

Exploring Parental Involvement in Rare Disease Research
and Advocacy

by

Leila Jamal, Sc.M., C.G.C.

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ABSTRACT

As patient engagement in research becomes increasingly common, it has grown important to develop best practices for its use. One aspect of patient engagement that remains empirically and conceptually under-explored is how to identify the appropriate patients to partner with for patient engagement in research. The limited available evidence suggests that researchers often partner with patient advocacy organizations (PAOs). Yet little is known about whether patient advocates have experiences and views of research that differ from those of patients who are uninvolved in advocacy work, and from a normative perspective, it is unclear whether and why it might matter if they did.

This dissertation seeks to advance our understanding of these issues by exploring whether individuals who are involved in patient advocacy work have different experiences and beliefs about research than patients who are not involved in advocacy, and how patients' beliefs about research are related to their degree of advocacy involvement in general. To explore these topics, interviews were conducted with parents of children who have one of three rare disorders: Childhood cerebral adrenoleukodystrophy, Duchenne muscular dystrophy, or sickle cell disease. The context of rare disease was chosen as a focus for this study because parents of children with rare diseases have been especially active in the research space over the past thirty years and little is known about how they view research.

The results of this dissertation are reported in three papers. The first paper explores the views that parents of children with rare diseases have about research and medicine in general, and their views related to biorepository research specifically. The findings reported in paper one suggest that parents who were patient advocates and

parents who lacked advocacy involvement had few systematically different experiences or beliefs about research, but that parents' views differed based on the nature of the condition their child had.

Paper two focuses on parents' experiences and beliefs related to patient advocacy. The second paper demonstrates that parents who are involved in patient advocacy were motivated to become involved because it helped them cope with their child's condition and because they wished to use their professional skills to help others. Parents who were uninvolved in advocacy cited the demands of caregiving, negative prior experiences, or a desire for privacy and space as reasons. Most parents believed that partnering with PAOs was a good strategy for researchers to use to engage patients, but some were concerned that marginalized patients may not be reached that way.

The third paper explores whether and why it might matter, from a normative perspective, if the volunteers who participate in patient engagement initiatives differ from patients who are uninvolved. Drawing upon existing literature and findings from my empirical study, paper three evaluates whether instrumentally or intrinsically worthy aims of patient engagement might be affected by differences between engaged volunteers and unengaged patients, and whether patient engagement should be considered a representative exercise in the first place. Paper three concludes that for ethical reasons, patient engagement efforts *should* endeavor to represent the experiences, values, and attributes of patients who are not engaged in research but that practical constraints also need to be taken into consideration when attempting to make patient engagement a more representative exercise.

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MANUSCRIPT 1: Experiences with and attitudes toward pediatric biorepository research among parents of children with rare diseases: A comparison of parents with and without advocacy experience

ABSTRACT

Background: In the United States, there is a growing emphasis on patient engagement in research. In research for rare diseases, patients who participate in patient engagement are often patient advocates. Little is known about how patients affected by rare diseases experience and view research, and in particular, it is unclear whether patient advocates' experiences and views of research differ from those of patients not involved in advocacy work. **Methods:** This qualitative interview study collected data about the experiences and views of parents of children with rare diseases (N=34) related to medicine and research. Interviews were audio-recorded, transcribed, and thematically analyzed using a primarily deductive approach. **Results:** Few differences were found in the experiences and views of parent advocates compared with non-advocate parents. Overall, most parents preferred to hear about research from physicians they trusted and felt respected by. Most parents did not believe re-consent was necessary for secondary research uses of their child's health data. Parents held divergent opinions about research priorities, the optimal time of biorepository recruitment, and the acceptability of having their child's data used in research for conditions other than their own. **Conclusion:** Parents' views appeared to be more related to the nature of their child's condition or their demographic background than to their degree of advocacy involvement. Future studies should explore disease- and population-specific differences in beliefs about research with a view to their implications for patient engagement.

INTRODUCTION

In the United States, there is a current trend of growing investment in patient engagement in research. Examples include work funded by the Patient-Centered Outcomes Research Institute (PCORI), the Patient-Focused Drug Development Initiative at the Food and Drug Administration (FDA), and plans to engage the public as part of the Precision Medicine Initiative (PMI)¹⁻³. Increased patient engagement is motivated by a belief that involving patients in multiple aspects of research, including planning, execution and results dissemination, can improve the relevance of research and express respect to study participants^{4,5}.

Often, in seeking to engage patients, researchers turn to patient advocates as partners⁶. One unexplored question is whether patient advocates have experiences with and views about the research enterprise that differ from those of patients who aren't involved in advocacy work. The work presented in this paper is drawn from a larger project that interviewed advocate and non-advocate parents of children with rare genetic diseases in order to learn about their experiences and views of research and of disease advocacy. The data presented in this paper examine whether parents' experiences with advocacy are related to their attitudes about research in general and biorepository research in particular. Discussed elsewhere is the degree to which parents' views about advocacy differ based on the nature and degree of their advocacy involvement.

BACKGROUND

Rare diseases are defined as those that affect <200k people in the United States⁷. Many rare diseases are disabling or life-limiting, and an estimated 80% of them are

significantly influenced by genetic factors. Since rare diseases by definition affect small numbers of patients, it is challenging to study them, and many clinical trials of rare disease therapeutics are halted early when they fail to demonstrate significant effects on study outcomes in early trial stages^{8,9}. Since there are few treatments for rare diseases, rare disease patient advocacy organizations have been highly active since the early 1980s in advocating, fundraising and building infrastructures for biomedical research, especially genomic research^{10,11}. Many of these organizations are run by parents of affected children¹².

Given the role that genetics plays in the etiology of many rare diseases, rare conditions are often studied using registries and biorepositories that aggregate information from geographically-dispersed families. These registries and biorepositories generally collect genetic and phenotypic data for future observational and natural history studies¹³. This type of database-driven research, while efficient for research learning, also raises controversial policy questions about informed consent and data stewardship. Such questions include how research participants should be recruited to contribute data and biospecimens, whether and when it is necessary to obtain repeat informed consent for the use of a research sample in a study unrelated to the one for which it was originally obtained, and for which purposes a research database should be used¹⁴⁻¹⁶. As large investments are being made in national research databases to study both rare and common diseases,^{17,18} patient engagement is being used as a tool to help answer these questions. Increasingly, patient engagement is being viewed as key to the success and ethical conduct of research using large datasets containing personal data¹⁹.

One challenge related to patient engagement is the lack of guidance about how to identify the individuals or organizations with whom researchers should partner⁴. In a systematic review of approaches for engaging patients in rare disease research, Forsythe and colleagues found that rare disease patient advocacy organizations are often used as partners or intermediaries⁶. While an efficient strategy for finding partners, it remains unclear whether rare disease patient advocates have experiences and views about research that differ from those of parents not involved in patient advocacy. Such information would shed light on whether patient advocates are well-positioned to represent the views and interests of all patients and their families related to research, or indeed, whether this ought to be the expectation we have of them.

This paper reports the findings from a qualitative interview study designed to address this question. Interviews were conducted with parents (N=34) of children who had one of three rare pediatric-onset genetic disorders: Childhood cerebral adrenoleukodystrophy (CALD), Duchenne muscular dystrophy (DMD), or sickle cell disease (SCD). Parents were purposively sampled to include 1) parents who have held formal roles in patient advocacy organizations, either currently or in the past, and 2) parents with no advocacy experience. Parent advocates' and non-advocate parents' experiences and views about general and biorepository research were compared. Data analysis also explored how parents' views were related to the condition their child(ren) had. In addition, parents were asked about their prior experiences in medicine, for contextual purposes.

METHODS

The objectives of this qualitative interview study were 1) to characterize the experiences and attitudes of parents of children with rare diseases with respect to research for their child's condition and 2) to compare the experiences and views of parents who have had formal roles in advocacy with the views of parents who have not been involved in advocacy work. In-depth interviews were conducted over the phone with parents of children with CALD, DMD, or SCD. A qualitative descriptive approach was used, aiming to comprehensively describe the phenomenon under investigation²⁰. This study was approved by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board (JHSPH IRB).

Sampling and Recruitment

The characteristics of the three diseases affecting children of parents in this study are described in Table 1.0 and detailed more extensively in Appendix 2: Extended Methods for Empirical Study. Childhood cerebral adrenoleukodystrophy (CALD) is a progressive neurodegenerative condition affecting mostly boys, which typically results in death between ages seven and fifteen. Duchenne muscular dystrophy (DMD) is a more slowly progressive muscle disorder affecting mostly boys which involves a loss of ambulation, cardiomyopathy, and respiratory decline, leading to death between the second and fourth decades of life. Sickle cell disease (SCD) is a chronic hematological disorder affecting both boys and girls which is more common in individuals of Asian and African descent. It involves pain crises, recurrent infections, strokes, and pulmonary hypertension. Affected individuals typically live into their fourth or fifth decades of life.

