EXPERT OPINION

Cystinosis research network – a patient advocacy group

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Our son was diagnosed with a rare chronic metabolic disorder at the age of 5. The frustration and sense of powerlessness was overwhelming at times. After an endless number of physician appointments, tests, consultations, and the like, we finally had a diagnosis. Our son was afflicted with cystinosis. Cystinosis is a rare, autosomal recessive genetic disease that attacks the body at a cellular level and leads to kidney failure, muscle wasting, diabetes, gastrointestinal challenges, hypothyroidism and premature death. The amino acid cystine accumulates in the lysosome of the cell and forms cystine crystals that invariably compromise every organ of the body and result in premature death. Despite the somberness of the diagnosis, there was cause for celebration as we finally knew what we had to contend with. Regardless, it would be untruthful to claim that we felt capable of coping with all of the complexities associated with said diagnosis. How do you contend with the fact that your child has a chronic disease he will need to manage his entire life? Where do you go for answers for a disease that is so rare that even by the National Institutes of Health's (NIH's) definition of rare diseases (disorders with < 200,000 confirmed patients) is rarer still? Cystinosis has ~ 2000 diagnosed patients around the world. What hope is there for the discovery of a cure for a disorder that has such a small number of benefactors and very little potential for commercial value to the pharmaceutical industry? Where do we go from here?

Armed with our diagnosis and a multitude of questions, we began our journey initially focusing on learning how to assist our son in living a full and thriving life. This was followed by a focus on identifying a means to advocate for the discovery of improved treatments and a cure for the disorder. There are a myriad of courses of action one can take but one of the most powerful is engaging with a patient advocacy organization. The organization we aligned ourselves with is the Cystinosis Research Network (CRN). The CRN is a nonprofit organization with a vision and mission that strongly resonated with our family:

- Vision – The discovery of improved treatments and a cure for cystinosis
- Mission – Dedicated to supporting and advocating research, providing family assistance and educating the public and medical communities about cystinosis

As with most special interest, grassroots organizations, CRN has evolved from the initial days of its creation. Its scope and priorities has continued to increase as its capabilities to enable and promote research has increased. One of the areas in which CRN has had made significant contributions is in assisting pharmaceutical companies in their efforts to secure US Food and Drug Administration (FDA) approvals. Securing FDA approval is an expensive proposition. It takes an average of 12 years and over US$350 million to get a new drug from the laboratory onto the pharmacy shelf. Once a company develops a promising drug, it undergoes approximately three-and-a-half years of laboratory testing before an application is made to the

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FDA to begin testing the drug in humans. Only one in 1000 of the compounds that enter laboratory testing ever make it to human testing.

If the FDA gives the green light, the 'investigative' drug will then enter three phases of clinical trials:

- Phase I: 20 – 80 healthy volunteers to establish a drug's safety and profile (about 1 year)
- Phase II: 100 – 300 patient volunteers to assess the drug's effectiveness (about 2 years)
- Phase III: 1000 – 3000 patients in clinics and hospitals who are carefully monitored to determine effectiveness and identify adverse reactions (about 3 years)

The company then submits an application (usually about 100000 pages) to the FDA for approval – a process that can take up to two-and-a-half years. After final approval, the drug becomes available for physicians to prescribe. At this stage, the drug company will continue to report cases of adverse reactions and other clinical data to the FDA. The research-based pharmaceutical industry currently invests an estimated US$50 billion a year in new drug development. Historically, the drug development figure doubles every 5 years [1].

The aforementioned process is for those drugs where a viable business case can be made to justify the investment of significant amount of money. In today's world, patient advocacy groups are taking on an increasingly significant role by providing significant sums of funding. According to data from Thomson CenterWatch, 'funding by patient advocacy groups has increased 13-fold over the level in 2000. For example, the Cystic Fibrosis Foundation of Bethesda, Maryland, has awarded biotech companies more than $300 million over the past 10 years'. The patient advocacy groups focusing on rare disorders make equally as impressive contributions relative to the targeted constituencies. Therein lies the challenge for organizations focused on rare disorders. How does one justify the investments necessary for the development of drugs that have a small number of potential consumers? As one can imagine, a significant challenge for the community of rare diseases is that the number of potential consumers is limited. As such, any funding and means of reducing the associated costs for the respective pharmaceuticals is meaningful. CRN contributions are varied but one of the most tangible is its ability to quickly identify candidate pools that meet the clinical trial specifications. The ability to accurately identify trial participants cannot be overemphasized, as outcomes, effects and conclusions are based on having qualified participants.

