an efficient pituitary adenoma model.

by Leslie Edwin, featuring an interview with **Dr. Ning-Ai Liu,** Endocrinologist and Researcher at Cedars-Sinai, Los Angeles, CA

In 2019 we attended the annual Endocrine Society meeting and sat in on a popular session about the development of a transgenic zebrafish that could model a pituitary tumor in the lab. Further, this scientific team discovered a molecule that seemed to lower cortisol, and an early trial confirmed they were on the right path. The pandemic slowed their work, but the trial design has been updated and is currently enrolling.

We recently sat down with Dr. Ning-Ai Liu, ironically at Legal Sea Foods in Boston, MA, to discuss her work with the zebrafish over the last two decades and to learn more about the trial.

Dr. Liu and her colleague, trial Principal Investigator Dr. Shlomo Melmed, represent the Pituitary Center at Cedars-Sinai where patients are treated in all phases of Cushing's.

Dr. Liu, the first time I heard about your zebrafish model was also the first time I grasped that pituitary research has probably been frustratingly slow for scientists because there has not been a readily available and replenishable supply of pituitary cells to study. After we spoke recently, I looked at your publications and saw that you've been working with the zebrafish since 2000, with a first look at hypothalamic-pituitary-adrenal axis (HPA-axis) development published in 2003. [1] How did this little fish cross your radar as a candidate?

Dr. L: I joined Dr. Shlomo Melmed's lab in 2001 as one of the endocrinology fellows under a training grant. I previously worked with basic science biologists using zebrafish to understand vertebrate animal development. For my pituitary fellowship research project, Dr. Melmed inspired me to study human pituitary pathophysiology using zebrafish as a model. Unlike mice, who have a low breeding capacity and lengthy internal gestation, zebrafish embryos are transparent and display all major organs just 24 hours after fertilization. Zebrafish also have a genome that is highly homologous to humans. Over 80% of the genes known to be associated with human disease have a zebrafish counterpart, making zebrafish an optimal model organism for studying human diseases.

In 2003, we published a zebrafish transgenic line allowing us to observe pituitary corticotroph cell development in live embryos as early as 24 hours after fertilization. [1]

In 2011, you and Dr. Shlomo Melmed published a paper that describes how effective the zebrafish model is for pituitary tumors - while the Cushing's phenotype (appearance) is fully present by three months of age, they are already developing signs of tumor growth and

activity within the first two days of embryonic development. What are some of your discoveries using this model?

Dr. L: We introduced a particular gene discovered in Melmed's lab into the zebrafish, which predisposed it to develop pituitary corticotroph tumors. Within the first few days of embryonic development, our transgenic fish recapitulates hallmark features of Cushing disease, i.e., "pituitary lineage-specific corticotroph expansion partially resistant to glucocorticoid inhibition". By the adult stage, the fish develop hypercortisolism, insulin resistance, glucose intolerance, fatty liver, and cardiomyopathy. [2]

The same paper discusses how you tested different molecules using the zebrafish model and found several that were promising, with the best being R-roscovitine. How do you decide which ones to try?

Dr. L: We choose to test compounds that have been studied in human clinical trials and are commercially available for research purpose. We identified R-roscovitine (also known as Seliciclib), which suppress pituitary expression of the pituitary precursor of ACTH, proopiomelanocortin (POMC). We then showed that R-roscovitine blocks ACTH production in zebrafish, mouse and human corticotroph tumor cells. [2, 3]

Early studies showed that relatively mild side effects and oral dosing would make R-roscovitine feasible for long-term treatment of Cushing's Disease. Your team began testing this compound in a proof-of-concept study at Cedars-Sinai in 2014; promising initial data was published on four participants which led to funding from the FDA's Office of Orphan Products Development for a pilot multicenter study [3], but then the pandemic happened. That must have been so frustrating. How did you manage the trial through those years?

Dr. L: One year after initiating the multicenter study, COVID-19 restrictions constrained patient recruitment efforts and also affected our ability to collect complete data on secondary endpoints. This second study saw five patients treated before it was closed to modify the study protocol per FDA recommendation. We are pleased that FDA approved the revised study protocol and our trial reopened in September 2023.

From the first study to today's trial, what changes have been made to study protocol?

Dr. L: A major change from the first study is a lower drug dose in today's trial. In the first study, patients received 400 mg twice daily for four consecutive days each week for four weeks. In the current study, the dosing regimen is 40 mg twice daily continuously for four weeks.

Your current clinical trial is available to any patient with pituitary Cushing's Disease who meets the eligibility criteria: aged 18 or older with persistently elevated urinary cortisol levels and an ACTH-producing tumor (pituitary) that is causing Cushing's Disease, including newly diagnosed and recurrent or persistent Cushing's Disease.

Dr. Shlomo Melmed and Dr. Ning-Ai Liu

The full criteria can be found on ClinicalTrials.gov by searching for the trial identifier NCT03774446 or scanning the QR code at the end of this article. Sites are only in Los Angeles, CA, so how can interested patients from other cities, states, or even countries join this study?

Dr. L: We accept patients from all geographic areas including international patients. For more information about the trial and to discuss your travel needs, you can contact study coordinator Daniel Gomez at phone: 424-315-2362 or email: GroupPituitaryResearch@cshs.org.

Unlike most clinical trials we learn about, this one is not being led by a pharmaceutical company; your team at Cedars-Sinai made the discovery of both the zebrafish model and the effectiveness of R-roscovitine. Later down the line, how will the drug be manufactured and distributed?

Dr. L: Seliciclib was developed by Cyclacel who has an agreement with Cedars-Sinai for our current clinical trial, and we believe our collaboration will continue in the future.

Thank you Dr. Liu, for everything you do for Cushing's patients today and in the future, and we hope that this trial is a success!

Dr. L: Thank you for allowing me to introduce our clinical trial. I look forward to working with you all.

References:

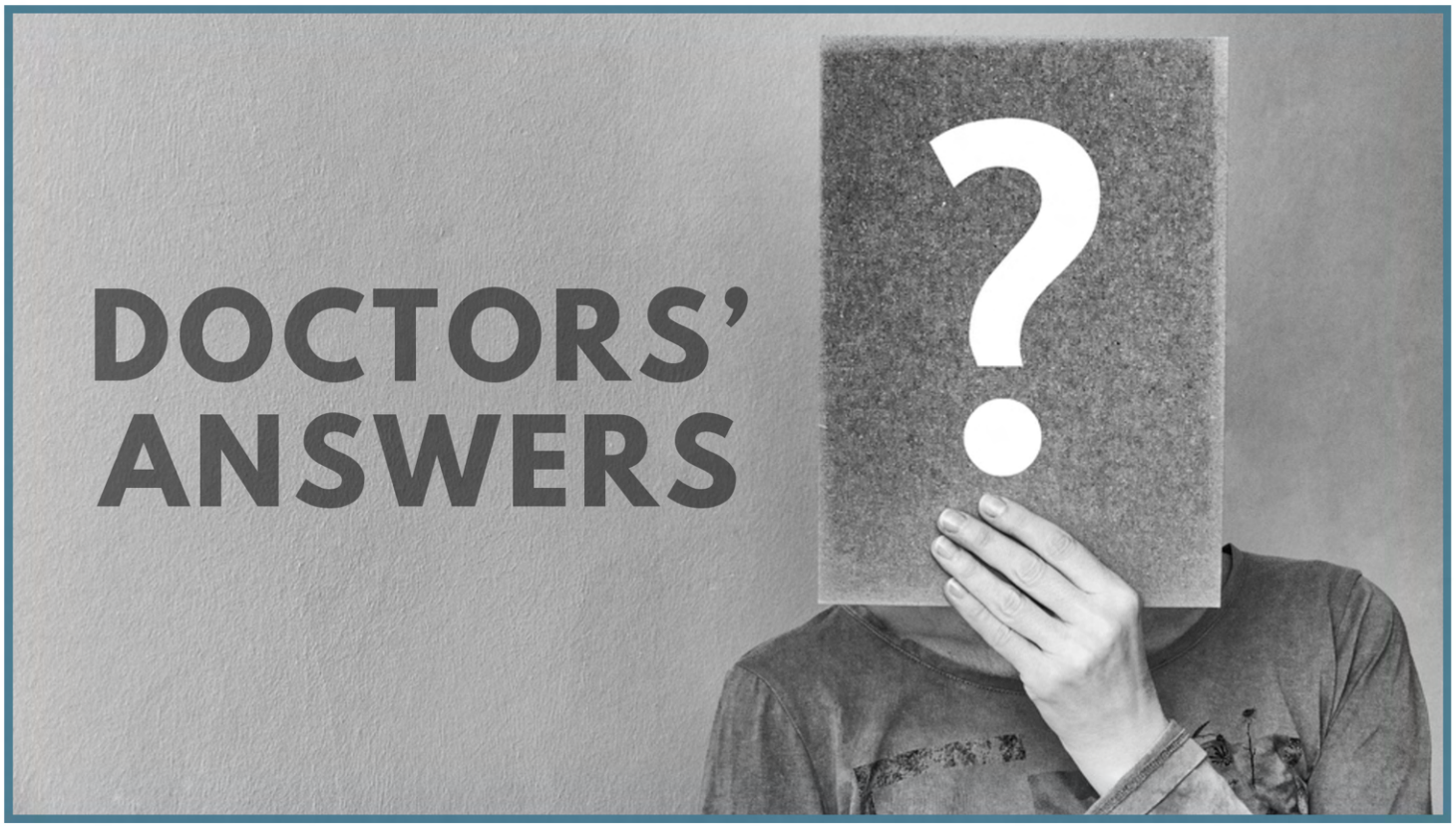
[1] Liu, NA, Huang, H., Yang, Z., Herzog,W., Hammerschmidt, M., Lin, S. and Melmed S. Pituitary Corticotroph Ontogeny and Regulation in Transgenic Zebrafish Mol Endocrinol 2003 May;17(5):959-66. doi: 10.1210/me.2002-0392. Epub 2003 Feb 6. PMID: 12576489

[2] Liu NA, Jiang H, Ben-Shlomo A, Wawrowsky K, Fan XM, Lin S, Melmed S. Targeting zebrafish and murine pituitary corticotroph tumors with a cyclin-dependent kinase (CDK) inhibitor. Proc Natl Acad Sci U S A. 2011 May 17;108(20):8414-9. doi: 10.1073/pnas.1018091108. Epub 2011 May 2. PMID: 21536883; PMCID: PMC3100964.

[3] Liu NA, Ben-Shlomo A, Carmichael JD, Wang C, Swerdloff RS, Heaney AP, Barkhoudarian G, Kelly D, Noureddin M, Lu L, Desai M, Stolyarov Y, Yuen K, Mamelak AN, Mirocha J, Tighiouart M, Melmed S. Treatment of Cushing Disease With Pituitary-Targeting Seliciclib. J Clin Endocrinol Metab. 2023 Feb 15;108(3):726-735. doi: 10.1210/clinem/dgac588. PMID: 36214832; PMCID: PMC10210614.

To read the details about the Seliciclib trial for Cushing's Disease, scan this QR or visit clinicaltrials.gov and search study **#NCT03774446**

The Melmed Lab Team at Cedars-Sinai



Q: I had Cushing's Disease 11 years ago and at that time was asked to stop using the steroid inhaler I took for asthma, leaving me with just the rescue albuterol inhaler. Without the steroid, I use albuterol several times a day, more if I'm sick. My doctor retired last year and I recently had an appointment with a new one who doesn't want me to keep using albuterol this way and wants to know if I can safely go back to using the long-acting steroid inhaler since I have been in remission for almost five years. Is there any reason not to do this?

A: Patients with Cushing's disease can take inhaled glucocorticoids ("steroid inhalers"), if indicated for asthma. As always, the lowest effective dose should be used, keeping in mind that a small amount of the medication is absorbed into the bloodstream and can potentially lead to symptoms and signs of Cushing's. For that reason, it is important for the medication to be prescribed and monitored by a physician with expertise and experience in the treatment of asthma. The inhaled glucocorticoid should be temporarily held if testing for excess cortisol is being conducted. *(Dr. Nicholas Tritos, Mass General Hospital)*

A: This is a great question and I suspect the concern your previous doctor had regarding the use of your steroid inhaler was to not add insult to injury with adding additional steroids to your body on top of what it had already been exposed to from your Cushing disease. While some of the effects of too high steroid levels improve and abate over-time, there can be long-term adverse effects to bone health, blood pressure etc. Now clearly asthma is also a very significant medical condition and depending on how severe it is, it can be very serious so I think the risk of taking additional steroids versus controlling a disorder such as asthma safely and adequately must be carefully balanced and discussed with all of the

medical teams that manage your asthma and your prior Cushing disease. Suffice to say that for anyone, if you absolutely need to take a steroid, then you need and should take a steroid (whether it's a steroid inhaler or an injection into a joint for arthritis, etc) but they should be used as sparingly as possible taking into consideration the potential short-term and longer-term side effects. *(Dr. Anthony Heaney, University of California - Los Angeles)*

Q: I've had some high and some low cortisol testing for several years and have some but not all Cushing's symptoms. I had an MRI done with and without contrast and the radiology department and my endocrinologist said they didn't see anything on the scan. I decided to get a second opinion somewhere else and this new doctor told me that the high tests I have are enough for a diagnosis and he DOES see a tumor on my scan. That is very confusing, and when I ask in support groups it sounds like that happens sometimes. I can't afford a third opinion, I feel frozen. How do I move forward with one or the other?

A: The diagnosis of Cushing's requires consistent positive results on tests and the presence of a tumor so that one can proceed to the successful treatment of the tumor, usually by surgery. In your case, the lack of consistency makes the diagnosis difficult, although not impossible. It is not unusual for a pituitary tumor to be small (less than 3 mm) and so, it may be hard to see. However, more than 20% of the population has such small tumors in the pituitary gland. So, seeing or not seeing a tumor so small is not really helpful for the diagnosis. It may be that you have something called cyclical Cushing syndrome or that you have occasionally high cortisol levels that are not due to a tumor. This uncertainty makes going forward with a treatment difficult. *(Dr. Constantine Stratakis, Athens Research and Innovation Institute)*

Q: I knew something was wrong before my labs ever caught up and proved it enough for doctors to take me seriously. I didn't have as many physical symptoms in the beginning, but waiting made them all come out. Thanks to the internet, I knew the name of what was happening long before I could produce the blood and urine to prove it. Is there anything in the works for a more precise cortisol test that can detect the beginning of Cushing's earlier?