Purposeful sampling was used across three disease groups with the goal of identifying and recruiting parents who had assumed roles in patient advocacy organizations and parents who had never had such advocacy roles for the purpose of comparing their views. Eligible parents were English-speaking, residents of the United States with one or more affected children currently aged 0-25, or whose affected child(ren) were 0-25 years of age when they died. Eligible parents were notified about this study in one of three ways: 1) An e-mail sent to them by a patient advocacy group for their child's condition, containing a link to an online screening questionnaire (see supplemental materials); 2) A flyer distributed in clinics at Johns Hopkins Hospital or Kennedy Krieger Institute, containing a link to the screening questionnaire, or 3) word of mouth from patient advocacy group leaders who agreed to help with study recruitment. The CALD and DMD patient advocacy groups that agreed to help with study recruitment were based throughout the continental United States. The SCD advocacy groups that agreed to help were in the Greater New York and Mid-Atlantic regions.

The online screening questionnaire was designed to learn about the nature and degree of parents' advocacy involvement, in order to select both advocates and non-advocates for recruitment. The screening questionnaire also included questions about parent demographics, child well-being, and the types of research parents had pursued for their children, to assist with efforts to build a varied sample of parents in each group. For parents not recruited online (e.g., through advocacy organizations or clinics), the demographic/background information obtained from screening questionnaires was asked of them at the end of the research interview.

Interview Procedures

Oral informed consent was obtained before each interview. All interviews were audio-recorded and transcribed either by the interviewer (LJ) or by a professional transcription service. The interviews followed a guide exploring parents' experiences seeking medical care for their child, experiences with and beliefs about research, experiences with patient advocacy organizations, attitudes toward advocacy, and views about four aspects of biorepository-based research: informed consent for secondary re-use of their child's research data, research recruitment, research uses of children's data, and their beliefs about researcher trustworthiness.

Before the study began, two cognitive interviews were conducted with parents of children with rare diseases other than CALD, DMD, or SCD. The interview guide was subsequently modified to improve clarity.

Data Analysis

Interviews were conducted until informational redundancy was reached. Data collection and analysis occurred iteratively using a primarily deductive. The initial coding scheme was developed based on the study's research questions and domains and questions in the interview guide. Some inductive codes were added as new themes emerged. To ensure reliability, a second coder was trained who coded four transcripts independently from the interviewer/lead investigator (LJ). Double-coded transcripts were reviewed and any discrepancies discussed and resolved, and clarifications made to the codebook. After all transcripts were coded manually, the coded text was entered into Atlas.ti (version 7) for further sorting and analysis.

RESULTS

The results of this study will be reported in the order they were discussed in the interview. First, participants' characteristics and prior experiences in medicine will be reported. Subsequently, their general attitudes to research and specific attitudes to biorepository research will be reported.

Participant Characteristics

Interviews were conducted with 34 parents (12 parents of children with CALD, 12 parents of children with DMD, and 10 parents of children with SCD). Sixteen parents described having an active formal role in patient advocacy (“parent advocates”), and 18 described having done little to no prior advocacy work (“non-advocate parents”). Interviews lasted 40-65 minutes.

Participants’ self-reported background characteristics are summarized in Table 1.1 and 1.2. All participants had at least some college education, although more than one-fourth (n=10) had not completed their undergraduate degree. Half of the parents (n=6) from the CALD group had lost their child to the disease; only one other parent had lost their child (DMD, n=1).

Parent advocates were, on average, older, more likely than non-advocate parents to hold a graduate degree and more likely to have had their child diagnosed more than ten years prior to the interview.

Parents of children with DMD reported the most research involvement, with nearly half (n=5) of DMD parents reporting that they had enrolled their child in a

randomized clinical trial and two-thirds (n=8) reporting they had enrolled their child in a registry or another form of observational research. In the CALD and SCD cohorts, no parents reported having enrolled their child in a randomized clinical trial, although a quarter of CALD (n=3) participants and one SCD participant reported enrolling their child in another type of clinical trial. More than half (n=7) of SCD parents reported never having enrolled their child in a research study of any sort. The advocacy roles held by parent advocates are summarized in Table 1.3.

Experiences in Medicine

Half of all parents (n=16) expressed some kind of complaint about their experiences with their child's clinical care. No notable differences were evident between the comments of parent advocates and non-advocate parents. However, parents' complaints about medical care did differ by disease group. Parents of children with CALD or DMD were more likely to voice concern about having noticed their child's symptoms before their pediatrician did (CALD =8 of 12; DMD n=8 of 12) or to report experiencing a protracted diagnostic odyssey. Most CALD parents (CALD n=10 of 12) reported that their child had been misdiagnosed with ADHD, and that the correct diagnosis was reached "too late". By contrast, SCD parents reported being dismissed or mistreated when seeking help to alleviate their children's pain (SCD n=8 of 10). Some SCD parents (SCD n=4 of 10) also reported that they had experienced racial discrimination in healthcare.

Slightly more than a third of parents in the overall sample (n=12) expressed positive views about their experiences in medicine, with four of these parents expressing

a mixture of positive and negative views. Again, no notable differences were evident between advocates and non-advocates or among the three disease groups. The most common positive theme was that parents had established close bonds with the primary medical specialists following their child. Parents reported high levels of trust and attachment to healthcare providers specializing in their child's condition, whether that provider was a physician, physical therapist, or palliative care specialist.

Experiences and Beliefs About Research in General

When asked about their experiences and beliefs about research in general, most parents understood the term "research" to refer to a clinical trial. Across all three groups, a majority of parents (n=24) reported that they learned about research from the medical specialist managing their child's condition. In most of these instances parents reported that their doctor initiated a discussion with them about research, although in a handful (n=4) of cases parent advocates (but no non-advocates) described asking their doctors about research first.

Roughly half (n=18) of parents in the overall sample asked the interviewer what research is available for their child's condition or expressed some confusion about research for their child's condition. Nearly all of these parents (n=17) specifically expressed confusion or concern about their child's eligibility for existing studies. Some parents in each disease group (n=10) also mentioned the challenges of conducting research for rare diseases, including small sample sizes and lack of adequate funding. There were no notable differences in the prevalence of these themes between advocates and non-advocates or across disease groups.

There were few differences in themes mentioned by parent advocates and non-advocate parents. However, parent advocates in the DMD and CALD cohorts were more likely to volunteer opinions about U.S. federal research policy than non-advocate parents. Of the 12 parents who voiced opinions about research policy, nine were advocates for either DMD or CALD. By contrast, only three non-advocate CALD or DMD parents voiced unsolicited opinions about federal research policy. No SCD parents discussed federal research policy.

Parent advocates who did volunteer opinions about research policy spoke about the Food and Drug Administration (FDA)'s evidence thresholds for rare disease drug development, the interpretation of the Common Rule by Institutional Review Boards, and the challenges to research recruitment posed by the Health Insurance Portability and Accountability Act (HIPAA). These parents all voiced some frustration with existing policies, for example:

My son would be eligible for the next round of the exon skipping, but it's been a frustrating process to see, again, how the FDA says you've got to send your child up this way, and the study has to be placebo-controlled. At the site I was working with in [ACADEMIC MEDICAL CENTER NAME]- they put in a new protocol that the drug company had done with FDA guidance and that IRB had major issues with some of the procedures in the control arm. So they are further delaying now, and now we can't go get screened. So this has been a back and forth of feeling like, you're damned if you do it the FDA way, and you're damned if you don't...there's all this natural history data, a set disease progression model that they're not using, and then you have an example like this with a local IRB fretting about child research, questioning whether it is ethical to give a child a biopsy. If anything else is it unethical to keep him not on the drug. –DMD261 (parent advocate)

Some experiences and beliefs were more closely related to which condition a parent's child had, rather than their degree of advocacy involvement. DMD parents were

most likely (DMD n=10 of 12) to describe their child's research participation as burdensome, while fewer CALD parents (CALD n=3 of 12) expressed this view, and no SCD parents mentioned it. Research burdens mentioned included the effort in travel, the discomfort of study procedures, the disruption of a child's normal routine, and the costs of study participation, which were not always reimbursed.

Parents in the SCD cohort were more likely to articulate concerns about the risks of research than parents of children with either CALD or DMD (SCD n=7 of 10; CALD n=2 of 12; DMD n=2 of 12). Some of these parents said they would be willing to enroll their children in risky research only if their children were not faring well:

So if I have a situation where my daughter was so chronically ill, that you know her quality of life was just poor, I would then maybe consider it. Although I don't know if that would violate the protocol or not, if they are that sick if they can even be in a study. But I think she would have to be so sick to the point of never being able to go to school, for me to take that extra risk, ever. –SCD313 (parent advocate)

Parents of children with SCD and DMD (SCD n=5 of 10; DMD n=3 of 12) also cited a desire to preserve their child's future decision-making autonomy as a reason for not enrolling their child in research. These parents valued their children's right to make their own decisions about research later on. No CALD parents mentioned this theme.

Beliefs About Specific Practices in Biorepository Research

This section describes parents' views about biorepository recruitment, re-consent for secondary research uses of data, acceptable uses of research data, and the

trustworthiness of researchers. For each topic, differences in views related to parents' advocacy involvement and the disease their child(ren) had are reported.

