Dravet Syndrome Foundation

SEPTEMEMBER 2022

STRATEGIC PLAN PROGRESS REPORT

In 2018, Dravet Syndrome Foundation (DSF) developed a 5-year strategic plan to articulate the long-range direction and priorities for our organization. The content for our strategic plan was derived by examining the Dravet syndrome landscape. We listened to a broad range of input from key stakeholders within our community regarding current community priorities, emerging needs, and organizational strengths and vulnerabilities.

We are pleased to offer our final annual update on our progress from July 2021 - July 2022.

SPECIAL NOTE RE: COVID-19

While conditions have greatly improved and we were able to host our biennial conference in person and several fundraising events in the first half of the year, we have still had some restrictions resulting from the pandemic that have impacted attendance. Thanks to our rigorous financial development and management over the years, DSF has remained stable in times of uncertainty, and we have not had any cutbacks on our programs or services.

GOAL 1: RESEARCH AND PROFESSIONAL EDUCATION

Through collaboration and communication with our research community, we can improve the timeline for better treatments and a cure. By supporting opportunities that allow for greater education on Dravet syndrome throughout the healthcare system, we can increase diagnosis and assure the best quality of life.

Accomplishments from July 2021 - July 2022

- Hosted the 12th annual *DSF Research Roundtable* and began planning the 13th annual event. Due to pandemic concerns, we moved to a hybrid model, offering attendees the option to join in person or virtually.
- Hosted our 5th Biennial Conference on June 23-25, 2022, in collaboration with Cook Children's Medical Center in Fort Worth, Texas. The event brought together over 300 family members, researchers, clinicians, and industry partners to hear the latest on research and clinical care for Dravet syndrome, as well as for the unique opportunity to connect in person. Recordings of the sessions are available on our website.
- During our conference, we hosted adult neurologists and held a roundtable to discuss transition from pediatric to adult care.
- Held a virtual *Externally-Led Patient-Focused Drug Development Meeting* on Dravet syndrome. This meeting was a long-awaited opportunity for the Dravet syndrome patient community to educate representatives of the Food and Drug Administration (FDA) and pharmaceutical companies, as well as academic researchers and clinicians, about the challenges that individuals living with Dravet syndrome face daily. A *Voice of the Patient Report* was developed from this meeting. Details on the meeting and the report can be found on our website.

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- Funded the *International consensus on diagnosis and management of Dravet syndrome* project, led by Dr. Elaine Wirrell and a team of top experts in the field of Dravet syndrome, which resulted in a publication in *Epilepsia* in July.

GOAL 2: INCREASE REVENUE TO SUPPORT OUR PROGRAMS

Funding growth is challenging particularly for a rare disease nonprofit. By increasing and diversifying our revenue streams we can ensure we have a sustainable operating model that meets the demands of our continuously growing community, and guarantee our success and longevity.

Accomplishments from July 2021 - July 2022

- Hosted our 2nd virtual *Party in Your PJs* for Dravet in place of our annual signature gala. This year we honored our Scientific Advisory Board Members.
- Held our 2nd virtual *Steps Toward a Cure* fundraising walk in the fall of 2021 to replace our in-person events.
- Began rescheduling our postponed 2021 gala events for new dates in 2022 and 2023. We were able to host in-person events for *Dance for Dravet*, *Double Down Peoria*, and *Double Down for Dravet* from Fall 2021 through Summer 2022.

GOAL 3: EXPAND FAMILY EDUCATION & ADVOCACY

We will continue to support patients and families with disease education and advocacy needs through maintenance and expansion of patient resources, as well as family-to-family support.