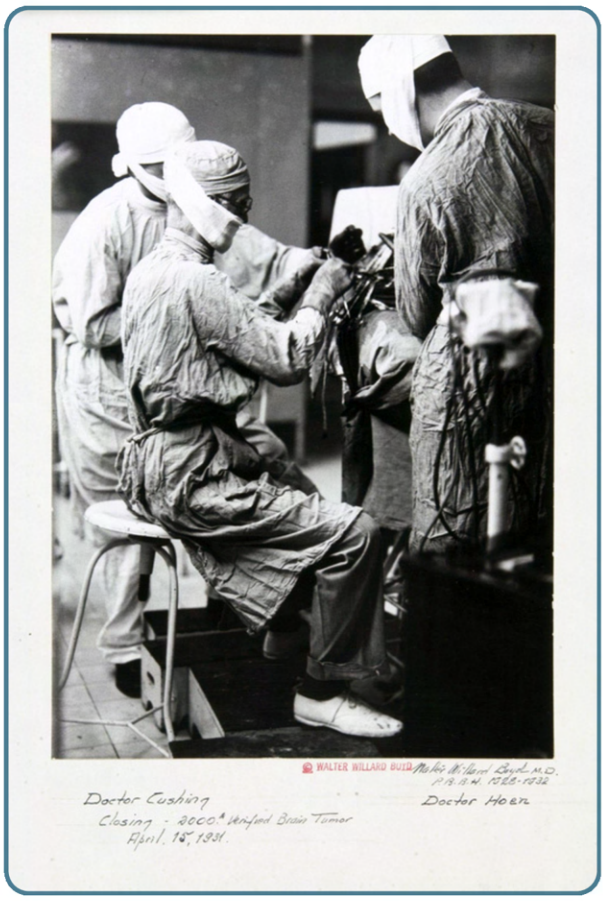
A: Late night salivary cortisol testing is generally accurate and can detect excess cortisol in some patients with Cushing's disease who have normal 24 hr urine cortisol tests. The test is readily available and involves collection of saliva specimens in collection tubes between 11 pm and midnight on at least 2 nights, which can be mailed to an appropriate laboratory for cortisol testing. However, this test should not be done if patients work night shift or have markedly irregular sleep cycle. *(Dr. Nicholas Tritos, Mass General Hospital)*

Q: Do pituitary tumors grow? I'm 65 and have a very small pituitary tumor and extremely mild symptoms. I'm on a trial for a medication and it's working well with no side effects I can't tolerate. I don't want to have surgery. Am I ok taking a daily medication? Is this a realistic plan?

A: Pituitary tumors can certainly grow; however, they generally do so slowly. Patients with Cushing's disease need treatment regardless of tumor size. Pituitary surgery is generally the recommended treatment for patients with Cushing's disease. Taking a medication to control the cortisol can be helpful before surgery for some

patients and may also be recommended for those who are not cured or those who relapse after surgery. However, with very few exceptions, pituitary surgery is the preferred treatment for Cushing's disease. *(Dr. Nicholas Tritos, Mass General Hospital)*

A: You don't give the size of your pituitary tumor but you do say its small, so that's good, and you say that you have only mild symptoms. Again, you don't tell us what the medication you are taking is but you say it's working well without side effects. As you seem to understand, the other option you might have is to have the tumor surgically removed and you state that you don't want to have surgery. So, it sounds like your plan to stay on the medication is a good one right now and of course can always be re-evaluated at any time should the situation change. *(Dr. Anthony Heaney, University of California - Los Angeles)*



LOCAL SUPPORT CONTACTS AND GROUPS

Need to talk?

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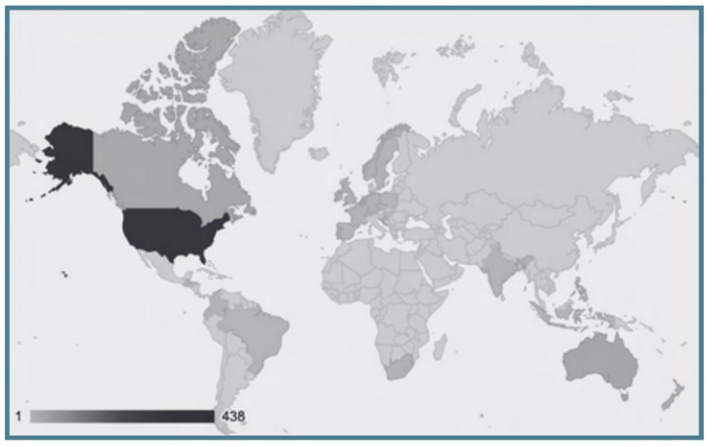
In 2020, CSRF formed a patient advisory committee to discuss topics we felt needed to be introduced into the framework of Cushing's care. A multiple question survey was developed using the substantial notes from these meetings, and we then distributed the survey to our membership. There was about a 10% response rate and enthusiasm for the results, and after sharing this data far and wide for over a year, we decided to do another one in 2022. Scan QR code below to read about these two studies, or visit:

https://csrf.net/reportsandpresentations

At that point we were already pretty sure that developing a patient registry was in our future, and began conversations with our Medical Advisory Board and others about the feasibility of CSRF hosting and "owning" this type of database.

In 2023, we designed a third quality of life survey, similar to the other two but intentionally created for a broader global audience. We partnered with several international advocacy organizations to distribute the survey, and within weeks we had over 400 responses from 38 countries. CSRF has presented pieces of this data at three professional conferences in 2023-2024, and you are now in possession of the final report that contains the full data (copies of the posters can be found by scanning the QR code to the left). We have



inserted certain datapoints into the introduction of this report, and the remainder of the survey data is contained in the charts that follow.

We are grateful to every single person who took the time to answer this large volume of questions. We are humbled every day to know that going through Cushing's leads so many of us to want to change things so others do not have to suffer the way we did. At the time of this report's release, CSRF is about 2/3 of the way through a patient registry build with a proposed soft launch in February 2025. The registry will allow us to fully professionalize these concepts and studies we have done amongst ourselves, and produce data sets that can and will be used by researchers around the world. **Thank you.**

METHODOLOGY

This report represents a quality of life study designed by CSRF in 2023 that was distributed globally through partnership with international advocacy organizations including Pituitary Foundation Ireland, Australian Pituitary Society, and World Alliance of Pituitary Organizations (WAPO). Surveys were translated and offered in French and Spanish to expand access.

DEMOGRAPHICS

A total of 435 respondents from 38 countries successfully completed the survey. Women made up the majority (91.95% to mens' 7.36%), with two non-binary individuals and one trans woman rounding it out. More than half of participants were in the 40-59 age range:

18-29	8.97%	**30-39**	17.01%
40-49	29.43%	**50-59**	26.90%
60-69	14.25%	**70+**	3.45%

As we built the survey, we considered that the "ethnic background" question probably looked different in non-US countries. We did our best, but in the future we will do better to try to ensure that everyone is represented fully. For this survey, our breakdown looks like this:

86.9% Caucasian

6.44% more than one / other

2.76% Hispanic / Latino

2.30% Asian

1.38% African / Black

0.23% Native / Indigenous

Pituitary was the most prevalent source of Cushing's in this study (76.21%) with **adrenal** coming in second (16.26%). About 4% of people had a diagnosis but were still testing to find the source, and about 1% each reported exogenous Cushing's, autonomous cortisol secretion (MACS/ACS), ectopic in the lung, and ectopic elsewhere.

When these 435 respondents filled out the survey, two thirds (66.44%) of them reported that they had successful surgery and were in remission, 12.65% were in recurrence or still active after unsuccessful surgery, and about 6% had been diagnosed but had not yet had surgery. Around 2% of participants were either waiting for radiation to work, on cortisol-controlling medication, or had an exogenous source. Around one tenth (9.43%) of responses were from people who listed more than one status, in most cases because a first surgery did not work or they were in recurrence.

Eight people did not list their year of diagnosis, but of the rest, 21.31% were within two years of their diagnosis, 27.40% were 2-5 years out, 23.65% were 5-10 years out, 20.84% were 10-20 years out, and 6.79% were answering the survey with more than 20 years since their diagnosis.

SIGNS AND SYMPTOMS

The majority of us (84.60%) agreed that looking at symptoms as "part of a package" instead of individually is vital for earlier screening. Even a self-aware person can be overwhelmed by the number and severity of comorbidities that Cushing's Syndrome brings, and it's difficult for almost all of us (93.10%) to understand this complicated diagnosis, especially in the beginning. It's no surprise that trying to manage those complex symptoms negatively impacts nearly everyone (95.86%) too.

We have explored some of the less-commonly reported signs, symptoms, and long-term residual effects of Cushing's in this survey. We know that there is room to do a much more thorough job of this and are motivated by the many comments that shared great ideas to include in symptom studies through the registry.