The following are three discreet pharmaceutical trials that CRN has contributed to:

- 1994 – Mylan Pharmaceuticals. As the organization was still in its infancy, patients participated in trials at the NIH in the 1980s which lead to the eventual approval of cysteamine bitartrate (Cystagon®) by Mylan for the treatment of cystinosis.
- 2012 – Raptor Pharmaceuticals. In June 2012, Raptor's new drug application for RP103, cysteamine bitartrate delayed-release capsules (DR Cysteamine) for the potential treatment of nephropathic cystinosis was accepted by the US FDA. Raptor received FDA approval for RP103 (Procysbi) on April 30, 2013. Raptor received validation of its marketing authorization application from the European Medicines Agency (EMA) for RP103 for the potential treatment of nephropathic cystinosis. Raptor anticipates a decision from EMA in the second half of 2013.
- 2012 – Sigma Tau Pharmaceuticals. In October 2012, the FDA approved CYSTARAN™ (cysteamine ophthalmic solution) 0.44% for the treatment of corneal cystine crystal accumulation in cystinosis patients. Sigma Tau took over development of Cystaran from initial trials conducted at the NIH over the past 20 years.

Additionally, CRN collaborates with international pharmaceutical companies such as Orphan Europe to work toward providing treatments to patients on a worldwide basis. CRN has made significant contributions in collaborating with these pharmaceutical companies and the NIH in their efforts to secure FDA-approved drug treatments for cystinosis.

Another critical area that CRN expends significant resources toward is promoting collaboration with international research and professional organizations. The importance of sharing information and coordinating research efforts cannot be overemphasized. For example, CRN is currently sponsoring joint investigative research with Cystinosis Foundation Ireland which is focused on the study of skin changes in cystinosis patients under cysteamine therapy. Additionally, CRN has an extensive array of relationships with other nonprofit organizations focused on cystinosis:

- Association for Information and Research on Genetic Renal Diseases (AIRG France)
- Egyptian Group for Orphan Renal Diseases
- Cystinosis Australia
- Cystinosis Group Netherlands
- Cystinosis Foundation Germany
- Cystinosis Foundation Ireland
- Cystinosis Foundation Italy
- Cystinosis Foundation United Kingdom
- Cystinosis Foundation United States
- Cystinosis Mexico AC
- Cystinosis Research Foundation
- Cystinosis South Africa

CRN has been very proactive in its efforts in establishing relationships both nationally and internationally. On the national level, CRN is aligned with the National Organization for Rare Disorders (NORD). NORD is a federation of voluntary health organizations dedicated in helping people

with rare 'orphan' diseases and committed to the identification, treatment and cure of rare disorders through programs of education, advocacy, research and service [2]. The saying 'there is strength in numbers' is most appropriate and the need to have a collective voice cannot be overemphasized.

Attending and displaying at professional conferences to heighten awareness among medical professionals is one of the differentiators of the organization. CRN believes that the number of confirmed, diagnosed individuals with cystinosis is directly related to the medical profession's awareness of this rare disorder. As such, CRN exhibits and sponsors symposia on cystinosis at medical conferences sponsored by the following professional organizations:

- American Society of Nephrology [3]
- American Society of Pediatric Nephrology [4]
- International Pediatric Nephrology Association [5]
- Latin American Pediatric Nephrology Association [6]

As a parent, one must take an active role in securing treatment and advocating for their children. Once the mist rises and you begin to see a path forward, become engaged with the broader issues that need to be addressed. Find or create a nonprofit organization that will multiply the results of your efforts and take action. You will find a world filled with people and organizations willing to assist and collaborate with you.

Declaration of interest

The author states no conflict of interest and has received no payment in preparation of this manuscript.

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