Accomplishments from July 2020 - July 2021

- Unveiled a new brand identity in June to reflect the organization's history and its strategy for the future.
- Launched our new website on June 23rd. Among the new features are ADA accessibility, website translation capabilities, an updated physician and comprehensive care center directories, caregiver & hcp resource pages, educational video directory and a consolidated news page.
- Awarded over $15,000 in travel sponsorship to our conference, assisting 20 families to attend.
- Continued distribution of our *Newly Diagnosed Patient Kit*, which includes a printed guide for newly diagnosed families, as well as a medication bag and other materials to assure families have the tools and resources they need to manage their loved one's care.
- Began planning a virtual *Day of Dravet* workshop scheduled for September 24, which will replace our annual in-person events this year, with a focus on daily living and caregiver concerns.
- Distributed $16,508 through our *Patient Assistance Grant Program*.
- Increased membership in our private parent support group by approximately 9%.
- Developed three new resources for families of adult patients to assist them with long-term planning for their loved one.

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GOAL 4: ENHANCE COMMUNITY DEVELOPMENT & COMMUNICATIONS

By increasing the leadership roles of our staff, board, volunteers, and donors we can build on current strengths through internal capabilities and resources, while strengthening our community connections. We recognize the importance of an ongoing assessment of our role within the community and the most effective use of our resources, as well as the need to continually communicate our priorities, goals, strategies, and accomplishments to inform and engage our stakeholders.

Accomplishments from July 2021 - July 2022

- Established our 2022 initiatives, based on the goals and objectives set forth by our Board of Directors
- Rebranded to further clarify our mission, programs, and goals, and better share them with our patient community and stakeholders.
- Hired a communications company to expand and oversee our messaging and outreach to help increase awareness of Dravet syndrome and the accomplishments of DSF.
- Participated in a specialized segment of *The Balancing Act on Lifetime TV* dedicated to Dravet syndrome that followed the diagnosis and treatment journey of a Dravet patient and family and helped bring national attention to this rare disease.

RESEARCH STRATEGY

Our 5-year strategic plan addresses the three highest priorities for research in our community. 1) Cure; 2) Treat; and 3) Learn. By distributing resources among these arms, DSF will continue to balance the need for progress toward a cure and the immediate need for better treatments and new pathways toward that cure.

Since originally drafting our 5-year strategic plan in 2018, DSF has awarded an additional $2.07M in research grants, $740K of which was invested into research on genetic approaches to treating Dravet syndrome.

Accomplishments from July 2021-July 2022 under each of the Research Priorities

(1) **Cure:** DSF has continued to focus on supporting and encouraging research that could cure Dravet syndrome by targeting the genetic cause.

- DSF funded a postdoctoral fellow to investigate a genetic therapy targeting Scn8a that prevents the onset of seizures in mouse models of Dravet syndrome. Previous work suggested that Scn8a may be an effective therapeutic target in Scn1a haploinsufficiency models, and this project seeks to test it as a one-time gene therapy in mice.

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RESEARCH STRATEGY (continued)

- DSF funded a research project investigating a gene that may modulate the impacts of SCN1A haploinsufficiency. The research plans to deliver the gene to mice and test the impacts on brain communication and seizures in mouse models of Dravet syndrome.
- Research previously funded by DSF led to a publication providing proof-of-concept in mice that symptoms of Dravet syndrome may be reversible via gene therapy long after symptom onset and not just when administered at very early developmental stages (Valassina et al, Nature Communications 2022).
- Another research group funded by DSF posted a pre-print of a manuscript that details an alternative approach to delivering a healthy copy of the SCN1A gene using a specialized delivery vector large enough to carry the entire gene, addressing one of the largest hurdles to a classic gene therapy approach for Dravet syndrome (Fadila et al, bioRxiv 2022).
- DSF continues to support Stoke Therapeutics, a biotechnology company developing an antisense oligonucleotide (ASO) treatment aimed at increasing healthy *SCN1A* expression. Following the previous publication of their preclinical work in 2020, an additional paper was published through collaboration with another group of academic researchers at the University of Virginia that again exemplified the efficacy of this approach in a mouse model of Dravet syndrome (Wengert et al, Brain Research 2021). Their investigational therapy (STK-001) is currently in Phase 1b/2a clinical trials in both the US and UK to determine safety and effective dosing levels, and patients completing these studies are eligible to enter an open-label extension study to continue receiving doses of the experimental treatment. Early data reports from the trials support a good safety profile and give the first indication of seizure reductions in patients receiving the therapy.
- DSF also continues to support Encoded Therapeutics, a biotechnology company developing a one-time gene therapy that would permanently enhance expression of the remaining healthy copy of SCN1A. Encoded published their preclinical work showing efficacy of their approach in mouse models of Dravet syndrome (Tanenhaus et al, Human Gene Therapy 2022).
- DSF continues to seek and maintain relationships with biotechnology companies that are in early stages of pre-clinical development of disease-modifying therapies for Dravet syndrome.