Changes to our physical appearance are a top concern, and it goes way beyond simply how we look. Sometimes people we know don't recognize us in active Cushing's (68.51%), we often feel rejected by our friends (69.66%), and three-quarters (74.94%) of survey respondents identify with the classic, grotesque image of the "Cushing's phenotype" we find when we search online for information about this disease.

Brain fog, cognitive impairment, and physical limitations affect our careers and the volume of work we are able to do; about 30% of respondents said they have lost motivation to do their jobs. Just over 40% are still motivated to do the job, but their effectiveness has been reduced by Cushing's. Almost half of us (47.13%) report a temporary interruption in work because of this illness, while about a third (31.26%) have had to make the difficult decision to quit their job.

Struggling to keep up when you previously thrived in your career strikes at our identity and makes us question everything; 59.54% of us have found ourselves in this position to some degree.

DIAGNOSIS

Sometimes the biggest challenge is getting the diagnosis! CSRF intends to use its research platform to further explore what we mean, and what doctors think, when we talk about "how long we had it before we got a diagnosis". The published average delay to diagnosis is listed as 5-7 years in peer-reviewed literature, and respondents' answers reflected that:

26.7% less than two years to diagnosis

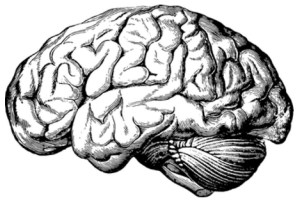
28.4% 2-5 years to diagnosis

24.1% 5-10 years to diagnosis

20.8% more than 10 years to diagnosis

We need better screening programs, and patients are unanimous that primary care providers must be educated and supported. We're nearly unanimous that obesity doctors (97.70%) and gynecologists (93.33%) receive education and support as well. CSRF has recently broadened its scope of professional outreach due to this kind of feedback.

Overall, we are optimistic that things will get better (82.53%), but we want to have realistic expectations. For the best possible outcome with this complicated disease in any of its forms, it's clear that we must have the full picture so we can weigh our options and make the best choices for ourselves and our lives.



LIMITATIONS

As we build the registry and look back on the way these and earlier survey questions were designed, we see so much room for improvement! We'll look at it as progress, learning to be more specific to be more effective. Here are some additional observations to share with you, to give you an idea of some back-end logistical work we did to present final results to you:

-We found three respondents who listed themselves as still seeking a diagnosis, but they answered questions about the post-treatment period. We removed those few files to ensure that only responses from people who listed a diagnosis would be included. In the future, we can improve qualification questions at the beginning of a survey.

-A related thought is - do undiagnosed patients, or those with "non-neoplastic endogenous" Cushing's Syndrome, need a platform, and what would it look like?

-There were many questions where "n/a" did not need to be an option, but it was used by some people. It is a very imperfect method, but for this report we decided to combine "no" and "n/a" responses into one column. If you, Reader, have any questions about individual responses, we will be happy to get on a zoom with you and show you the raw data and how we calculated certain percentages.

-There were four individual questions about how long it took to reach diagnosis with no way to limit a respondent to just one choice, and they should have been combined into one single question. We ended up with 13 respondents who chose more than one option, and three who did not choose any option.

Because of this, we excluded those 16 for this question ONLY, to end up with:

<2 years = **26.73%** (112/419)

2-5 years = **28.40%** (119/419)

5-10 years = **24.11%** (101/419)

>10 years = **20.76%** (87/419)

-The question about the type of Cushing's a respondent has did not include enough options to ensure everyone sees themselves in at least one. The question about current status of Cushing's needs more options as well, and should require at least one answer.

-We go back and forth among tenses - have, had, have or had - and it might have been confusing to answer questions that bounced back and forth from active Cushing's to remission.

-Our coverage of adrenal insufficiency (AI) was sparse - we only asked about how you received information about it, and if you had permanent AI now. It's a huge topic that deserves future exploration on its own. If you are interested in joining a registry to contribute your experience with AI, please check out the *my*AI registry sponsored by the National Adrenal Diseases Foundation (NADF) by scanning the QR code below or by visiting the website:

https://www.nationaljewish.org/clinical-trials/myai-registry-for-people-with-adrenal-insufficiency

-We polled ourselves about some of the things we don't feel are well understood or represented in current literature, but we missed an opportunity to explore some of the positive things that can come out of this experience. Having Cushing's changes a person, but oftentimes recovery also brings clarity, resolve, autonomy, and courage in various parts of our lives. Encouragement and a balanced outlook must be present whenever we talk about this disease and what it does to us. If we're going to share our problems, we must also have some solutions in mind!

And now, the data:

PHYSICAL	YES or AGREE	NO, DISAGREE, N/A
I have or did have leg and hip muscle weakness.	90.34%	9.66%
I lost physical strength with Cushing's.	97.24%	2.76%
I experience(d) pain.	91.26%	8.74%
I have problems with vertigo that I believe are from Cushing's.	45.06%	54.94%
After Cushing's I have bad balance.	62.53%	37.47%
I suspect I have had an increase in dental problems because of Cushing's.	55.86%	44.14%
I have not had any dental issues related to Cushing's.	38.62%	61.38%
I have or have had sores on my scalp that I believe are related to Cushing's.	30.34%	69.66%
I was or am diagnosed with peripheral neuropathy and believe it is from Cushing's.	28.05%	71.95%
I do not or did not have the classic Cushing's appearance and I feel like that delayed my diagnosis.	28.97%	71.03%
People do not or did not recognize me after surgery.	30.80%	69.20%
The classic Cushing's image is harmful because not every patient has stretch marks, a hump, or extreme weight gain.	69.89%	30.11%
I experience(d) insomnia.	90.34%	9.66%
I went or currently go to a dermatologist because of very bad acne or other skin conditions from Cushing's.	35.63%	64.37%

COGNITION AND NEUROPSYCHOLOGY	YES or AGREE	NO, DISAGREE, N/A
My job depends or depended on my ability to learn and retain information; cognition impairment affects this.	79.77%	20.23%
My short-term memory has been negatively impacted.	89.20%	10.80%
My long-term memory has been negatively impacted.	70.11%	29.89%
Memory problems have led me to use adaptations such as lists and notes to myself, and I did not do this before.	80.92%	19.08%
I have had neuropsychological testing and I would recommend it to any patient who has access to it.	19.54%	80.46%

DELAYS TO DIAGNOSIS	YES or AGREE	NO, DISAGREE, N/A
I experienced fat shaming or bias in my quest for diagnosis.	79.54%	20.46%
I experienced gender bias in my quest for diagnosis.	34.94%	65.06%
I have had to fight my insurance company or healthcare provider for one or more treatments I needed for Cushing's.	44.60%	55.40%
I have had an unnecessary surgery due to not being diagnosed properly with Cushing's.	16.09%	83.91%
My non-specialist doctors do or did not seem to understand how to interpret cortisol lab results.	64.83%	35.17%
I have experienced a delay in care when a specialist and my General Practitioner (or Internist, or Primary Care Provider) have both stated that an issue was not their responsibility and referred that care to the other.	56.55%	43.45%

SUPPORT	YES or AGREE	NO, DISAGREE, N/A
Beyond the medical care team, I believe it “takes a village” to support a Cushing’s patient – family, friends, workplace, etc.	97.93%	2.07%
I attend or have attended a support group specifically for Cushing’s.	37.24%	62.76%
I have not but wish I could attend a support group.	58.62%	41.38%
I would like to have access to an online discussion group that is only open to verified patients so I know that I am talking to people who actually have or had Cushing's.	91.49%	8.51%
It is beneficial to share experiences with other patients.	97.93%	2.07%
A "peer sister" or "peer brother" to guide a patient along the way would be helpful.	94.25%	5.75%
I work with a mental health therapist.	39.54%	60.46%
I do not speak with a mental health therapist because of negative stigma.	8.51%	91.49%
I do not speak with a mental health therapist because of financial barriers.	29.66%	70.34%
I need or needed a caregiver in active Cushing's to help with things like bathing, shopping, household chores.	47.59%	52.41%
I need a caregiver's help now after Cushing's to help with personal tasks and errands.	34.71%	65.29%
I am curious about service and emotional support animals and how to get one.	47.82%	52.18%
I have access to an online patient portal where I can see my labs, scans, and communicate with my medical team.	78.39%	21.61%

