Patients as Partners in Rare Disease Diagnosis and Research

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There is great value in understanding the patient perspective in rare disease diagnosis and research, and in partnering actively with patients and their families throughout the process. Meaningful and respectful interaction between patients and researchers leads to learning on both sides, and ultimately, to better research outcomes. Researchers can help patients understand how research is conducted and what the latest advances and perceived gaps in research are, and patients, who have direct experience living with their health conditions, can impart to researchers what is most important to them. We describe our engagement with patients in the Undiagnosed Diseases Network (UDN) program, as well as the lessons we have learned to date. In the UDN, patients have been instrumental in bringing meaning to the work of clinicians and researchers, building patient communities, making the network aware of unmet patient needs, advocating for additional research funding, and disseminating UDN research findings. Although patient engagement in the UDN has already had a significant positive impact on our work, we continue to strive to involve patients earlier in the process, in the research design itself, and in addressing power dynamics that may arise between clinicians, researchers, and patients.

INTRODUCTION

We believe that there is significant value in partnering with patients in clinical research in order to better understand the patient perspective and to ensure that research addresses patient needs[1]. In the case of rare disease diagnosis and research, the patient perspective is paramount. Extremely rare or undiagnosed conditions are not well understood by many clinicians. As a result, patients have, of necessity, become experts in their conditions. Primary care physicians often refer these patients to specialists, who, in turn, may refer them to additional specialists. For each of these encounters, patients must be prepared to explain the course of their condition, the tests that have been administered, and their understanding of the findings of each of the specialists to date. In our view, when these patient experts engage with researchers, they have much to offer.

Patient engagement in research can take different forms and involve varying levels of participation. For example, in the late 1990s, the then National Institutes of Health (NIH) Director, Harold Varmus, established

the Council of Public Representatives (COPR) to advise him on enhancing public participation in NIH activities. The 1998 report of the Institute of Medicine had, in fact, specifically recommended such a group for the purpose of helping NIH set its research priorities as part of a "two-way exchange of information" [1]. COPR appears to have existed for more than a decade [2] and was judged by some of its participants to be not as effective as it could be, noting that NIH did not fully utilize or value the group. As one member said, "COPR was an audience, not a participant [3]." A survey of patients and caregivers who participated as "active partners" in studies supported by the British National Health Service found that patients were primarily motivated by an altruistic desire to improve healthcare and health research. While many felt glad to have been given the chance to participate, they were disappointed when they were "underused" and not necessarily recognized for their expertise [4]. Other studies note that initiatives to involve patients are often "tokenistic" (ie, a "false appearance of inclusiveness") [5-7]. An example where patient expertise was recognized was reported by a Dutch health advisory group that found that when they solicited advice from patients for a specific medical research agenda, the patients' experiential knowledge was well acknowledged and contributed to the "high visibility" of the patients' perspectives in the final advice given [8].

When and how consistently patients are involved throughout the course of a research project can determine the impact they are able to have. For example, patients might participate at the proposal design and preparation stage; during the conduct of the research itself; or once the project is complete, especially in the dissemination phase [9,10]. Levels of engagement can also be described on a continuum, increasing from 1) some engagement, for example, where patients are invited to research meetings, but don't actively participate, or patients provide input to researchers through surveys or focus groups; to 2) a greater level of engagement, where researchers solicit advice from patients and their contributions are publicly acknowledged; to 3) the highest level of engagement, where patients are true collaborators who are compensated for their efforts, share leadership and have decision-making power, and, perhaps, even fund or advocate for further funding [11,12].

We agree with others who suggest that meaningful and respectful interaction between patients and researchers leads to learning on both sides, and ultimately, to better research outcomes. Researchers can help patients understand how research is conducted and what are the latest advances and perceived gaps in research, and patients, who have direct experience living with their health conditions, can impart to researchers what is most important to them. These interactions allow for the possibility

that research can be made more relevant for patients and may also have the potential to influence future research directions [13-15]. The effectiveness of patient engagement in research depends on many factors, including, importantly, whether the organization is fully committed to involving patients as partners in research and, if so, whether they are provided with the appropriate training, resources, and support to be successful [16].

In the following, we describe our engagement with patients in the Undiagnosed Diseases Network (UDN) program. We briefly describe the UDN, the several ways in which patients have engaged with the UDN, and the lessons we have learned to date, including areas for improvement. We conclude with a discussion of the value and benefits of the patient-researcher partnership for rare disease diagnosis and research.