(2) **Treat:** DSF has continued to support the development of clinical treatments aimed at reducing seizures in Dravet syndrome by working with pharmaceutical and biotechnology companies to bring their treatments to the market. Since the inceptions of the Strategic Plan in 2018, three medications have received FDA approval for the treatment of Dravet syndrome.

DSF supports companies developing and running clinical trials for Dravet syndrome by providing feedback, aiding in access to the patient and caregiver voice, and raising awareness of study participation opportunities within the community. **Clinical trials are currently underway for the following investigational treatments:**

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RESEARCH STRATEGY (continued)

- TAK-935 (soticlestat, inhibits 24-hydrocholesterol synthesis to restore glutamate levels). Ovid completed the Phase 2 trials for TAK-935 in 2021 and published the results in July of 2022 indicating a favorable safety profile and significant seizure reduction in patients with Dravet syndrome (Hahn et al, Epilepsia 2022). Takeda took over the global rights for TAK-935 and began an international Phase 3 clinical trial (SKYLINE) at the end of 2021.
- EPX-100 (clemizole, repurposed antihistamine, 5-HT modulation). EPX-100 emerged from zebrafish studies that were funded in-part by DSF. Epygenix Therapeutics is currently enrolling for a Phase 2 trial (ARGUS) in the US and Canada with intentions to expand further internationally.
- E2023 (lorcaserin, repurposed weight-loss drug, previously marketed as Belviq, 5-HT modulation). Eisai, Inc. began a Phase 3 trial (MOMENTUM I) for lorcaserin in 2020 and sites continue recruitment in the US and Canada.
- LP352 (5-HT2C superagonist). Longboard Pharmaceutics, Inc. began recruiting for a Phase 2 trial (PACIFIC) in the US in 2022 to investigate LP352 in patients with developmental and epileptic encephalopathies.

Clinical trials are also investigating new options for seizure rescue medications:

- Valtoco (intranasal diazepam). Valtoco was approved for patients over the age of 6 years in 2020. Neurelis is currently sponsoring a Phase 1/2 study (STELLINA) now enrolling in the US to assess safety and efficacy of Valtoco in patients from ages 2-5 years.
- Staccato Alprazolam (novel inhaler device containing alprazolam). UCB is sponsoring a Phase 3 study (STARS) to assess the efficacy and safety of this investigational rescue medication in patients ages 12 years and older. The trial began in late 2021 and is currently enrolling globally.

Basic research supported by DSF is also focused on therapeutic discovery and advancing clinical care:

- Funding for a postdoctoral fellow to identify a novel metabolic target led to a publication detailing a molecule that could target the metabolic pathway to reduce seizures in a zebrafish model of Dravet syndrome (Banerji et al, Brain Communications 2021).
- In 2021 DSF funded the same laboratory that did the zebrafish work above as part of a collaborative project with an expert clinician to further investigate metabolic disruptions in cells from patients with Dravet syndrome. This project will additionally create a new bioresource of patient-derived cell lines.

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RESEARCH STRATEGY (continued)

- DSF funded a group to investigate the molecular mechanisms of the ketogenic diet and metabolic disruption in a mouse model of Dravet syndrome using novel imaging techniques to understand the impacts of the ketogenic diet on the brain.
- DSF funded and helped to lead an International Diagnosis and Treatment Consensus Project that was published in 2022 and outlined expert consensus on the presentation and priority treatment choices for Dravet syndrome that can help guide the clinical management of patients.