COPING	YES or AGREE	NO, DISAGREE, N/A
I am familiar with the Spoon Theory, the pain/price index, or another energy management analogy used by patients with chronic illnesses	46.44%	53.56%
There are so many negative things happening with Cushing's that it can be difficult to determine what is related and what is not.	95.17%	4.83%
I feel that I need to learn how to retrain my brain to not always expect the worst, or for something else to go wrong, because that is how life has felt with Cushing's.	85.98%	14.02%
Before surgery I found so many things stressful, and it was difficult to cope.	80.92%	19.08%
After surgery I have found so many things stressful, and it has been difficult to cope.	64.83%	35.17%

MENTAL HEALTH	YES or AGREE	NO, DISAGREE, N/A
I believe that my emotional and mental health is just as important as my physical health.	99.31%	0.69%
Mental health support should be part of a treatment "package" recommended for all patients.	99.31%	0.69%
I experience or did experience anxiety and/or depression.	95.86%	4.14%
There is a need to process trauma afterwards.	91.95%	8.05%
I have developed excuses for my feelings and behaviors rather than validating the disease and healing process and being kind to myself.	61.15%	38.85%
I believe that therapy can be helpful even if a patient has good coping skills.	95.63%	4.37%
I have supportive family and friends, but that does not prevent me from having negative thoughts and feelings.	90.34%	9.66%
Apathy is sometimes stronger than symptoms of depression.	73.79%	26.21%
I have had suicidal thoughts.	50.57%	49.43%
Grief has been constantly present from diagnosis to recovery.	72.18%	27.82%
I feel or have felt that my health problems are all-consuming.	90.34%	9.66%

POST-TREATMENT	YES or AGREE	NO, DISAGREE, N/A
I think there is a perception by most people that everything does or should go back to normal after surgery.	91.49%	8.51%
I was not prepared for what it was going to be like after surgery.	72.41%	27.59%
Knowing what to expect the first month after surgery was a big concern for me.	78.62%	21.38%
Following surgery, I felt that I had little to no support from the medical team I'd been with throughout my diagnosis and surgery.	42.07%	57.93%
Cortisol withdrawal after a successful surgery is something that makes me nervous / afraid.	66.90%	33.10%
I was told I would be all better and back to work about 6 weeks after surgery.	47.82%	52.18%
You might need to prepare yourself to take much longer than 6 weeks, or even 6 months after surgery to return to work or normal activity.	87.36%	12.64%
I wish I had been told before surgery about hydrocortisone tapering and what to expect.	60.69%	39.31%
After surgery, I have recovered back to pretty much my "old normal".	15.17%	84.83%
After surgery, "old normal" is gone and I'm still trying to determine what my "new normal" really looks like.	75.17%	24.83%
After surgery, I am vigilant for any new sign of illness or return of high cortisol.	81.61%	18.39%
All of my pituitary hormones have been tested to see if I need to supplement anything.	57.70%	42.30%
Healing is a slow process and does not only include normalization of cortisol.	94.94%	5.06%
I want and need to gain confidence back about my body and appearance.	90.34%	9.66%

SECONDARY HEALTH ISSUES	YES or AGREE	NO, DISAGREE, N/A
I have had a hysterectomy because of Cushing's.	14.71%	85.29%
I have or did have low libido from Cushing's.	79.77%	20.23%
I am or was diagnosed with diabetes insipidus / arginine vasopressin deficiency	36.09%	63.91%
It was or is difficult to manage my diabetes insipidus.	19.08%	80.92%
I developed kidney disease because of Cushing's.	12.41%	87.59%

OPINIONS	YES or AGREE	NO, DISAGREE, N/A
It bothers me to not know why I got Cushing's in the first place.	77.01%	22.99%
Cushing's can be lonely.	97.24%	2.76%
Determining what is "normal" after diagnosis is difficult.	98.85%	1.15%
I think visits to other specialists like pulmonologists and cardiologists should be part of the standard of care.	90.80%	9.20%
I believe that validating the patient experience is one of the most important things doctors can do.	97.70%	2.30%
Just because my blood test results fall in normal ranges, that does not mean my symptoms are gone or that I am ok.	94.02%	5.98%
I struggle to stay compliant with my medication dosing routine every day.	27.13%	72.87%
I believe that all the various names for high cortisol lead to misinterpretation, self-diagnosis, and confusion.	72.64%	27.36%
The patient voice and experience must be included in the planning and development of any new product, service, treatment, or clinical trial that is intended for our community.	98.62%	1.38%
This is a disease where it seems that most patients must get very sick before it can be diagnosed and treated.	97.47%	2.53%
I wish I could get all my doctors to the same table to discuss my case and create a plan across their specialties.	88.28%	11.72%
It is exhausting to be a full time patient to so many doctors.	91.72%	8.28%
I've been called a hypochondriac.	52.41%	47.59%
I believe to some degree that chronic stress throughout my life might have caused my tumor.	54.02%	45.98%

MEDICATIONS AND DEVICES	YES or AGREE	NO, DISAGREE, N/A
I am interested in learning more about the cortisol-lowering medications available to Cushing's patients.	60.92%	39.08%
I am interested in learning more about pumps, patches, test kits, and other devices in the pipeline.	77.47%	22.53%

RELATIONSHIPS	YES or AGREE	NO, DISAGREE, N/A
Cushing's has changed expectations and needs in my closest relationships.	88.05%	11.95%
You can almost literally be a different person after treatment, and that can cause challenges with relationships where you once had a clearly defined role and now it's different.	73.33%	26.67%
My children seem or seemed negatively impacted by my sickness.	41.38%	58.62%
I am or was negatively impacted by a family that does not understand or has lost patience with a treatment process that has been going on for a long time.	50.34%	49.66%
Relationships have suffered because I lost respect for people who refused to believe my illness.	57.24%	42.76%
I'm worried my marriage will end because of this experience.	21.61%	78.39%
My marriage or long-term relationship did not survive Cushing's.	19.77%	80.23%
My partnership/marriage has gotten stronger as we have gone through this journey together.	44.60%	55.40%
It is helpful and important to the patient for their loved ones to be present throughout their journey, even if they don't know what to do.	98.62%	1.38%

DIET	YES or AGREE	NO, DISAGREE, N/A
I would like to improve nutrition absorption problems associated with Cushing's.	84.60%	15.40%
If there were dietary changes I could make that would help with stamina, energy, and brain fog, I would do it.	97.70%	2.30%
I would consider an anti-inflammatory diet if it could truly help with arthritis and joint pain.	87.59%	12.41%
I recognize that I do not know how to start a healthy diet after having bad habits for years.	26.21%	73.79%
I would consider a diet that can reduce gastrointestinal issues related to Cushing's.	79.54%	20.46%
I struggle with diet and exercise.	69.20%	30.80%
I tried or considered extreme diet or exercise to lose weight while in active Cushing's	75.40%	24.60%
I am very knowledgeable about healthy food and how it plays a direct role in my health.	84.60%	15.40%
I would follow an exercise plan adapted for physical limitations and weak muscles.	92.41%	7.59%