Views about Recruitment

Most parents (n=30) said they would prefer to be asked to contribute their child's health information to a research biorepository by their child's doctor. Parents who believed this were roughly equally split across disease groups and were roughly equally likely to be parent advocates or non-advocate parents. Many parents said they believed it would be best to hear about a research biorepository from their child's doctor because he or she was an individual with whom they had a familiar, trusting relationship and who could answer questions:

It would have to be coming from someone I trust and can ask questions in person. If [physician name] and the other doctors at [hospital name] really supported it, I would trust that it was helpful and legitimate. If it was some company that I never heard of I would probably just throw away the flyer or delete the email. -ALD122 (non-advocate parent)

A minority of parents (n=5) said they would prefer to be invited to contribute their child's data to a research biorepository by e-mail, phone, or social media. One parent was skeptical about the merits of recruiting parents via their doctors in clinics, because of her perception that hospitals can be inefficient and disorganized:

I mean, the thing about reaching me through my doctor is that different hospitals operate differently with varying degrees of success. My son's neurologist had MRI results that said he had CALD for four days before calling me. I don't think she actually saw it, but the office didn't get it to her....so by

reaching out to doctors, sometimes, I think you're not always going to get the patients. –CALD140 (non-advocate parent)

Overall, roughly one third (n=11) of parents believed that it would be acceptable or even desirable to be recruited soon after their child's diagnosis, while almost as many believed it would not be acceptable or would be a bad idea (n=9). Roughly equal proportions of parent advocates and non-advocate parents believed that recruitment soon after diagnosis would be acceptable or desirable; fewer parent advocates (n=3 of 16 parent advocates) than non-advocate parents (n=6 of 18 non-advocate parents) believed it would be an unacceptable or bad idea.

Some parents who felt it would be desirable to be told about a research biorepository soon after their child's diagnosis explained that it would have been comforting to know that researchers are interested in their child's disease. Other parents said that they thought recruitment soon after diagnosis was important in order to capture complete data about the natural history of their child's condition. Irrespective of their own views, several of these parents acknowledged that other parents could reasonably disagree:

There are definitely different personality styles and coping styles that come into play. Some people are more private than others, some people are more suspicious than others, and some people do not cope well, with, you know – talking about Duchenne. For those that don't want to hear about it in the early stages for those reasons, that makes sense. -DMD236 (parent advocate)

Parents who believed it would be unacceptable or a bad idea to be recruited soon after their child's diagnosis said they would have been emotionally unprepared to process information about research participation at that time. A handful of parents who felt that

recruitment soon after their child's diagnosis would be a bad idea said that the appropriate time for recruitment should be assessed on a case-by-case basis. This theme was related to the common belief that physicians are ideally situated to approach parents about research:

I think the neurologist would know best when to approach you emotionally. You know, they are in a position to say, 'is she someone I should approach at this point? Probably not, but maybe in a couple of years, this would be someone you can approach and she will really understand and get it'. So that's another reason that the doctor would be better than an e-mail. I think an e-mail is... like, screw you, there's no way I'm giving anyone permission to take my kid's blood and store it over e-mail. It has to be someone I know. -DMD291 (non-advocate parent)

Views about Re-consent

Nearly two-third of parents in the overall sample (n=21) felt it would be unnecessary or undesirable for researchers to re-contact parents to obtain informed consent each time they wanted to use a child's health data in new research project if the parent had already given informed consent for its use in research. This belief was expressed by roughly equal numbers of parent advocates and non-advocate parents and was voiced much more frequently by parents of children with CALD and DMD than by parents of children with SCD (n=7 of 12 CALD parents and n=11 of 12 DMD parents compared to n=3 of 10 SCD parents). Many parents who believed that re-consent would be unnecessary or undesirable cited a desire to reduce barriers to research as the reason. Others felt it would be onerous for them to be contacted by researchers repeatedly.

Several parents of children with DMD or CALD believed a preference for re-consent was petty or paranoid:

I don't know why people freak out about the data. Who gives a crap? I just wonder why people waste so much time and energy into getting/needing permission. Come on. I mean, we are trying to save lives here. So I couldn't care less. –DMD203 (parent advocate)

A minority of parents in the overall sample (n=7) expressed a strong preference for having researchers ask them for re-consent each time their child's health data was used in a new research project; similar numbers were parent advocates (n=4) and non-advocate parents (n=3). Most parents who held this view were parents of children with SCD (n=5 of 10 SCD parents). Several of them justified this preference by describing it as a way to avoid repeating the historical mistreatment of African Americans in U.S. human subjects research. Two parents who stated a preference for re-consent were parents of children with CALD. Parents' most common reasons for desiring re-consent were to retain some control over the use of their child's data and a wish to stay informed about the research being conducted for their child's condition. Three parents of children with SCD also cited a preference for re-consent to respect their child's future ability to make his or her own decisions about research participation. For example:

Right now while he's a child I'm trying my best to protect him every way I can, and I don't know how he's going to feel when he gets older, like what if he doesn't want everyone in the world to know he has sickle cell anemia? I'm just trying to make sure I'm making the best decisions possible for him...so if I don't have control over it, or if I feel I don't have control over it, maybe I should just hold off for a little while, until he gets a little bit older and we can talk about stuff like that. -SCD309 (non-advocate parent)

When probed, parents with different preferences about re-consent expressed some shared values. For example, several parents who expressed the belief that re-consent was undesirable because it would hinder research also expressed a desire to remain informed about research for their child's condition and/or valued some way of opting out of research. One parent who did not believe re-consent was necessary suggested a tiered-consent system:

It's a lot of administrative burden for researchers to go back continuously to every parent and say 'Here, can I have permission for this piece of this, that piece of that'. But as a parent, yeah, I would want to know. Keep me informed and keep me in the loop, and let me make some decisions. There might be the odd thing I would want to say no to. Like if I thought the value of where that data is going is not where I want it to go, then yeah, I feel like I should have the opportunity to say no. Like maybe you could put data in there and have a checklist, like 'these are the types of things I consent to, but this I definitely don't want.' Something as proactive as possible up front, to avoid the re-consenting. - DMD261 (parent advocate)

Views about Acceptable Research Uses of Children's Health Data

Many (n=17) parents found it difficult to articulate what types of research a biorepository should be used for and either hesitated or required prompting when this question was asked. Nearly one-third (n=10) of parents (roughly equal proportions advocates and non-advocates) expressed the view that research priorities should be determined by professional scientists, with several expressing that they did not have the technical expertise to suggest types of research for which biorepository research should be used (DMD n=5 of 12; CALD n=6 of 12; SCD n=3 of 10).

Parents in all three disease groups (n=18) expressed a belief that parents' ideas about research priorities are shaped by their own experiences with their child's disease,

making research priority-setting an especially challenging topic for parents to weigh in on. This seemed to be especially challenging for groups whose children have a disease with variable expression:

I think if we had found out that my son were too far progressed for the transplant, I would have been pushing very hard for newborn screening. If he were eligible for the transplant, I think my focus would have been on the bone marrow transplant. But his most immediate life threat is adrenal insufficiency, so I tend to focus on that, because I feel like that's something that can affect all of our boys, immediately. Any day. I think it can cause a bit of tension in the community just because, we can all get very passionate about our own focus and the reasoning behind that focus. Sometimes our personal biases can, I dunno – I hate to say pit us against one another, but maybe make us not quite so open to the other parent's view. –ALD160 (non-advocate parent).

In the CALD cohort, more than half of parents also expressed a view that newborn screening is more important than supporting research for CALD, because of a belief that disease prevention efforts are more hopeful than any of the current proposed approaches for treating CALD. In general, newborn screening was the most common advocacy issue discussed by CALD parents.

Parents held different opinions about the acceptability of using their child's health data for research on a condition other than the one affecting their child. Nearly half of parents in the overall sample (n=15) said they would not mind this or thought it would be actively desirable for their child's data to be used in research on a condition other than the one their child had. A roughly equal number of parents (n=14) expressed discomfort with the idea of their child's data being used in research for conditions other than their child's. Parents of children with SCD (n=7 of 10 SCD parents) were more likely to take

exception to non-SCD research than they were to view it as acceptable or desirable (n=3 of 10 SCD parents).

When probed, a few parents admitted that if they did contribute their child's data to research for other conditions, they would prefer if that research stood some chance of benefitting people with their child's disease:

Like I said, a lot of studies are for cancer-related concerns really, and sickle cell has benefited from that, from those research efforts, so that wouldn't bother me. As long as I can tell that there would be some benefit. If, in their stated goals for the research or hypotheses that somehow this would have a hand in sickle cell, I would go for it. I would hope that there would be some kind of benefit from this research to sickle cell patients. -SCD313 (parent advocate)

Trustworthiness

Nearly two-thirds of parents in the overall sample (n=20) reported that they trusted researchers with whom they had a personal connection, or who had a personal connection with children with their child's condition. This theme was referenced by both non-advocate parents (n=12 of 18 non-advocate parents) and parent advocates (n=8 of 16 parent advocates) and across all three disease groups. The value of having a personal connection to affected children was a reason why many parents believed that their doctors were ideally situated to discuss research opportunities with them.