THE UNDIAGNOSED DISEASES NETWORK

For patients with undiagnosed conditions, uncovering answers related to the cause of disease can involve years of significant and costly medical evaluation and intervention [17]. The UDN, a large multi-disciplinary national network, was established by the NIH with the dual objective of finding diagnoses for patients, many of whom have exhausted all other avenues in their quest to find an answer, and gaining insight into the pathophysiology of disease, thereby advancing the science of biomedicine [18-22].

Prospective UDN patients apply directly through the UDN website and are asked to provide a referral letter from a health care provider [23]. Applicants are also invited to provide a brief narrative describing their condition with accompanying photos if they desire. This allows UDN investigators to get a valuable and early understanding of the condition from the patient's perspective. Interest in the UDN is high, with some 40% of applicants being accepted into the study [24]. Applicants with objective findings, rather than with primarily subjective findings, are more likely to be accepted as they are more likely to benefit from further diagnostic processes [25].

UDN methods involve multiple experts working collaboratively to evaluate and diagnose patients. The exceptional resources of the network, which include a coordinating center, 12 clinical sites, four research cores, and an extremely active patient engagement group, have enabled its successes and have facilitated diagnosis for more than one-third of the patients who have enrolled in the study [24].

PATIENT ENGAGEMENT IN THE UNDIAGNOSED DISEASES NETWORK

PEER Patient Engagement Group

Shortly after the UDN began seeing patients in the fall of 2015, we at the UDN coordinating center (CC) proposed forming a patient engagement group, members of which would be drawn from patients who had undergone a UDN evaluation. UDN investigators were enthusiastic about this proposal, and the clinical sites were quick to propose candidates for initial membership in the group. With the support of the coordinating center staff, and after a series of introductory meetings, the group coalesced. The members decided to name themselves "PEER" (for Participant Engagement and Empowerment Resource), and they developed a mission statement and charter[2]. The mission statement reads:

"The purpose of the UDN PEER is to support participants and family members in part by creating and sharing resources, and to provide the participant and family perspective on UDN research goals and participant experience. The PEER provides a "post-UDN visit voice." Their goal is to advocate for participants, improve participant experience, "get the word out" about the UDN, and facilitate interactions between participants and the UDN [26]."

The PEER is self-governing and continues to operate with the support of the coordinating center, whose role is made explicit in the charter: "The role of the UDN CC is to facilitate and provide the infrastructure to support the leader(s) and the PEER, and to serve as a liaison to the UDN Steering Committee." Membership is on a rotating basis and members nominate, agree on, and elect co-chairs on an annual basis, with renewal possible.

The group has become increasingly active since its inception. It connects the UDN patient community through social media (Facebook, Twitter, and Instagram) and through in-person or virtual meetings. PEER also serves as a resource for the broader undiagnosed and rare diseases community through its dissemination activities, which include the publication of a quarterly newsletter that features news about innovative UDN research as well as stories about UDN families. The group recently launched a public "Tell Me More" lecture series, featuring notable speakers who present the results of high impact research [27].

On a regular basis, PEER members provide input to UDN investigators through attendance and participation at research meetings, designing and responding to surveys, and making researchers aware of unmet participant needs. As the UDN explores numerous pathways for sustainability, PEER members have joined as valuable members of the sustainability working group and are engaged in advocacy initiatives at the national level. Their input has been crucial in discussions about the future of the UDN and how the network will operate in the years to come.

Partnering for Case Matching

Identifying individuals with similar phenotypic and genomic profiles allows researchers to associate genes with diseases with a greater degree of certainty, often the rate limiting step for rare disease diagnosis. Existing research applications, such as Matchmaker Exchange, facilitate such matching for rare and undiagnosed conditions [28,29]. These efforts are generally limited by their restricted set of users, typically clinicians, researchers, and laboratories. GeneMatcher, a component of Matchmaker Exchange, does give patients the opportunity to share their data and to connect with interested researchers directly, and reportedly several hundred patients have done so [30], and MyGene2 is a patient portal that allows families to contact others who have the same condition or mutations in the same gene [31]. Additional innovative methods for patients to partner directly with researchers through case matching have the potential to significantly accelerate the scientific discovery process.

Some UDN patients already collaborate with UDN scientists and clinicians in a web-based project to facilitate case matching [32]. The project was designed together with a former UDN patient advisor who subsequently joined the project as a collaborating investigator. In 2012, a blog post describing his son's diagnosis of NGLY1 deficiency resulted in the identification of others who had been diagnosed with the same condition. Since then, many clinicians and patients have come across the post and website, facilitating diagnoses for these patients, and resulting in substantial growth of the NGLY1 community [33].