LONG-TERM	YES or AGREE	NO, DISAGREE, N/A
I want to know long-term health data (20+ years), even if it might be scary.	95.63%	4.37%
I would like to know how patients are doing who had radiation 20 or more years ago.	65.29%	34.71%
I am concerned about long-term cardiovascular damage from Cushing's.	85.75%	14.25%
I am concerned about negative impact from Cushing's on white and grey matter in the brain.	88.05%	11.95%
I wonder if the roller coaster ever subsides – I feel like I'm ok some days but barely able to function on others.	86.21%	13.79%
I believe that recovery from Cushing's doesn't truly begin until a patient is completely weaned off steroid replacement.	51.03%	48.97%

ADRENAL INSUFFICIENCY	YES or AGREE	NO, DISAGREE, N/A
I have not been given detailed information about adrenal insufficiency from my clinical team other than "double your dose for sick days".	49.43%	50.57%
My clinical team has given me excellent, detailed information about how to manage adrenal insufficiency after successful surgery.	31.95%	68.05%
I have learned the majority of what I know about how to manage adrenal insufficiency from other patients instead of my doctor.	57.24%	32.76%
I have permanent adrenal insufficiency now because of Cushing's.	32.64%	67.46%

FAITH AND OUTLOOK	YES or AGREE	NO, DISAGREE, N/A
This experience has negatively affected my faith in my God/religion/greater power.	21.84%	78.16%
My faith has been strengthened throughout the challenges of this disease.	43.22%	56.78%
Cushing's has caused me to learn new ways to manage stress and find peace that help me in other areas of my life.	72.87%	27.13%
I have decided to take better care of myself as a result of this experience.	76.32%	23.68%
My outlook on life has become more focused and intentional after surviving this battle with Cushing's.	74.02%	25.98%

PATIENT STORIES

Jaci

Cushing's Adventure

About six years ago one of my uncles needed a kidney. I was the correct blood type but his clinic said I needed to lose about thirty pounds before they could do any testing. I joined a program that had been successful for me in the past, but the weight didn't budge. I found that I did not have the energy or the drive to exercise as usual, so when I heard about another program with impressive results, I switched. I was over 200 lbs, more than during my two pregnancies. I lost 20 pounds, but couldn't lose any more than that.

My hair was thinning. I asked for advice from hair stylists and even a friend who did hair replacement, but they did not know what to say. I worked at a restaurant, and one day two of my high school classmates came in. They looked exactly the same as they did back then. We chatted, but as I walked away I heard one of them say, "I didn't even recognize her." The other one said, "You have to look at just her face, but even that has changed."

I ended the exercise program that summer when my menstrual cycle became irregular. My last period was March 2019. Things had been stressful in our life. My grandpa had passed away in September and the following month my uncle passed away. In May 2019, I went to my primary doctor to report my irregular cycle, and while there she noted my blood pressure was starting to elevate. She guessed that the stress of the diet, loss of family, and a new part-time teaching position may be the culprit, but seven months later my blood pressure was still elevated. My doctor thought it was strange because I have no family history of high blood pressure, and during my pregnancies it was always perfect. I suspect she thought I was not telling the truth about my habits and self-care. In early 2020, I had a follow up about the blood pressure. I really did not understand how blood pressure worked or how it was read, I was just always told my numbers were perfect. At that appointment my blood pressure was 182/116 and I weighed 200 lbs. The nurse tried to help me take deep breaths, meditate, and use aromatherapy to lower my blood pressure. It wasn't going down, it was actually climbing. She left the room to find the doctor (not my primary) who came blasting into the room and said if I did not agree to medication on the spot, she was going to admit me to the hospital. I had to pick up my kids from school in less than a half hour so I agreed to medication. I thought this was a death sentence and I was going to have to be medicated for the rest of my life. I had worked hard to wean off of antidepressants after I had an episode in 2015. My husband had a procedure so I wouldn't need to be on birth control pills. I was absolutely devastated. I asked if there were alternatives but she said we were beyond that.

That winter I attended a community group meeting on a sledding hill with my kids. I was anxious because I knew my snow pants would be

tight and I had no leg muscles to climb a hill. I didn't tell my husband how I was feeling and instead made jokes about my clothes - I was so large on top but my legs were thin and purple looking. After the meeting we had to walk back up a substantial hill, and when we got in the car I must have looked awful because my husband asked if he needed to call 911.

Shortly after that, I met with a gynecologist. She did not do any exams or order labs. She prescribed progesterone since I did not have a period. There was no inquiry into why I did not have my cycle, and I was not in early menopause.

For the next year, there were a lot of medication adjustments, monitoring, and lab visits. I could no longer squat and stand back up without using my whole body, and I used to be able to do both with no hands while holding both my kids. I was so tired all the time. My hands and feet would cramp when typing or even just laying in bed. My doctor always said at every appointment that it really bugged her that she didn't have an answer for me as to why my blood pressure was high. I could tell she trusted that I was doing what I could to make changes in my health but nothing was showing progress.

I was not enjoying my career as a preschool teacher, so I interviewed for another position in the building. I would go from part-time to full-time, but in all honesty, it was probably better for my kids to have a break from me. Things that never bothered me before, set me off.

I had noticed my fuse was short and I had little to no patience for anyone. I wasn't pleasant and I always felt on edge. One day I was having a hard day at home and my sweet neighbor boy came up to me and asked, "Is it tough for you to be a parent? You seem to be having a hard time."

I was so miserable inside. That same neighbor boy came up to me multiple times that summer and asked, "Are you sure you are not having another baby?" Physically, I felt disgusting. I kept thinking, "How can I not even be forty but I feel like I am eighty?"

The breaking point for me was when I noticed my shirts were not fitting the same around my neck. One night I was in the bathroom and noticed this hump on my back, at the base of my neck. I went into our bedroom and to my husband said, "What the hell is this?" He touched it and couldn't give me an answer if it was bone or a mass. I just kind of let it go and figured it was because I was so overweight the fat needed a new place to accumulate. It went well with the purple stretch marks I had on my sides and breasts.

A few days later my husband sent me a text with a link and said, "Check this out. I think this is what you have." I looked quick then ignored it. I thought to myself he's not a doctor and neither is Google. After a few days I thought I better really look at it just so I could tell him he was wrong. I read through the symptoms and he was spot on. I had every single one. I sent it to my doctor and told her that I thought my husband had just found what was wrong with me, and asked if she would test my cortisol. She responded with a referral to an endocrinologist. On June 21, 2021, I had that appointment. He ordered a dexamethasone suppression test to "rule it out", but little did he know that I was about to be the first Cushing's patient in his career. After seeing my lab results he asked if I really took the dexamethasone because my cortisol level was so high.

The following weekend we went to a fishing resort for a getaway. We took a fishing charter one night. When it came time to step up out of the boat, I fell onto the dock because I had no

leg muscles to step up. I had to lay on my stomach and push myself up. It was mortifying. I was so glad it was dark as I am sure I looked like a beached whale. When we got back to our cabin my husband asked if I was ok. I told him I had no muscle in my legs anymore and that I couldn't take large steps and could barely make it up our basement stairs. He had no idea. I hid it from him because I was embarrassed and thought he would think I was doing this to myself. He looked so hurt that I kept it from him.

I did a urine collection at the end of July. The results indicated an adrenal source, so we moved on to a CAT scan of my adrenals and found an adenoma on the left. It was a relief to know something was behind all these symptoms, and to know I could apologize to my kids and say, "Your mommy isn't always going to be like this."

Things moved rather quickly. Surgery was scheduled for September 28, 2021. The night before my surgery I cried when I said goodnight to my kids. I knew I had a great surgeon and care team but I was so nervous something might go wrong due to my high blood pressure. But surgery went great and only required one overnight in the hospital to monitor my blood pressure. My recovery went fairly well. I was not prepared for how painful my stomach area would be after surgery, but I only needed Tylenol for the pain.

