

Fighting for Their Lives: The Battle of the BPAN Warriors



by Mark Kiel and Lauren Chunn

Sarah Chisholm didn't want to start a rare disease foundation – she had to.

Her life changed forever when her daughter Eva was diagnosed with beta-propeller protein-associated neurodegeneration, or BPAN, a rare genetic condition caused by mutations in the *WDR45* gene.

Despite her initial shock and grief, 10 months after Eva's diagnosis, Sarah launched BPANWarriors.org, determined to provide a voice for the BPAN community.

Sarah's rare disease story is more common than you might believe.

BPAN Warriors has become a conduit for connection in the BPAN community, emphasizing, *"You are not alone."* Sarah and BPAN Warriors are fighting daily to bring their story before key industry stakeholders. To researchers and biotech and pharmaceutical executives focused on diseases with large patient populations that drive profits, she exhorts – *"We exist too."*

The Cumulatively Common Prevalence of Rare Diseases

Beta-propeller protein-associated neurodegeneration, or BPAN, is a rare genetic condition caused by mutations in the *WDR45* gene. Seizures and complex epileptic encephalopathies and developmental delays are often the first symptoms to present in infancy. As the children enter late adolescence, they progressively lose cognitive abilities and muscle function, and experience neurodegenerative symptoms similar to those found in Parkinson's Disease.

Since the discovery of *WDR45* mutations in 2012, diagnosing BPAN patients remains challenging.¹ Treatment options have been limited to symptom management and palliative care. Worldwide, there are about 500 patients with BPAN and an estimated 2,500-7,500 patients having sister diseases with similar iron deposition in the brain.

Spotting rare diseases remains a persistent challenge. According to a 2010 report from Rare Disease UK, 20% of their patients waited over 5 years and 10% waited over 10 years to receive a diagnosis.¹ Perhaps worse, close to half of their rare disease patients received an incorrect diagnosis initially, and almost a third received more than 3 incorrect diagnoses. This raises huge concerns, as an accurate diagnosis is crucial to receiving proper care.

Pharma's Rare Disease Dilemma

Beyond the diagnostic challenge, most rare disease patients in the United States have few options for treatment, and those that do often face high costs and frequent rejection by health insurers.² According to Global Genes, a rare disease advocacy group, 95% of all rare diseases lack a designated, FDA approved, therapy.³ The lack of therapeutic options is primarily due to a dilemma that pharmaceutical companies have always faced – how to recoup investment costs when the patient population that could be served by the medication is prohibitively small.

In recent years, increased interest in developing therapeutics for rare diseases (known as orphan drugs) has come from a cohort of small, medium, and biotechnology pharmaceutical companies (SMBs). This interest is driven by the Orphan Drug Act (ODA) of 1983; the ODA provides incentives such as market exclusivity to pharmaceutical companies who develop therapies for rare disease indications.⁴ Since 1983, the FDA has approved over 600 orphan drug therapies (see current List of FDA Orphan Drugs at <https://rarediseases.info.nih.gov/diseases/fda-orphan-drugs>); in comparison,

fewer than 10 drugs were approved in the 10 years prior to the ODA.⁵ This substantial growth appears to be a sustained trend.

Current State of Pharma's Role in Rare Diseases

Big pharma's interest in rare diseases often takes the form of investment in opportunities at SMBs, either by support in later stages of trials or licensing with intent of evaluating all possible novel drug indications. In particular, pharma is looking for innovative medicines, formulations and applications; orphan drugs may create those opportunities.

A 2018 report released by EvaluatePharma indicates that by 2024, orphan drugs will capture a fifth of worldwide prescription drug sales, equivalent to \$262 billion.⁶ Sales of these drugs are set to grow by 11% each year between now and 2024, contrasted with only 6.4% for the rest of the pharmaceutical market.^{7,8} Overall, the development of orphan drugs appears to be an economically viable strategy for these companies, as the effect of a smaller patient population is offset by higher pricing, increased market share, longer market exclusivity, and a faster uptake rate as a result of high unmet medical need in these populations.⁹ In fact, R&D costs for orphan drugs have been shown to be nearly half that of non-orphan drugs.¹⁰

Genomenon's Mastermind provides immediate insight into the published genomic research for every disease and DNA mutation found in the medical literature. Genetic evidence is readily accessible through a search interface, where results are prioritized to highlight the most clinically relevant information. Mastermind is used by hundreds of genetic labs around the world to assure comprehensive genomic interpretation, and by pharmaceutical companies to understand the genomics associated with any disease.

Despite this encouraging increase in orphan drug development, high prices remain a substantial problem for rare disease patients. EvaluatePharma indicated that the median cost of orphan drugs was about \$147,000 per patient per year in 2017, compared to \$30,708 for non-orphan drugs.¹¹ Newer therapeutic options such as gene therapies come with a much higher price tag.