(3) **Learn:** While tremendous progress toward better treatments and curing the underlying cause has occurred since 2018, there is undoubtedly still much to learn about Dravet syndrome and the manifestation of disease in human patients. DSF has awarded grants and supported research to better characterize understudied areas.

- A DSF-funded study of gait and movement issues in adult patients with Dravet syndrome was published in 2022 with some of the first longitudinal data on these issues to-date (Selvarajah et al, Neurology 2022). DSF continues to support the efforts of this line of research, including raising awareness of participation opportunities in a Natural History Study of adult patients with Dravet syndrome conducted by the same research group.
- DSF helped to raise awareness and provide continued support to Natural History Studies of Dravet syndrome sponsored by Encoded Therapeutics (ENVISION) and Stoke Therapeutics (BUTTERFLY), and initial data from these studies has been presented at scientific conferences. Encoded also published their ENGAGE study that gathered information from caregivers on their perspectives, needs, and particularly as they pertain to outcomes of clinical research, a study for which DSF advised and helped to recruit participants.
- DSF provided funding for an academic-led Natural History Study that will begin in the second half of 2022 in the UK. This study will provide unprecedented detail on the progression of symptoms and comorbidities in Dravet syndrome as well as provide a model for the implementation of broader Natural History Studies.
- DSF increased funding for postdoctoral fellowship awards to $75K/year to further support and encourage early-career scientists to focus on research relevant to Dravet syndrome.



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RESEARCH STRATEGY (continued)

SHORT-TERM GOALS (1-2 years)

(1) Cure	(2) Treat	(3) Learn
Discover the effects of therapeutically increasing SCN1A expression on symptoms and disease course	Establish a Clinical Research Award	Support organoid and other models of Dravet syndrome
Determine whether targeting specific interneurons is necessary	Work towards establishing an ICD-10 code specific to Dravet syndrome	Explore mechanisms related to SUDEP, including breathing
If necessary, investigate mechanisms for specifically targeting interneurons to increase SCN1A expression	Prepare the patient community for involvement in research	Identify and describe the natural history for Dravet syndrome
Investigate viruses with interneuron-specific promoters	Identify and describe the natural history of Dravet syndrome against which new treatments can be measured	Continue research on the mechanisms of Dravet syndrome and identification of potential pathways for treatment

LONG-TERM GOALS (3-5 years)

(1) Cure	(2) Treat	(3) Learn
Target SCN1A upregulation to interneurons	Identify the best interventions for seizures and comorbidities	Support researchers as they explore new models
Explore other mechanisms of increasing expression	Support clinical studies through research grants and patient engagement	Examine new imaging techniques to assess network dysfunction at the cellular level
Investigate gene therapy techniques that may prove useful in future Dravet syndrome studies		

Not Started
In Progress
Significant Progress/ Complete

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Overall Progress on Research within the Strategic Plan 2018-2022

In the early years following the establishment of DSF, our greatest impact was in stimulating the outset of research efforts into understanding and treating Dravet syndrome (DS). In 2022, DSF's impacts extend beyond stimulation, now supporting projects that delve into deeper understanding and that are leading to better treatments in the clinic. Nearly every tangible measure of the field of DS-related research has increased. The DSF Research Roundtable went from a small gathering of 30 to a consistent audience of over 150. Despite being a rare disease, presentations on DS abound at scientific and medical conferences. In the first years following the genetic discovery associating SCN1A mutations with DS, research was growing, but publications still averaged at only about 30 scientific papers each year by 2009. Following the establishment of DSF, publication numbers grew extensively averaging over 100 publications each year from 2010 to 2017. In the years since the establishment of the strategic plan, publications rates continued to increase to over 220 publications each year. While slow to pick up in the early 2000s, NIH-level funding for DS averaged over $10M each year since 2014. There are now three FDA-approved medications specifically for DS and 13 active clinical trials in the US studying investigational medications and characterizing the disease course of patients. DSF has acted as a hub for research advancements, serving as a liaison between pharmaceutical and biotechnology companies, health care providers, scientists, governmental agencies, and the patient community; encouraging collaborations, providing seed funding for promising research, advocating for patient-family needs and priorities, raising awareness, and creating an overarching roadmap to reach meaningful outcomes.