The UDN case matching project builds on this success. Interested patients work with the coordinating center to post pertinent information about themselves and their conditions on the UDN website. To date, some 180 patients have chosen to post their information, and matches have been found for approximately 25%[3] [34]. These matches, like the case of NGLY1, have resulted in patients being connected with one other and have contributed to the establishment and growth of condition-specific communities.

Understanding the Patient Experience

At the onset of the UDN, we recognized the importance of understanding and assessing the UDN patient experience. We designed post-evaluation and annual patient surveys to collect details about satisfaction with the UDN visit, understanding of recommendations, and ongoing clinical and research status[4]. These surveys are primarily distributed by email; however, individuals who do not have an email address or speak languages other than English complete surveys via phone with coordinating center representatives. We perform a weekly re-

view of responses and identify immediate problems with corresponding action plans. Themes from responses are included in quarterly reports and in presentations to the UDN Steering Committee. In addition, we are currently conducting a focus-group project with patients to identify outcomes of the UDN evaluation that are of importance to them. Results from this project will help guide UDN operations moving forward.

In addition to these data collection efforts, we invite patients to join UDN Steering Committee meetings to share their perspectives on UDN participation. As part of these sessions, clinicians and researchers present medical and scientific findings, followed by patients sharing their views on the UDN evaluation and meaning of a diagnosis. Their participation allows for discussions to move beyond a purely clinical focus to the human impact. We have witnessed UDN clinicians and researchers, especially those who do not interact with patients daily, express that these perspectives bring significant meaning to their work. As a result of these presentations, close collaborations have developed between researchers and UDN patients. Several of these stories are highlighted in the Spring 2021 PEER newsletter [27].

Lessons Learned and Areas for Improvement

While our engagement with patients in the UDN has been positive, enriching, and growing over the course of the project, in our view, there is more that we must do to reach full partnership between researchers and patients.

Prospective patients were not involved in the proposal phase of the UDN. As we work to sustain the UDN model and extend its impact, we recognize that the patient voice will be critical to its continued viability and success. We intend to work closely with our patient community in the design and submission of future proposals to government agencies and other funding sources.

PEER members receive some minimal compensation for their efforts on behalf of the UDN, and patients are reimbursed for expenses incurred when attending our in-person meetings. As we design our next phase, patient leaders will be included as collaborators who need to be fairly compensated for their time and expertise.

We have not yet developed and offered formal training to patients and researchers on the optimal approach to patient engagement in rare disease diagnosis and research. We intend to develop such a training program that will necessarily include an evaluation component to assess the value of patient engagement to patients and researchers. Training for both groups is helpful in building a culture of respect, equitable power, and trust, key foundational principles of patient engagement [35]. If patients are not valued as equal contributors, a true partnership cannot exist.

CONCLUSIONS AND OUTLOOK

There are significant advantages to engaging patients in every stage of rare disease diagnosis and research. Many patients with rare diseases are experts in their conditions and can bring their lived experiences to research design and execution. In the UDN, patients have been instrumental in bringing meaning to the work of clinicians and researchers, building patient communities, making the network aware of unmet patient needs, advocating for additional research funding, and disseminating UDN research findings. Although patient engagement in the UDN has already had a significant positive impact on our work, we continue to strive to involve patients earlier in the process, in the research design itself, and in addressing power dynamics that may arise between clinicians, researchers, and patients. Patients are valuable contributors to clinical research, especially rare disease research, and organizations need to be fully committed to patients acting as partners and provide the required support. This is the culture we are striving to create in the UDN and in the rare disease diagnosis and research community more broadly.

Members of the Undiagnosed Diseases Network:
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Footnotes

1. We use the terms "patient" and "patients" to refer to patients, their families, and caretakers throughout this essay. For the purposes of this essay, we also use the terms "patient" or "patients" to refer to the participants in research studies.
2. The PEER charter and application are available as part of the UDN Manual of Operations. https://undiagnosed.hms.harvard.edu/udn-manual-of-operations/
3. Sharing information on the UDN website is not a requirement to participate in the study. All patients whose profiles are on the website have given their explicit consent to share their information.
4. Patient surveys are available as part of the UDN Manual of Operations. https://undiagnosed.hms.harvard.edu/udn-manual-of-operations/

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