Ensuring that therapeutics for rare diseases are accessible is an urgent matter for patients. Novartis' drug for SMA – Zolgensma – has the potential to cure children who would normally not live past 2 years of age, but

For doctors in training, there is a strange allure for rarity. So common is a medical student's tendency to gravitate to the exotic before the everyday that medical educators suppress this urge with the aphorism, "When you hear hoofbeats in the night, look for horses, not zebras". In other words, what is common occurs commonly, and thus the more likely explanation is often the correct one. This is perfectly practical advice, so eventually the opposite tendency sets in and rare disease is left behind. However, with an invigorated interest in personalized medicine and a better appreciation of the aggregate frequency of rare disease, we might modify this aphorism to say, "Look first for horses, but be sure to spot the zebras".

whether patients' families can afford it at the cost of a cost of \$2.1 million per treatment is dubious.^{12,13} Concerns regarding the accessibility and affordability of this therapy have largely overshadowed the initial excitement over its life-saving capabilities for those affected by SMA.¹⁴

Reducing R&D Costs: The Role of Patient Advocacy

Struggling to access therapies in time to improve or save the lives of children affected by rare conditions is not uncommon. In fact, one-third of children with rare disease will not live to see their fifth birthday.¹⁵ This has prompted the formation of a large number of patient advocacy groups, covering approximately half of all rare diseases. Typically, these groups are composed of parents without scientific or medical backgrounds who dedicate a large portion of their lives to raising awareness and gathering funding for research initiatives, hoping that their children will have a chance at a normal life. For many patients and their families, these communities are their main, if not the only, source of information and support.¹⁶

One of the main goals of rare disease foundations and patient advocacy groups is disseminating accurate and actionable information about the rare disease to physicians, researchers, and patients. In order to ensure accurate and timely diagnosis and develop effective therapies, an exhaustive search of the medical literature must be conducted to understand the genomic landscape and clinical impact of the disease. With over 30 million medical publications, over 7 million of which contain genetic information, the task of finding and assembling a genomic database on a rare disease can be overwhelming. In her efforts to understand her daughter's disease and generate interest from research groups, Sarah Chisholm encountered this very problem. ▶

BPAN Warriors Take a New Approach

Early on a Sunday morning, team members at Genomenon noticed that Sarah had signed up for the Mastermind Genomic Search Engine. Intrigued, they reached out to her to learn more about what she sought.

Her search for help and answers deeply affected a number of Genomenon's team members, who were motivated to help. Within a day's time, the genetic curators at Genomenon produced an annotated database of 94 unique variants (genetic mutations) in the WDR45 gene linked to BPAN. The database was annotated according to the guidelines for variant interpretation provided by the American College of Medical Genetics and Genomics (ACMG), which helps determine a variant's role in causing disease.

Fulfilling these categories requires several types of evidence: population data (i.e. how rare the variant is in the healthy population), computational data (i.e. whether the variant is predicted to be disease-causing), and most importantly, literature evidence (i.e. detailed

In the United States, a rare disease is defined as one that affects fewer than 200,000 people. It is estimated that 25-30 million Americans have one or more of approximately 7,000 rare diseases. This amounts to nearly 1 in 10 individuals in the United States, or 350 million worldwide.¹⁸ Thus, while it may be uncommon to have a *specific* rare disease, having a rare disease *in general* is not quite so rare.¹⁹

not only in the diagnosis of patients with rare diseases but also in facilitating the development of therapeutics by aggregating and interpreting genetic evidence from the medical literature. The organization and annotation of this evidence can improve diagnostic rates, shorten drug development cycles, reduce R&D costs, and help incentivize pharmaceutical companies to pursue the research in the first place.

Genomenon has been so inspired by Sarah's story and the potential to make a difference in these parents' quest that they announced a partnership with the BPAN Warriors to make the comprehensive genomic landscape freely

"I believe that we can make great strides in research and treatment if we learn how to more efficiently navigate the complexities of genetics and drug discovery. My sense of urgency and motivation is completely selfish – I want to save my daughter or in the least, measurably improve the quality of her life. I will not be dissuaded from this path. As a parent and patient advocate, I walk this path with every parent who is on this rare disease journey."

Sarah Chisholm, Founder, BPAN Warriors

clinical information and studies describing the functional consequence of the variant). The database integrated all of these forms of evidence and provided a comprehensive overview of the genetic and clinical landscape for BPAN.

The new database identified a functional study describing a potential avenue for the development of therapies for BPAN, which initiated a conversation with Sarah regarding a number of additional strategies to help her in her effort to gain the attention of pharmaceutical companies.¹⁷

Genomenon Partners with BPAN Warriors to Make BPAN Database Open to All

Genomenon's team is passionate about helping rare disease foundations like the BPAN Warriors. Mastermind can assist

available to any pharmaceutical company or researcher interested in exploring the data. The availability of this data will not only help researchers better understand this rare disease, but will provide a solid foundation for pharmaceutical companies to begin the search for a cure with a resource that would otherwise take years to assemble.

While there is still a tremendous amount of work ahead for advocacy groups like BPAN Warriors, Genomenon's comprehensive genomic landscape has cut years from the search for a cure by providing the genetic details of BPAN for researchers to better understand the molecular drivers of the disease. Armed with this information, the BPAN Warriors are now fully prepared for their journey towards a cure.