Nearly two-thirds of parents in the overall sample (n=19) also believed that an affiliation with a reputable institution was a marker of researcher trustworthiness. This theme was referenced commonly by both non-advocate parents (n=11 of 18 non-advocate parents) and parent advocates (n=8 of 16 parent advocates) and across all three disease groups. When probed for further detail about the characteristics that made an institution

reputable, parents cited an institution's transparency and visibility as characteristics they associated with high repute. As an illustration, several parents mentioned that they would not have enrolled in this interview study if it had not been run by investigators at Johns Hopkins. While most parents said they would trust researchers from the government, industry, or academic medical centers equally, a handful of parents in all three groups mentioned some mistrust of government research, related either to their own political beliefs or historical transgressions of research ethics.

Nearly half of parents in the overall sample (n=15) said that "good communication" was a hallmark of a trustworthy researcher. When probed, several parents explained that "good communication" entailed using clear, comprehensible language, being honest and transparent, or expressing respect to parents of affected children. In the words of one SCD parent:

They have to take the time to get to know the patient and get to know the family unit. The fact that they do not assume that you can't understand what is going on with your child, and that they interact with you. And the fact that they not only are researchers but they are treating physicians, too. For me it was that they don't have sickle cell, God bless them, but they were totally immersed in sickle cell, but they are so dedicated to trying to help my child and myself. So it is the communication, it is the dedication it is the sincere interest in trying to make things better. It is the long hours, and that I know they missed their own family events trying to attend to it. A lot of medical professionals do that. It is the sitting down saying thank you for coming, you know. It is about that interaction and respect. -SCD313 (parent advocate)

DISCUSSION

This study sought to understand the experiences and views of parents of children with rare diseases with respect to research in general, and in terms of whether and how their more specific views about biorepository research were related to their degree of

formal involvement in advocacy. In this study, parents' views about research appeared to be more related to the nature of their child's disease than to their degree of advocacy experience. These findings contribute to the literature on public attitudes to biorepository research by shedding light on the perspectives of parents of children with rare diseases, which have not been extensively studied thus far.

Experiences and Views Related to Medicine and Research in General

Most parents in this study initially understood the term "research" to refer to clinical trials. While parents' general views about research did not differ notably by advocacy status, some views appeared to be related to their child's diagnosis. For example, consistent with the findings of Burstein and colleagues' (2014) study of parental attitudes to research data sharing, parents of children with DMD and SCD were worried about making decisions about research data use that their children might disagree with when they were older. This theme was not expressed by CALD parents, most likely because children with CALD usually die in childhood.

In addition, parents of children with SCD expressed less trusting and more risk-averse attitudes to research than parents of children with DMD or CALD. For example, SCD parents were most likely to want researchers to obtain repeat informed consent each time their child's data was used in a new study. In a handful of instances, these attitudes were explicitly linked to the history of systematic mistreatment of African Americans in U.S. research and healthcare. This finding is consistent with a large body of literature showing that African Americans in the U.S. are somewhat more reticent to participate in genomic research owing to a history of mistreatment from researchers²¹⁻²³. In SCD

families, this mistrust of research institutions may be compounded by the common experience of being mis-treated or under-treated for chronic pain²⁴. These observations are reminders that historical and social contexts are critical in shaping research participants' perceptions of research.

Experiences and Views Related to Biorepository Research

With respect to their views about specific practices in biorepository research, parent advocates did not express any views that systematically differed from those of non-advocate parents. Regarding research recruitment, most parents said they would prefer to be told about a research biorepository in-person, by the specialist managing their child's care. This finding is consistent with what Bendixsen and colleagues (2016) found in a focus group study enrolling parents of children with DMD, in which the authors learned that parents especially valued face-to-face communication and in-depth conversation about research.

Given that parents also said that personal connectedness and communication were hallmarks of a trustworthy research relationship, it is not surprising that most parents preferred to hear about research from the physicians they trusted and knew well. Indeed, physician-specialists caring for rare disease patients may be ideally-situated to engage parents in rare pediatric disease research, because of their access to relatively large numbers of affected families, their knowledge about a condition, and their ability to gauge the emotional appropriateness of approaching and recruiting parents. This being said, several studies have found that while physicians can serve as bridges between

research and clinical realms, they may experience problematic role conflicts that require special training to be able to navigate^{25,26}.

Most parents felt that re-consent would be unnecessary or not desirable for secondary uses of their children's research data. Their most common reason was a belief that re-consent would unduly hinder research. However, when probed, many of these parents said they would want to receive periodic updates about how their child's information was being used. The minority of parents who felt that re-consent for secondary research was necessary or desirable (mostly parents of children with SCD) expressed similar values. Staying informed about research opportunities for their child and holding researchers accountable for conducting high-quality, ethical research were the main reasons why some parents valued the practice of re-consent.

Interestingly, these results suggest that parents have a desire to "stay in touch" with researchers, irrespective of their beliefs about the necessity of re-consent for secondary data use. Seeking repeat informed consent for secondary research uses of data may not be the only way to respect parents' underlying desire to hold researchers accountable while remaining abreast of research activity related to their child's disease. The more general biobanking literature documents a wide range of parental views about the necessity of re-consent for secondary research uses of pediatric research samples, with some studies showing a majority preference for re-consent^{27,28} and others reporting the opposite finding²⁹. Future studies might examine whether parents' preferences related to re-consent are influenced by the degree of ongoing communication they have with a biobank containing their child(ren)'s samples or data.

With respect to their views about research priorities, many parents found it difficult to articulate precisely what they thought a research biorepository should be used for. Parents in all three disease groups felt that parents' ideas about research biorepositories are shaped by their personal experiences with their child's disease, making it hard for parents with different experiences to see eye-to-eye about which topics are most important. These results echo the findings of Silverman (2008) and Pelicano and colleagues (2014) in the context of autism research^{30,31}. Both found that parents of children with autism disagreed about which specific interventions were most important to test, depending on the type of autism their children had. These data suggest that patient engagement about research priorities may be especially challenging in the context of research for diseases with variable expression.

Irrespective of their advocacy status, most parents in this study said that they trusted the clinician-researchers whom they felt personally connected to, who communicated with them clearly and respectfully. This finding supports prior empirical and conceptual work by Beach and colleagues (2007; 2015) and Elander and colleagues (2011) which conceptualizes trust in physicians as a product of their expressed respect to SCD patients³²⁻³⁴. The results of this study imply that expressions of respect may also help to facilitate trust in researchers, even in populations that have been historically exploited.

LIMITATIONS

This study had a number of limitations. The parents interviewed were relatively highly educated, as all of them had at least some college education. Thus, participating

parents may have had different views compared to those who declined participation. Furthermore, more female parents were interviewed in this study than male parents, which is another potential source of bias in our findings given evidence that there can be gender-based differences in attitudes to research^{35,36}. Finally, as mentioned earlier, patient advocates who were interviewed were identified because they currently occupied formal roles in PAOs. It is therefore possible that the views of some advocates who do not work for PAOs are different from those who do and thus this study does not adequately represent the views of all patient advocates related to these three rare conditions.

CONCLUSION

Parent advocates expressed few different views about research than those expressed by non-advocate parents. In this study, parents' experiences and beliefs about research appeared to be more closely related to the condition a child had. Future research might explore whether and how disease-related differences in parents' experiences and beliefs about rare disease research are ethically and practically relevant to the design of patient engagement efforts.

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MANUSCRIPT 2: Experiences and attitudes toward patient advocacy among parents of children with rare genetic diseases: Insights from parents with and without advocacy experience

ABSTRACT

Background: For more than thirty years, patient advocacy organizations (PAOs) for rare genetic conditions have been involved in all aspects of health research. Many such organizations are run by parents of affected children. Little is known about why some parents of children with rare genetic conditions become involved in patient advocacy and others do not, or how parents experience and view patient advocacy generally. **Methods:** This qualitative study interviewed parents of children with rare diseases about their experiences and views related to patient advocacy. Parents with and without advocacy experience were interviewed. Interview transcripts were coded and analyzed thematically using a combined deductive and inductive approach. **Results:** Thirty-four parents completed interviews. Sixteen had formal experience in advocacy organizations and 18 had no formal experience. Parent advocates were motivated to be involved in advocacy to cope with their child's condition, contribute skills, or by a perceived duty. Those who were uninvolved in patient advocacy cited their caregiving obligations, a desire for privacy, negative prior experiences, or a desire to protect their children as reasons. Most parents thought it made sense for researchers to partner with PAOs for patient engagement but noted limitations to this approach. Some parents felt that PAOs have difficulty collaborating with each other. **Conclusion:** Both parents with and without advocacy roles report positive and negative experiences with patient advocacy organizations. Many parents who participate in patient advocacy are motivated by personally compelling reasons. However, not all patients and their families find patient

advocacy helpful, and some parents see limitations to using PAOs as partners for patient engagement.