I was started on a replacement dose of 20mg prednisone daily for seven days, 15mg prednisone for the next seven days, and 10mg for the following four weeks. After that we dropped to a 5mg dose and also dropped the progesterone I had been taking to see if anything would change with my cycle.

A month later we tried to end the prednisone dosing, but I was so tired and my body hurt, even my knuckles hurt. I had to really talk myself into moving at all. I sent a message to my endocrinologist, we did testing, and I went back on 5mg of prednisone daily. During this time my menstrual cycle came back (has been regular since), plus my blood pressure returned to normal and I was able to reduce my medication.

By the end of January 2022 I was off of all blood pressure medications. My mood and energy levels were coming back to "normal". By April I was able to reduce my prednisone dose to 3mg. In June my ACTH was improving but not quite where we wanted it. I was down to 1mg daily by December 2022, and in February 2023 I passed the stim test and have been prednisone-free ever since! When my endocrinologist sent me the message I had to re-read it a number of times because I just could not believe it. When you have been sick for so long it takes awhile to process that you just might be ok again.

Through this journey I learned Google just might be your friend. Always ask more questions and keep fighting. Have a team behind you who want answers and won't give up on you. Some days, I really can't believe my husband stayed with me. I was not a nice person and for awhile I wasn't much like the person he married. I am so grateful he was persistent in helping me get to diagnosis and through treatment, and that he always had faith that he would get ME back.

Today I feel so much better mentally and emotionally. I do have a little brain fog and trouble with names. I have lost some weight but I know I can do better with exercise. I have body aches and stiffness some days but not like I did during Cushing's. And I can't say it strongly enough: I am so lucky to have the husband I have and the team of doctors behind me that would not give up on finding answers for me!

Romy

With bias, my dad said that I was one in a million. As it turns out, I was one out of every 10-15 per million. Not too shabby. But not in the way I imagined. Here's my story...one that I hope you will find filled with inspiration in the face of fear and possible death.

It's been two years since my diagnosis. I'm fortunately in remission and regaining strength each day. I have a renewed spirit with a love of life, a clearer perspective, and an appreciation of what's true and important. I've come to live by the mantra "first steps first" with all of my daily challenges. Humor, and surrounding myself with people who care, helped with my relentless need to get to the bottom of my medical condition. Grace, the will to be a strong and courageous role model for my children and others, and a can-do attitude led me on the path to a healthier me.

For years, it was like "Groundhog Day," the same grueling nighttime routine. I'd hit a wall around 7:00pm and fall asleep for four consecutive hours. Thereafter I'd repetitively wake in 45-minute increments. In between, I'd read, bake, exercise, do laundry, work remotely, anything to pass the time. Going back to sleep seemed cruel, like my body didn't want me to rest and replenish. In simplest terms, imagine shooting down a triple espresso when all you want to do is sleep. The day often started at 5am. Sometimes, I'd have to pull over while driving and nap in a parking lot.

Insomnia was just one of two dozen challenging medical conditions I experienced daily: muscle fatigue resulting in poor balance and embarrassing falls, swollen feet and hands, the onset of osteoporosis, loss of dexterity in my hands, dry eyes, acne, styes requiring painful procedures, dry skin, occasional dizziness due to lack of sleep, hair loss, my Raynaud's was exacerbated, easy bruising, breathing difficulty, reddening of the skin, skin blotches, grinding teeth (due to anxiety), anxiety, mood swings, excessive weight gain around my central body, and a rounded face.

For decades I ate healthy and regularly exercised. The weight gain, especially around my midsection, was very distressful. I went to Pilates 6-7x per week, walked a few times a week with girlfriends, and I ate healthily. How could I put on 32lbs?

I had seen so many doctors repeatedly - primary doctor, neurologist, gynecologist, optometrist, endocrinologist, rheumatologist, ophthalmologist - to get some sort of diagnosis. They ruled out so many chronic diseases. None fit. I had a hard time keeping track of their names and the ensuing list of appointments. My health became more than a part-time job on top of my real job and being a parent, wife, daughter, sister, and friend. I became increasingly distraught about the troubled medical landscape; the insistence that what I was going through was normal for my

age, "just hormones", made me angry.

In December of 2022, I went with my husband Michael and our friends to Cabo San Lucas. Michael was applying sunscreen to my back by the pool when he said, "There's a hump on your upper back." When we returned from that trip, he did more online research on my health symptoms, this time focusing in on the "hump." Cushing's Disease came up in the search engine. It clearly described all my symptoms. He said, "You need to go back to your endocrinologist and ask to have your cortisol tested."

When I went to see that doctor, he did the "eye roll" thing and said he didn't see the hump. After I protested that my husband of 26 years knew my body and saw and felt the hump, coupled with my printed list of all my medical conditions, he gave in and agreed to test my cortisol.

I followed his instructions on what to do to prepare for the blood work, which revealed that my cortisol was 3x higher than normal. My doctor questioned if I followed his pre-blood work test instructions because "he had never seen numbers like this." He had me test again with the same results. Urine and saliva, same results. At this point, he said, "he didn't know what to do except refer me to Stanford or UCSF."

Well, those doctors were right in that it was "just hormones." Where they were critically wrong was that it was cortisol, the stress hormone, that was 3x higher than normal. If not for the Cushing's diagnosis, thanks to my loving husband, I would not be here to speak of it. Cushing's can be fatal if not diagnosed and treated.

With Michael by my side, we made our first visit to Stanford to see an endocrinologist who specialized in Cushing's. An overwhelming feeling came over me, and I cried. The doctor asked me a lot of questions based on my previous labs. He reviewed the photo collage I had compiled showing how my body had physically changed. He did a physical exam and declared that he thought I had Cushing's, but a procedure would be needed to verify. I realized that my tears came from a deep place of relief. I now had a clearer path forward and I felt heard and validated. He explained "first steps first," as this would be a long process. These were words that became my mantra.

Two years ago, I had not one but two pituitary surgeries. The recovery was anything but smooth. Laying in the uncomfortable hospital bed, I felt like I was dying, which the staff said was positive because that meant they got the tumor. I hit a low of lows where I was not producing any cortisol. I could barely talk or move. My endocrinologist said that recovery would be more difficult than pre-surgery, and he was 100% accurate.

After returning home, I experienced varied symptoms for months: my body was itchy all over due to an allergic reaction to a key medication, I was blowing unrecognizable "stuff" out of my nose that no human should be capable of producing. I was so very, very, tired. My doctors worked with me to develop the right medicinal cocktail, including a daily shot of growth hormone.

I now have the beginnings of a cataract suited for someone 20 years my senior and I lost 2" in height, but I lost the 32lbs! My visits to Stanford are now limited to an annual check up and an infusion to keep my bones strong. I sleep like a baby. My hair is long and full. My face glows with life.

Through this scary and lengthy battle with the unknown, I never said I can't. Instead, I said I can look for solutions and surround myself with people who support me, and I did. I am still doing Pilates, walking with girlfriends, eating healthily, and laughing. I am stronger than I was pre-surgery, and I have some nicely toned biceps to boot! I have survived a difficult time in my life. I know what I am capable of. I know that I cannot control the unknown, but I can control how I view it. I am more at ease than I have been my entire life. Perspective, I suppose.

As a woman who was suffering, knowing something was wrong, I had to keep pushing, demanding, and begging for attention. I had to tuck away the intimidating looks of dismissal and head nods of their expertise. My entire life was changing, and my body and mind knew it. The true struggle and challenge before me was convincing the medical world of my disease.

The physical and emotional scars are real, but I am grateful for this experience that has allowed me to grow in ways I never considered possible. Daily challenges don't feel or seem so significant anymore. And that mantra will forever reside in my tumor-free head, "first steps first."

Thank you to all the phenomenal medical professionals who saved my life and gave me a new beginning. Thank you to my family and friends who stood by me in so many selfless ways. Thank you to my Pilates instructors who gave me an encouraging place to become my strongest self, literally and figuratively. And, to Michael, who put a name to my disease and stood by my side before, during, and after such a formidable experience, I will forever be grateful. In sickness and in health...