It is through *information* that we can empower rare disease advocates like Sarah, who dedicate their lives to finding a treatment. 

To view the list of variants tied to BPAN and request access to the genomic landscape, go to www.genomenon.com/bpan-warriors



Mark Kiel, MD, PhD. Mark completed his MD PhD and Molecular Genetic Pathology Fellowship at the University of Michigan, where his research focused on stem cell biology, genomic profiling of hematopoietic malignancies, and clinical bioinformatics. Mark's passion is to power the practice of precision medicine by organizing the world's genomic knowledge. He is the founder and Chief Science Officer of Genomenon, where he supervises the scientific direction of the Mastermind suite of software tools.



Lauren Chunn is a data analyst and bioinformatician for Genomenon, where she works on increasing the speed and accuracy of variant interpretation. She holds a bachelor's of science degree in cell and molecular biology and philosophy from Grand Valley State University, where her focus was on bioethics, culminating with an internship in clinical ethics at Spectrum Health Hospitals and a research project concerning whether the genome should be considered private property. She is also a passionate advocate for rare disease awareness.

References

- Experiences of Rare Diseases: An Insight from Patients and Families, Rare Disease UK report @ <https://www.rare-disease.org.uk/media/1594/rduk-family-report.pdf>
- Why health insurers won't cover this \$300,000-a-year rare disease drug, Market Watch news Patient Advocates Warn Against New Insurance & PBM Policy That Increases Patient Out-of-Pocket Drug Costs, National Organization for Rare Disorders (NORD) news @ <https://www.marketwatch.com/story/why-health-insurers-wont-cover-this-300000-a-year-rare-disease-drug-2016-12-29> <https://rare-diseases.org/patient-advocates-warn-against-new-insurance-pbm-policy-increases-out-of-pocket-drug-costs/>
- Rare disease facts and statistics, global genes website @ <https://globalgenes.org/rare-facts/>
- Meetings et al. "Orphan Drug Development: an economically viable strategy for biopharma R&D." Drug Discovery Today vol. 17, 13-14 (2012): 660-664.
- Developing Products for Rare Diseases & Conditions, FDA Website @ <https://www.fda.gov/industry/developing-products-rare-diseases-conditions>
- World Preview 2018, Outlook to 2024 for Pharmaceutical Sales, EvaluatePharma report @ <https://www.evaluate.com/thought-leadership/pharma/evaluate-pharma-world-preview-2018-outlook-2024>
- Ibid.
- Miller, Kathleen L. "Do investors value the FDA orphan drug designation?" Orphanet Journal of Rare Diseases vol. 12, 114 (2017).
- Meekings et al. "Orphan Drug Development: an economically viable strategy for biopharma R&D." Drug Discovery Today vol. 17, 13-14 (2012): 660-664.
- Jayasundara et al. "Estimating the clinical cost of drug development for orphan versus non-orphan drugs." Orphanet Journal of Rare Diseases vol. 14, 12 (2019).
- World Preview 2018, Outlook to 2024 for Pharmaceutical Sales, EvaluatePharma report @ <https://www.evaluate.com/thought-leadership/pharma/evaluate-pharma-world-preview-2018-outlook-2024>
- At Over \$2 Million Zolgensma Is The World's Most Expensive Therapy, Yet Relatively Cost-Effective, Forbes news @ <https://www.forbes.com/sites/joshuacohen/2019/06/05/at-over-2-million-zolgensma-is-the-worlds-most-expensive-therapy-yet-relatively-cost-effective/#2e4dd3d45f5>
- About Spinal Muscular Atrophy, SMA foundation website @ <http://www.smafoundation.org/about-sma/>
- I have spinal muscular atrophy. Critics of the \$2 million new gene therapy are missing the point, STAT news opinion @ <https://www.statnews.com/2019/05/31/spinal-muscular-atrophy-zolgensma-price-critics/>
- Rare disease facts and statistics, global genes website @ <https://globalgenes.org/rare-facts/>
- Experiences of Rare Diseases: An Insight from Patients and Families, Rare Disease UK report @ <https://www.rare-disease.org.uk/media/1594/rduk-family-report.pdf>
- Rare Genomics Institute Uses Genomenon's Mastermind to Diagnose Patient, clinicalomics website @ <https://www.clinicalomics.com/topics/informatics-topic/bioinformatics/rare-genomics-institute-uses-genomenon-mastermind-to-diagnose-patient/>
- Facts about rare diseases, NIH Genetic and Rare Diseases Information Center (GARD) website @ <https://rare-diseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases>
- Danese, Elisa, and Giuseppe Lippi. "Rare diseases: the paradox of an emerging challenge." Annals of translational medicine vol. 6, 17 (2018): 329.

A Special Thankyou

A special thank you to Sarah Chisholm for letting us tell her story and to Lauren Chunn at Genomenon for leading the Genomenon team in building the BPAN database as well as co-authoring this article.