INTRODUCTION

Patient advocacy organizations (PAOs) are committed to “promoting and/or representing the interests of users and/or caregivers in the health arena”¹. The first PAOs for rare, genetic disorders were established over fifty years ago as mechanisms for educating the public about conditions like Cystic Fibrosis and Tay-Sachs Disease and for providing support to affected individuals and their families². In the 1980s and 1990s, as more genetic conditions were identified, the number of rare disease PAOs grew. In the United States today, more than 250 such organizations exist³.

Although PAOs are heterogeneous with respect to their origins, compositions, and activities, the past thirty years have witnessed a clear trend of rare disease PAOs being highly involved in all aspects of research⁴. This involvement has included fundraising for research, helping with study recruitment, collecting research data, assisting with study design, and establishing research infrastructures^{5,6}. Several systematic reviews have also found that PAOs are frequently used as partners in efforts to engage rare disease communities in research^{7,8}. Given the growing investment in patient engagement in research the United States, and given that researchers often turn to PAOs as their means of patient engagement, it has become important to examine how PAOs and patient advocacy are viewed by patients who are involved in advocacy and patients who are not. Such an understanding might help to identify advantages and disadvantages of having researchers partner with PAOs to engage patients in research.

In the United States, a disorder is considered rare if the prevalence in the U.S. is <200,000⁹. The National Organization for Rare Disorders (NORD) estimates that there are over 7000 rare diseases affecting a total of ~25-30 million people in the U.S. (8-12%

of the population)¹⁰. Most rare diseases are associated with life-limiting, chronic, or disabling symptoms, and there are few treatments for the people they affect.

Epidemiologic data on rare diseases is scarce, and the exact prevalence of different rare disorders is difficult to estimate¹¹. An approximate 80% of rare diseases are significantly influenced by genetic factors and most are incurable¹².

Much early research about the roles of patient advocates and PAOs in research focused on the efforts of HIV/AIDS advocates in the 1980s and 1990s. These advocates challenged Federal regulations to secure patient access to early-stage experimental therapies and more broadly contested the social marginalization of gay men¹³. This early HIV/AIDS advocacy likely influenced patient advocates for other diseases to expand their work into the context of research. Despite the influential legacy of HIV/AIDS activism, some sociologists and historians have questioned whether the HIV/AIDS advocacy movement was sufficiently inclusive to other social groups affected by the epidemic¹⁴, and similar concerns have been raised by social scientists who have studied patient advocacy for breast cancer and autism in the 1990s and 2000s when controversial questions about research funding allocation and the definition of disease itself splintered patient communities into competing factions¹⁵⁻¹⁸.

To date, only a handful of studies have examined patient advocacy for rare conditions. These studies used a variety of empirical methods to uncover how advocates challenge conventional definitions of expertise¹⁹⁻²² or tensions that arise in partnerships between PAOs and biomedical researchers²³. Several studies have also noted that many PAOs generally are disease specific and are run by parents of affected children^{4,5}. Few studies have examined how patient advocacy is experienced and viewed by patients

and/or their family members who have and have not been involved in advocacy, or what drives some people and not others to become involved in patient advocacy.

The goal of this qualitative study was to conduct interviews about advocacy and PAOs with parents of children who had one of three rare, pediatric-onset genetic conditions: Childhood cerebral adrenoleukodystrophy (CALD), Duchenne muscular dystrophy (DMD), or sickle cell disease (SCD). The study was designed to elicit views from parents who have held formal roles in PAOs and parents who have not ever held such roles, to enable comparisons between the experiences and views of the two groups.

METHODS

The methods of this study are described in detail in Appendix 2: Extended Methods for Empirical Study. Using a qualitative descriptive approach, in-depth phone interviews were conducted with parents of children with CALD, DMD, or SCD. This study was approved by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board (JHSPH IRB).

Sampling and Recruitment

Purposeful sampling was used in all three disease groups to identify and recruit parents who had assumed roles in patient advocacy organizations and parents who had never had such advocacy roles. Eligible parents were English-speaking, residents of the United States with one or more affected children currently aged 0-25, or whose affected child(ren) were 0-25 years of age when they died.

Eligible parents were notified about this study in one of three ways: 1) A flyer distributed in clinics at Johns Hopkins Hospital or Kennedy Krieger Institute, containing a link to a screening questionnaire (see supplemental materials), 2) word of mouth from patient advocacy group leaders who agreed to help with study recruitment, or 3) An e-mail sent to them by a patient advocacy group for their child's condition, containing a link to the screening questionnaire. The CALD and DMD patient advocacy groups that helped with study recruitment were based throughout the continental U.S.; the SCD advocacy groups that helped were in the Greater New York and Mid-Atlantic regions only.

The online screening questionnaire was designed to learn about the nature and degree of parents' advocacy involvement, in order to purposively select both advocates and non-advocates for recruitment. The screening questionnaire also included questions about parent demographics, child well-being, and the types of research enrollment parents had pursued for their children. Information about these domains were considered in building a relatively heterogeneous sample of parents in each group.

Interview Procedures

Oral informed consent was obtained before each interview. All interviews were audio-recorded and transcribed either by the interviewer (LJ) or by a professional transcription service. The interviews followed a guide exploring parents' experiences seeking medical care for their child, experiences with and beliefs about research, experiences with patient advocacy organizations, attitudes toward advocacy, and views about biorepository research (reported elsewhere). Before the study began, two cognitive

interviews were conducted with parents of children with rare diseases other than CALD, DMD, or SCD. The interview guide was subsequently modified to improve clarity.

Data Analysis

The goal of data analysis was to achieve informational redundancy. Data collection and analysis occurred iteratively and used a combined deductive and inductive approach. The initial coding scheme was deductive, developed based on the study's research questions and the domains and questions in the interview guide. Inductive codes were added as new themes emerged. A second coder was trained who coded four transcripts independently from the interviewer/lead investigator (LJ). Double-coded transcripts were reviewed and any discrepancies discussed and resolved, and clarifications made to the codebook. The coded text was entered into Atlas.ti (version 7) for further sorting and analysis.

RESULTS

The following section will report on data about participants' characteristics and advocacy roles. Then, it will report qualitative interview findings, including data about parents' prior experiences with advocacy, attitudes towards advocacy, and motivations for being involved or uninvolved in advocacy.

Participant Characteristics and Advocacy Experience

Sixteen parents with advocacy experience and 18 parents without advocacy experience completed interviews. The demographic characteristics and advocacy roles of

parent advocates are described in Tables 1.0, 1.1 and 1.2. All participants had at least some college education, with over one-fourth (n=10) of parents not having completed a college degree. Half of the parents (n=6) from the CALD group had lost their child to the disease; only one other parent had lost their child (DMD, n=1). Parent advocates were, on average, older, more likely than non-advocate parents to hold a graduate degree and more likely to have had their child diagnosed over ten years before the interview took place.

In the CALD cohort, parent advocates self-identified as either advocacy group founders or leaders, newborn screening advocates, or in one case, an advocacy group board member. In the DMD cohort, parents self-identified as advocacy group board members or chairs of conference organizing committees. One parent of a child with DMD was a volunteer-based public relations officer for an advocacy group, and one was a scientific reviewer for a patient advocacy organization that funds research. In the SCD cohort, all parent advocates had founded or established small, local patient advocacy organizations.

Qualitative Interview Findings

Experiences with Patient Advocacy Organizations

Overall, parents were equally likely to describe positive experiences with PAOs as they were to describe negative experiences. Parent advocates described their experiences with PAOs more often and in greater detail than non-advocate parents, with more parent advocates (n=10) expressing positive views than non-advocate parents (n=6). Notably, all parent advocates in the DMD cohort (n=6) reported having some kind of

good experience interacting with or being part of PAOs. In addition, 2 of 4 SCD parent advocates and 2 of 6 ALD parent advocates reported positive experiences. Six non-advocate parents mentioned having positive experiences interacting with PAOs (n=3 of 6 CALD non-advocate parents; n=2 of 6 DMD non-advocate parents, and n=1 of 6 SCD non-advocate parents). When reporting positive experiences, parent advocates and non-advocate parents mentioned similar examples, including: receiving emotional support from other parents, finding friends for their child, receiving financial support for their child's medical care, and learning about research opportunities.

Parent advocates and non-advocate parents were equally likely to describe negative experiences interacting with or being part of PAOs, with the same types of negative experiences being cited by parents in all three disease groups and by both parent advocates and non-advocate parents (n=3 of 6 CALD parent advocates; n=3 of 6 DMD parent advocates; and n=2 of 4 SCD parent advocates and n=3 of 6 CALD non-advocate parents; n=3 of 6 DMD non-advocate parents; n=2 of 6 SCD non-advocate parents). The negative experiences described by parents included: participating in or witnessing arguments among parents who disagreed about how to manage their child's condition, feeling depressed or emotionally drained by interacting with other affected children and families, not finding relevant information or help, and PAOs being disorganized or unresponsive.