Joanna

It's been almost 3 years since I had Pituitary surgery, and while things are definitely better than they were the last time I wrote about my Cushing's journey, I wish I could say that I made a full recovery. There were some unexpected things that happened, which I believe are directly related to having un-diagnosed Cushing's Disease for so many years.

For one, about 10 months after surgery I stared bleeding so badly that my Gynecologist thought I was hemorrhaging. It started like just a regular period, but then became so heavy and painful, that all night long I was in excruciating pain and going though pads every hour. I called my doctor first thing in the morning and she said that I needed to go to the ER quickly, but that it wasn't safe for me to drive myself to the hospital. I had to call 911 since none of my friends were available to take me. At the hospital they did a few exams to rule out endometriosis and anemia, so they felt I wasn't really hemorrhaging. It was just a terribly bad period, mostly due to the fact that my periods

had been absent for so many years because of Cushing's. This was my body getting back "on line" and my hormones regulating again.

I went to see my Gynecologist a few days later, and she did a uterine biopsy. The results showed that I had polyps and thick endometrial lining, so their recommendation was a hysteroscopy and D&C. No big deal I thought, since I had one done when I was 23. So a few months later, they did the surgery and the results showed I had pre-cancer cells. That was not expected at all, and it made me panic because now they said the best option was to have a hysterectomy so the cancer wouldn't progress or spread.

After a couple of months, in January 2023 I met with an Oncologist who went over all the options and what types of surgery I could have, and she assured me this was the best path to take. I set the surgery date for April and while I waited, I prayed really hard to make the best decision, and I did my research. My PCP, who also is a Gynecologist, agreed this was the best way to go, although he said I could just watch and wait. I could do repeat biopsies and see if things progressed if I didn't want to have a hysterectomy. I decided that was the route for me. I knew that my recovery would be really difficult since I hadn't fully recovered from the pituitary surgery, and they estimated a recovery of at least 4-5 months after the hysterectomy before I'd be feeling better. I didn't want to go through that again so soon.

My Gynecologist wasn't happy about my decision to cancel this surgery, but I stood my ground because I was hopeful that with a little time, everything would clear up. She reluctantly agreed to just keep monitoring it with routine biopsies every three months, which are quite painful. I needed another D&C in June 2023 because more polyps had grown back. Thankfully this time no pre-cancer was found. Since then I've had a few more biopsies, all with good results.

In September 2023, blood work confirmed that I am in perimenopause, which has been difficult to navigate because so many of those symptoms are similar to what I experienced with Cushing's. I'm irritable sometimes, and I have more depression and mood swings. I'm also having hot flashes, insomnia, and irregular periods again. And unfortunately, after losing 53 pounds since my pituitary surgery, I have now gained about 10lbs.

Another issue I experienced began immediately after my pituitary surgery and continued for about a year: terrible carpal tunnel in both hands. It was very painful and I wasn't able to sleep well or function properly because of it. I was sent to have a nerve conduction test done. That was the hardest procedure I've ever had to go through and I was crying the whole time because of the pain. They recommended that I have surgery to help with the carpal tunnel, but I wanted to see if my body could recover on its own. An Occupational Therapist helped me with different exercises and also suggested products I could try which could help relieve the pain. It took several months, but my situation improved. And while I'm not 100% cured, it's a lot better now, and I can manage the numbness which goes away when I rest my hands.

In July 2022, I was finally approved for SSI after initially being denied and then having to face a judge for another hearing when I applied again. That whole process was extremely stressful, and since some of my work credits had expired I'm getting less than I was hoping. I do realize that it's been a blessing, and I'm very grateful for it. I'm supposed to have a review next year to see if they think I still qualify, and while I have made some improvements, there's a lot that is still quite challenging for me physically and mentally,

especially due to anxiety and brain fog.

Some days I feel so exhausted and need to take it easy at home. Other times I have some energy to do a short workout, and I've been able to walk one mile on the treadmill a couple of times even though I'm fatigued afterwards. I was also diagnosed with plantar fasciitis last September, which at times makes walking or standing difficult because of the pain in my feet. And I still face chronic, widespread pain all throughout my body that's become a part of my daily life. Occasionally, with a lot of planning I can do some things all day, as long as I have time to rest in between the activities. I usually pay for it the next day though. I still use my cane most of the time, which helps me with dizziness or weakness.

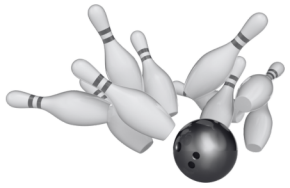
Because I can never predict how I'll feel throughout the day, it's hard to have any set routines. I'm also diagnosed with fibromyalgia and that has made everything extra difficult for me. My Cushing's recovery is still on-going nearly three years later; my Neurologist said I'd be fully recovered within 6 months but I'm certainly not back to "normal" yet.

I also still struggle with finding the right words to say, or I'll totally forget what I'm thinking. At times, when I read something, it feels like I'm just looking at words that don't make sense, unless I go really slow and concentrate. And in conversation, I'll insert words that don't belong, especially if I'm trying to speak quickly or I'm feeling nervous. It can be very embarrassing and it makes me feel badly about myself.

But I have had many good moments too. Starting in March 2022, I completed seven months of physical therapy. Thanks to my very devoted and patient therapist, my chronic shoulder pain, which limited a lot of my movement for over half a decade, has made remarkable improvement. He found ways to help me without irritating my nervous system, and encouraged baby steps toward recovery since mine was a unique case he had never treated before. We took a break for a few months so I could work on all the exercises at home, but when I got back to my second round of therapy, the focus of our sessions was my love of bowling! I hadn't been able to enjoy bowling since 2018, and since I was still experiencing dizziness and pain, my therapist found ways to help me overcome that. I have been able to bowl fairly regularly with my daughter for about a year now, and my scores are pretty good. I still get dizzy if I turn too fast, and the moving lights during Cosmic Bowling throw my balance off. I do get fatigued halfway through, but usually I can push past it, and then rest after I get home.

Just last week I was able to do Zumba again, which I haven't done for over five years. It felt great to dance again. I was only able to tolerate about 20 minutes before my feet really hurt and I got pretty shaky and exhausted. It makes me sad to think that years ago I used to be able to dance for 60 minutes and still have energy, but now I'm so limited in what I can do.

I am very grateful that all my blood tests, CT scans and MRIs have come back looking great each time. My cortisol and ACTH are normal again. My bone density scans have shown improvement, and I no longer have osteopenia. My Endocrinologist is very happy with my results, and he says that I don't need to test as often anymore. I hope that in time, I'll be able to keep working on my strength and energy so I can do more. I try to remind myself how far I've come, and thanks to my faith, I know the future holds endless possibilities.



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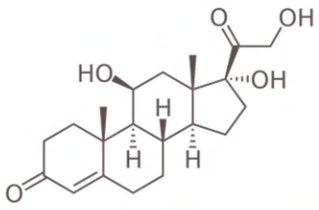

CSRF CORPORATE COUNCIL

Our Corporate Council was established in 2021 to create regular, transparent partnership opportunities and dialogue among its members who share many common goals with CSRF. Over the years we have collaborated on numerous patient-focused projects, programs, and offerings that have been met with enthusiasm and willingness to participate by many members of CSRF. Every company listed below has made LISTENING to and LEARNING from the patient experience a priority.

CSRF Corporate Council Membership is conditionally available to all - organizations, corporations, pharmaceutical companies, doctors' groups, philanthropists, or other entities (CSRF reserves final discretion) actively working toward real, science-proven solutions for our community. For more information, or if you are interested in potentially becoming a Corporate Council member, please contact us at **leslie@csrf.net**.

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