DSF's grant funding mechanisms have continued to make a major impact. As of September 2022, DSF has directed over $5.7M to support 51 research grants. Researchers funded by DSF have subsequently secured over $23M in NIH-level grants for DS-related projects. Of the grants funded by DSF, 71% resulted in publications related to the project (49 publications acknowledged as directly supported or focused on closely related topics). DSF continues to expand our grant funding, adding two grant mechanisms to specifically support clinical research efforts and in 2019 announcing a special call for grants developing genetic therapies to target SCN1A. Recognizing the need to invest early and train leaders in the field, DSF directed $545K since 2013 to fund 13 postdoctoral fellows. Of those 13 fellows, four have moved into professorial positions facilitating research on DS-related projects and/or treating patients with DS in their clinical practice; six are still in active research fellowships relevant to DS and related epilepsies; and three are in biotechnology or scientific support roles. Notably, two of the prior fellows secured additional $1.1M in NIH-level funding for DS-related projects. Since 2018, DSF has added additional grant mechanisms to encourage and support clinical trainees to enter research and increased our funding levels to better support postdoctoral fellowships.

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A great deal of progress on the goals within the Strategic Plan's research priorities has occurred since 2018.

1. Cure: DSF has now directed over $1.1M to projects that could lead to disease modifying therapies. Experiments revealed the interneuron populations most impactful for targeting via genetic therapies and exemplified proof-of-concept successes in mouse models of DS. Many approaches to overcoming SCN1A-haploinsufficiency are in development including focuses on alternative delivery approaches, regulation of the gene, regulation of RNA, and targeting compensatory genes. One RNA-based approach from Stoke Therapeutics began clinical trials in 2020, with initial positive readouts regarding seizure reductions in 2021. Encoded Therapeutics plans to bring a one-time AAV-based approach to clinical trials by the end of 2022. Several other biotechnology companies are developing pipeline gene therapy products for DS.

2. Treat: DSF expanded funding for clinical related projects and to support early-career clinical investigators. In 2021, the ICD-10 code for DS was implemented. The patient community is not only prepared, but has successfully participated in many research and clinical trial efforts. DSF continues to support research efforts through education of the patient-community, raising awareness of opportunities to participate, funding appropriate research grants and efforts, and providing critical input on research plans from the patient perspective. Representatives from DSF have been included in authorship on 14 scientific publications, often raising awareness of unmet clinical needs within the patient community including better treatments. In 2022, DSF held an Externally-led Patient Focused Drug Development meeting and developed the Voice of the Patient Report to ensure officials at the FDA understand and incorporate the patient voice regarding treatment needs into future regulatory decisions. DSF has funded research into comorbidities as well as advocated for research in understudied areas such as behavior, gait, and sleep. DSF has supported the development and enrollment in two industry-led Natural History Studies and provided funding for an academic-led Natural History Study in the UK. Following the approval of three new anti-seizure medications, DSF helped to fund and lead a new expert consensus study incorporating the new therapies into the treatment consensus. Diagnoses are happening earlier, and in the context of new medications with clear expert treatment guidelines, the clinical care and outlook for patients with DS is steadily improving.

3. Learn: The goals under this category are still in progress. DSF has continued to support researchers exploring questions across a variety of models including mice, zebrafish, and cells to understand the mechanisms of disease and create a foundation for development of improved treatments. DSF has funded research to establish new types of patient cell models and is seeking additional avenues to further expand the available bioresources for DS research. Since 2018, DSF has directed an additional $315K to basic science and clinical efforts to understand SUDEP. Finally, DSF has funded several labs to better understand neuronal networks, including novel imaging techniques in the clinical setting. Basic research has also advanced in this area, elucidating more about the neuronal populations and the developmental impacts on dysfunction.