Six parents of children with DMD and three parents of children with CALD described having a combination of positive and negative experiences with PAOs. Four of these parents were advocates and three were non-advocates.

Eight parent advocates (n=3 of 6 CALD parent advocates; n=3 of 6 DMD parent advocates; n=2 of 4 SCD parent advocates) mentioned that patient advocacy work was burdensome in some way, elaborating that they found advocacy work time-consuming or emotionally draining. This did not deter them from being involved in patient advocacy but made them want to take breaks from time to time. Some parent advocates lauded PAOs that allowed varying levels of involvement at different times, mirroring changes in the practical and emotional needs of parents and families at different stages of a child's disease progression:

Families still play a huge role in adulthood, and I think there's something about the cyclical nature of grief that makes people need to become more involved and then withdraw, become more involved and then withdraw, in a cyclical way. But I also feel like with Duchenne, you have this moment where you have a diagnosis without a lot of burdensome symptoms, for a long time, and then symptoms gradually become more attention-grabbing for families until it eventually many families find themselves in a position where they can barely get to the grocery store let alone think about running a fundraiser or being involved...So I think to have a loose structure that overlaps and allows movement works very well for the community. –DMD236 (DMD parent advocate)

Attitudes Toward Patient Advocacy Organizations

Parents also expressed some general attitudes to PAOs. They specifically focused on the roles of PAOs in research engagement, their collaborative efforts, and the role of affected children in parent-led patient advocacy. This section expands upon these themes.

In all three disease groups, when parents were asked if contacting PAOs was a good way to reach a broader sample of parents to communicate with them about research, most parents (n=21) said they thought that PAOs were a good place to start. Some

parents (n=13) said they weren't sure. There were no major differences in these views reported by parent advocates vs. non-advocate parents. However, of the 21 parents who thought that PAOs were a good place to start, seven parent advocates and two non-advocate parents voiced a concern that some families would not be reached if researchers relied on PAOs alone to spread the word about research.

In a related theme, roughly two-thirds of parents (n = 26) in the overall cohort (split roughly evenly between parent advocates and non-advocate parents) expressed some concern about the inclusiveness of advocacy organizations. Some specifically voiced a belief that participation in advocacy was difficult for socioeconomically disadvantaged families. Others acknowledged that PAOs do not draw on involvement from all parents because advocacy is not a helpful way for all personality types to cope with their child's condition:

My guess would be that the advocacy groups have very specific angles, and I think if you reach out to a broader audience, you might be hitting more people with my personality and you may realize that there's other stuff going on that the advocacy groups are not considering. –CALD122 (non-advocate parent)

Roughly half of the overall sample of parents (n=16) expressed a view that PAOs do not collaborate effectively with one another. This view was voiced more often by parent advocates than non-advocate parents and was mentioned across all three disease groups. It was more common for parent advocates (n=11 of 16 parent advocates) to believe that PAOs had deeply entrenched disagreements about which issues to support, which research projects to fund, which information to endorse, and which topics to focus on at patient conferences. Other parents believed that disagreements between PAOs

amounted to little more than personality differences between advocacy group leaders. A few (n=3 of 18) non-advocate parents believed that some PAOs had been established by a parent who wanted to raise money for his or her own child's care, not because of any broader need for a new PAO. These parents felt that the addition of multiple small organizations confused the mission and aims of the broader disease community:

I think that parents have different objectives and different goals and they fund raise in their own communities and they start their own groups. I don't like that. I think it complicates everything. I think it's really, it's just not, I don't find it helpful. And again it is not something I would ever discuss with a group of women with kids with Duchenne. Now we're bringing it up, like the [FOUNDATION X] has done a ton of awesome works, I think they advocate, they raised all kinds of money, they're wonderful. But then I think, why aren't you with [FOUNDATION Y]? Why are you spending all this time and money when maybe you could be working better as part of [FOUNDATION Y?] –DMD291 (non-advocate parent)

Five parents, four of whom were non-advocate parents (n=5 of 18), did believe that PAOs coordinated their efforts well. However, when probed they had difficulty coming up with examples of successful collaboration among PAOs. The remaining parents did not express an opinion about PAO collaboration.

Reasons for Being Involved or Uninvolved in Patient Advocacy

Parent advocates discussed their motivations for becoming involved in patient advocacy, and non-advocate parents discussed the reasons for their lack of involvement. In some cases, parent advocates also shared their views about why they thought other parents are not involved in advocacy, and non-advocate parents shared their views about why they thought some parents were motivated to become advocates. This section summarizes these themes.

In all three disease groups, the most common reason parent advocates cited (n=9 of 16 parent advocates) for being involved in advocacy was to help them cope with their child's disease and/or death. Engaging in advocacy was described as a way of turning a tragic situation into a more positive one or making meaning of a difficult experience. Several parent advocates (n=5) explained that advocacy work was therapeutic for them because of their proactive, goal-oriented personality types:

I think it helped with our coping and our functioning. Both my husband and I are very goal-oriented, task-oriented people. And I think just the philosophy of staying busy, staying immersed, staying involved in the research community was just a big driver for us to kind of feel hopeful, and you know, to help do something about it...I mean why is it that there's a core group of us at my children's school that we follow each other from elementary, middle school and high school? We are always the ones organizing this that and the other, always the ones involved, always the ones volunteering. –SCD333 (parent advocate)

One parent advocate in each disease group mentioned that being involved in advocacy would not have helped them cope with their child's condition in the months immediately following their child's diagnosis or death. Advocacy only became helpful to these parents after a period of private reflection and mourning.

Eight parent advocates (n=1 of 6 CALD parent advocates; n=3 of 6 DMD parent advocates; n=4 of 4 SCD parent advocates) said they had become involved in patient advocacy because they had relevant professional skills to contribute, such as scientific, legal, pharmaceutical, or pastoral training. These parents had taken on roles in PAOs that capitalized on their professional abilities:

They use me as their consumer to review drug candidates for the Congressionally Directed medical research program funds - they have a \$4,000,000 a year pot of

money from that. So I did go through the process of at least being nominated into that, to review research grants and help allocate those funds. But that's something that's because of my research background and knowledge of academics and research design and science. I am more comfortable helping with the research, rather than doing fundraising or something. –DMD261 (parent advocate)

Several (n=5) parent advocates across all three groups described their advocacy involvement as a duty. One CALD parent explained that the duty to become involved in advocacy originated with a promise she had made to her son before he died, in which she had told him that his death would not be in vain. Another DMD parent explained that his sense of duty to become involved in advocacy was motivated by reciprocity, knowing how much help his family would need from PAOs over the course of their affected children's lives. A couple of SCD parents said that their sense of duty emanated from a recognition that they were more socioeconomically privileged than other parents of children with the same condition:

I am a 38-year old woman, married with two children and a husband who works on federal government job and we are a tight-knit family. When I do outreach to parents, they're mostly single family households, they mostly don't have the type of income that I have, they are younger than I am, they don't really know how to take care of a child with the disease because their mindset...may not be the mindset of myself. So I feel a duty to support them, because in the African-American community that is affected with sickle-cell they were not raised in a setting of knowing how to take care of a child at a younger age, or from a bad economic standpoint, let alone a child with an illness. –SCD301 (parent advocate)

Few non-advocate parents commented on why they thought other parents became involved in advocacy. The four non-advocate parents who did believed that parent advocates used their advocacy work as a way of coping with the emotional pain, grief, and loss associated with raising a child with a rare condition. In the CALD cohort, half

(n=3 of 6 CALD non-advocate parents) expressed a view that most PAOs for CALD are run by parents whose children have died from the disease.

Reasons for Being Uninvolved in Advocacy

Nine non-advocate parents (n=5 of 6 CALD non-advocate parents; n=2 of 6 DMD non-advocate parents; n=2 of 6 SCD non-advocate parents) said their main reason for being uninvolved in advocacy was the competing burden of caring for a child with a rare condition. Parents who cited this reason said that their child's physical and emotional needs kept them busy 24 hours per day, or felt that their time with their children was too precious to sacrifice for other pursuits:

I don't have time to do this. I'm helping my son die. I don't have time to – I probably could have gone to the family meeting in Boston during the hurricane. But the thought of getting stuck up there and of my husband being alone with [son's name] and [his brother's name]- it's not worth it, because I'm his caregiver. Even if he'd had a nurse, I'm still his mother. He's dying, so I can't really leave him for that long, so I do think that could be why we aren't more involved. We're just too involved in caring for our children. –CALD140 (non-advocate parent)

In the DMD cohort, the most common reason parents cited for being uninvolved in patient advocacy (n=5 of 6 DMD non-advocate parents) was needing privacy or space to cope with their child's diagnosis. These parents had children who had been diagnosed between one and three years previously, and they were still deciding how publicly they wanted to share the news. A handful of CALD and SCD non-advocate parents (n=2 of 6 CALD non-advocate parents; 1 of 6 SCD non-advocate parents) also cited the need for privacy or space to cope as a reason for being uninvolved in patient advocacy. These

parents also tended to reference their or their family members' personality types as private or introverted:

Not only we haven't told our kids, we haven't told our parents. We haven't told any family. My business partner knows, and my wife has told I think one or two people. But we figure as soon as we told the grandparents the kids will find out so we just- we haven't told anybody. It's hard because I'd like to be more involved. I want to go out and try and raise money to save my son, but because we value our privacy, we made that decision. So we're not actively involved in any advocacy or fundraising. –DMD285 (non-advocate parent)

Seven CALD and DMD parents said they had decided to be uninvolved in advocacy (n=4 of 6 CALD non-advocate parents; n=3 of 6 DMD non-advocate parents) because they had had a negative experience interacting with other parents in a setting organized by a PAO. Some of these parents viewed PAOs as spaces where parents go to vent or argue about decisions related to their child's care. These parents had tried to attend PAO meetings or events but had witnessed or become involved in disagreements about the medical management of their child's condition:

The [other parents in the group] were unsupportive, it was almost like, 'my story is worse than your story.' Or if I would say, 'this is what happened,' they would tell me I was wrong, like they knew everything about CALD...so they kicked me out of the group because I disagreed with them. I think someone else has taken it over, who's a little bit better now. It just seems like when you get involved in any disease, but especially a rare disease where parents don't know about it and then they learn a little bit, they think they're experts. I don't know if it makes them feel better, like 'I'm doing everything for my son because I know this amount and you're wrong.' I don't really know why, but it's just not a supportive group. -- CALD140 (non-advocate parent).

Other parents' negative experiences were related to how hard they found it to watch other parents express emotion about their child's condition. Watching other

parents struggle to cope with a diagnosis elicited strong feelings of aversion from some parents. For example, one DMD parent stated:

When I do go to some of these conferences and meet with other people, I cannot sit around and watch other people's kids. I just can't do it. It's overwhelming. There's a woman sitting next to me who has got a three-year-old, and she's crying so hard she can't even speak; she can't get through a sentence. And she's got a brother approximately 20-years-old who is in and out of the hospital, he can't breathe, and their mom doesn't even know what to tell the ambulance when it comes. And I just think, oh my God, I just don't think any of that is worth our time. I really don't. So no, I don't really get too involved. –DMD291 (non-advocate parent)

Some non-advocate parents stated they were uninvolved in advocacy to protect the normalcy of their child's life during the early stages of his or her diagnosis. This reason was mentioned by DMD and SCD parents only (n=3 of 6 DMD non-advocate parents; n=3 of 6 SCD non-advocate parents). These parents believed that interacting with advocacy organizations would prematurely impose a “disabled” or “abnormal” identity on their children. Parents who mentioned this reason tended to have children whose DMD or SCD was in the early stages of progression:

I'm really, really just focused on trying to get him a normal life so to speak...and not focus too much on making his life be all about this disease. I want him to realize with Sickle Cell Anemia he still has a life to live, and we don't want him to solely focus on this thing, don't let it affect every aspect of your life. As he gets older and learns more about this disease himself, maybe we will get more involved in things like that, because maybe he would want to get in contact with people that can share in his pain or whatever it is that he'll need support for. Maybe as he gets older we would be doing more of those things but right now we just try to treat him just like our oldest son. –SCD309 (non-advocate parent)

Six parent advocates (n=3 DMD parent advocates; n=2 ALD parent advocates; n=1 SCD parent advocates) believed that some parents chose not to become involved in advocacy because of a quieter personality type or having more private, introverted coping styles. Four parent advocates (n=2 DMD parent advocates; n=2 SCD parent advocates) believed that parents with relatively low incomes might not be able to find the time to devote to being involved in advocacy.

DISCUSSION

The aim of this study was to learn about the experiences and views of advocate and non-advocate parents regarding patient advocacy, including their perceptions of PAOs and their motivations for being involved or uninvolved in patient advocacy.

Both parent advocates and non-advocate parents reported both positive and negative experiences with PAOs, with more parent advocates citing positive experiences than non-advocate parents. Parents reporting positive experiences appreciated that PAOs allowed them to meet other families dealing with their child's condition, to access resources, and learn about research. Parents reporting negative experiences described feeling judged by other parents, or recalled the emotional strain of interacting with other children and families who were openly struggling to cope with their child's diagnosis.

Most parents believed that PAOs are reasonably well-equipped to help researchers engage patients in research, with some limitations. One such limitation was that PAOs may not be able to make research involvement accessible to socioeconomically disadvantaged parents, because those parents may lack the time or motivation to become involved with PAOs. This concern was raised more often by parent advocates than non-

advocate parents, suggesting that parents involved in advocacy are concerned with the inclusiveness of their own efforts. In the patient engagement literature, there is some evidence that people with addiction problems, low levels of formal education, undocumented citizenship, complex support needs, advanced age, or minority status are less likely to be included in efforts to involve members of the public in healthcare and research^{24,25}. Future studies should compare the demographic characteristics of patient advocates and non-advocate patients to shed light on whether partnering with PAOs for patient engagement could potentially perpetuate or ameliorate these patterns of non-involvement.

Another general perception parents mentioned was that PAOs do not always collaborate well with one another. These findings corroborate earlier literature on patient advocacy for conditions like breast cancer and autism, in which a lack of smooth collaboration between PAOs has been documented^{17,18}.

Some parents found that participating in advocacy helped them to cope with their child's illness, while others did not. This finding is consistent with a growing body of conceptual and empirical literature which suggests that individuals adopt divergent strategies to cope with a genetic or other serious condition²⁶⁻²⁸. While some find social interaction and problem-solving to be therapeutic, others may need time to themselves.

The finding that some parents were motivated to become involved in advocacy because they had specific professional skills is supported by a literature which shows that many patient advocates draw upon both formal and informal expertise^{6,23,29}. On the one hand, patient advocates who have both experiential and professional expertise may help

to balance out the knowledge asymmetries between “researchers” and “patients” that some researchers have identified as challenging to patient engagement initiatives^{19,32}. On the other hand, there is evidence that the hybrid nature of patient advocates' expertise may raise issues in research, such as conflicts of interest³¹. Future studies should explore the opportunities and challenges that arise when patient advocates play dual roles as formally-skilled professionals and experiential experts about a condition.

The fact that many parents said they were not involved in advocacy because of their competing caregiver responsibilities is supported by a literature that associates a significant emotional and financial burden with raising a special needs child^{33–35}. In a related theme, several parents also reported that they were uninvolved in advocacy in order to protect their child’s right to lead a “normal” life. These findings suggest that some parents may be unwilling or unable to be engaged in research for reasons similar to those that prevent them from becoming involved in patient advocacy.

LIMITATIONS

This study had a number of limitations. First, the parents interviewed were relatively highly educated; all of them had at least some college education. Second, parents volunteered to be interviewed, and those participating may have had different views compared to those who did not volunteer to be interviewed. This could bias the results of this study or affect the transferability of these findings. Third, more female parents were interviewed in this study than male parents, which is another potential source of bias in our findings given evidence that mothers and fathers may form different perspectives about experiences related to their child's illness^{36,37}. Finally, this study did

not interview parent advocates who do not hold formal roles in PAOs, which may have resulted in the omission of some parent advocates' views from this study.

CONCLUSION

The findings of this exploratory study suggest that irrespective of their advocacy involvement, parents have both positive and negative experiences when they interact with PAOs. Most parents believed that it was a good idea to partner with PAOs for patient engagement in research, but a subset of parents –mostly those with advocacy experience- - noted that PAOs may not be able to engage marginalized patients in research. Future studies should explore whether partnering with PAOs for patient engagement is indeed associated with low inclusion of marginalized patients. Future research should also identify strategies for involving marginalized patients in research and sustaining that involvement.

Many parents who participate in patient advocacy are motivated to cope with their child's diagnosis, to advance a cause, or to help others similarly situated. However, some parents choose not to participate in patient advocacy for equally compelling reasons, including their caregiver responsibilities, emotional needs, or privacy preferences. That some parents were uninvolved in patient advocacy for these reasons suggests that some parents may be unwilling or unable to be engaged in research. These findings suggest that while PAOs may not always provide researchers with access to every type of patient they wish to engage, some patients may be difficult to engage regardless owing to the competing demands on their time.

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Paper 3: Why might it matter, from a moral perspective, whom researchers choose to partner with for patient engagement in research?

ABSTRACT

There is growing support for patient engagement in research in the United States. Ethical arguments in favor of patient engagement emphasize that it can help to make research more relevant and respectful to patients. However, from a conceptual standpoint, it remains unclear whether patient engagement should be considered representative exercise, and if so, what this means. Drawing upon research ethics, political theory, and patient engagement literature, this paper explores the concept of representation and argues that patient engagement should be considered a representative exercise in which the knowledge, expertise, and descriptive characteristics of engaged patients reflects that of patients who are not engaged in research. To the extent that engaged patients can represent the perspectives, values, and attributes of other patients, the entire process of patient engagement will be more effective at achieving its ethically-important goals of making research more relevant and respectful to patients. However, practical considerations and resource constraints must also shape how researchers approach the goal of conducting representative patient engagement.

INTRODUCTION

In recent years, there has been growing investment in patient engagement in research in the United States. Institutions including the Patient-Centered Outcomes Research Institute (PCORI), the Food and Drug Administration (FDA), and the National Institutes of Health (NIH) have initiated programs that involve patients in aspects of research including research priority-setting, research design, data-collection or analysis, and results dissemination¹⁻³.

Patient engagement is an umbrella term that refers to the involvement of patients in research in roles other than subjects⁴. Patients can be engaged in research in different ways, to varying degrees, and at different phases of the research process, including its preparatory, execution, and translational phases⁵. Patient engagement can also employ different methods, including focus groups, surveys, one-on-one interviews, or serving on advisory councils or research teams^{6,7}.

The literature on patient engagement identifies value in its ability to produce higher-quality, more accountable, and respectful research⁸. However, little attention has been paid to whether the representation of patient groups should be an explicit goal of engaging patients in research, or what "representation" means in this context. Without conceptual clarity about whether and why patient engagement is (or ought to be) a representative exercise, it is difficult to know whether it might matter if volunteers who participate in patient engagement initiatives differ from patients who are not involved.

In this paper, I will begin by defending literature that suggests that, from an ethical perspective, patient engagement has both intrinsic and instrumental value. However, I will point out that prior work describing the value of patient engagement says

little about whom patient engagement activities should engage. Specifically, prior work is silent on whether engagement should be thought of as a representative exercise, in which differences between engaged and non-engaged patients might matter morally. I will then argue that patient engagement in research should be viewed as a representative exercise, and that differences between engaged and non-engaged patients *might* matter most with respect to two ethically-important goals of patient engagement: the relevance of research to patients and the degree to which research expresses respect to patients.

METHODOLOGICAL APPROACH

This analysis is the product of a review of the literatures on patient, community, and public engagement in research, research ethics, and of political theory literature related to the concept of representation.

The review of the literature on patient engagement revealed that there is a lack of guidance about the methods that should be used to identify patients to include in patient engagement initiatives^{9,10} and claims that those chosen to participate in patient engagement initiatives are often sampled by convenience via patient advocacy organizations or other accessible populations¹¹. The patient engagement literatures also suggest that the concept of representation is loosely related to the goals of engaging patients in research; the notion of representation also is referenced in the public engagement and community engagement literatures^{9,10,12,13}.

Much of the analysis used in this paper relies on bioethics work that describes the value of patient engagement as conceptualized as either instrumental or intrinsic in nature. Instrumental value refers to the degree to which something contributes to a

worthy end, while intrinsic value refers to the degree to which something is valued in and of itself¹⁴.

Finally, a review of the political theory literature helped to clarify conceptual elements relevant to the concept of representation, allowing me to develop a more precise understanding of how the concept of representation does and does not apply to patient engagement in research.

BACKGROUND

The primary role of a researcher is to contribute to generalizable knowledge about health or to increase understanding of a health problem. To accomplish this, researchers enroll human volunteers in studies involving experimental procedures or monitoring over time. Since research can involve burdens and risks for those who participate, and since the primary goal of research is to benefit society and not research participants, there is the potential for the harms of research participation to outweigh its benefits to participating individuals and thus for research to be exploitative¹⁵.

In response to the mistreatment of research participants during the mid-20th century, in 1974 the U.S. Congress established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Through its landmark *Belmont Report*, The Commission put forward ethical principles to guide the conduct of human subjects research: respect for persons, beneficence, non-maleficence, and justice¹⁶.

Since the late 1970's, the Belmont principles have been further specified. One highly cited framework emphasizes that scientific validity and social value (component

parts of beneficence) are ethically necessary to justify exposing research participants to risk, that fair selection of research participants (relevant to justice) facilitates the generalizability of research results, and that respect for prospective and enrolled research participants involves sustained communication with them over time¹⁷. A later version of this same framework, developed specifically for research in developing countries, further suggests the importance of collaborative partnerships with research participants to minimize its exploitative potential¹⁸.

Several authors have pointed out that research has ethical considerations relevant to the treatment and well-being of communities and broader publics¹⁹⁻²¹. The literature on community-based participatory research (CBPR) stresses that involving community members in research may be valuable from a justice perspective, because it addresses structural, physical and other inequities through power-sharing partnerships between researchers and communities^{22,23}. The public engagement literature describes the value of involving members of the general public in research planning, execution, and priority-setting, which can improve public understanding and support of research^{4,8}.

The more recent literature on patient engagement focuses on partnerships between researchers and individuals or groups with specific diseases^{1,11,24,25}. While much of this literature describes the practical value of patient engagement in research, relatively few authors have explicitly made ethical arguments in favor of patient engagement (Ellis & Kass, forthcoming).

In order to explore whether differences between engaged and non-engaged patients might matter ethically, it is first necessary to clarify how patient engagement

advances the ethical principles of research ethics. The following section, I will elaborate on the ethical value of patient engagement in research.

WHAT IS THE ETHICAL VALUE OF PATIENT ENGAGEMENT?

Ellis & Kass propose a framework that maps the moral rationales for conducting patient engagement. The framework distinguishes between justifications for patient engagement as an *intrinsic* act of respect and arguments that view patient engagement as an *instrumental* means of achieving more relevant, accountable, and culturally competent research.

With respect to the intrinsic value of patient engagement, Ellis & Kass argue that the act of listening to patients and paying attention to their concerns is in itself constitutive of respect for persons. The type of respect researchers express when they show concern for the interests, comfort, and cultural practices of patients is an expansive kind of respect that goes beyond respecting a person's right to make autonomous, voluntary decisions about research participation.

This concept of respect for persons is supported by other authors. For example, Dickert (2009) describes respect as “a combination of appreciating what is valuable or important about a person, recognizing the constraints or demands that such a valuation places on one’s own conduct, and acting in a way that expresses that recognition”²⁶. Several other accounts of respect for persons conclude that it involves avoiding being rude or discourteous to others²⁷, expressing concern for others, and listening to them and speaking to them directly and attentively^{26,29}.

The outcomes of patient engagement can also have moral worth. Ellis & Kass provide three arguments for how patient engagement can have instrumental value. First, the authors argue that patient engagement enhances *research relevance*. Research that is relevant to patients is beneficial to them, and can be said to optimize the risk-benefit ratio of research and enhance its social value. To the extent that patient input expands what is examined in a study, or alters how questions are asked in ways that make the research more meaningful to target populations, engagement can enhance relevance and in turn improve the benefits and value of research. What patients believe to be a relevant research question or outcome may not be exhaustive of what constitutes relevant research, but it is clearly morally important what patients want researchers to ask and to measure.

The bioethics literature supports these claims. For example, Casarett et al. (2002) consider patients' views about the relevance of a research question to be a measure of research value³⁰; Grady (2002) views public perceptions of a research problem as an important determinant of research value³¹, and Wenner (2017) argues that ethical research should be responsive to the perceived needs of communities in order to minimize the risk of exploiting them³². In CPBR (a type of research that explicitly commits to addressing issues that are priorities for a community) two systematic reviews have also found that engaging research participants increases the relevance, usefulness, and uptake of research results by all partners involved^{22,33}.

Another outcome of patient engagement in research described to be instrumentally valuable is engagement better informing researchers *how* to express respect to prospective and enrolled study participants. Respect for prospective and

enrolled research participants, defined broadly as a concern for their dignity and well-being, it is suggested, can only be expressed to the extent that researchers are aware of what constitutes dignity or well-being to a particular set of patients or in a given cultural context. Because social meanings are varied and multiple, it may not always be clear how researchers should specify the concept of respect, especially when researchers work with unfamiliar populations.

Evidence supports the idea that patient engagement can teach researchers how to express respect and that expressions of respect enhance ethically-important outcomes. For example, Rotimi et al. (2007) have found that community consultation resulted in the development of four different informed consent processes tailored to the distinct needs and sensibilities of different cultural groups enrolled in the same genomic ancestry study;³⁴ Baker et al. (2016) found that patient engagement can help researchers learn how to use respectful labels for patients in situations where patients' preferences may differ from nomenclature scientists would otherwise use³⁵.

A third outcome of patient engagement that Ellis & Kass highlight as instrumentally valuable is that engagement can enhance the *transparency* and (relatedly) the *accountability* of researchers and their study-related actions to participants⁸.

Transparency refers to researchers making information visible and accessible to study participants, for example, about what they are doing in the study and why; accountability refers to researchers being answerable for their actions, and in particular for fulfilling the actions they promise to fulfill or achieving the goals they claim the research will accomplish. Accountability, for example, may include returning to participants later in

the study and describing how their input changed the study or why input was not ultimately used.

This paper will focus on three of the types of ethical value patient engagement has: its intrinsically respectful nature, its ability to make research more relevant to patients, and its ability to make research more culturally competent by helping researchers learn how to respect unfamiliar patient groups. As I will argue later on, differences between engaged and non-engaged patients might matter with respect to these aims of patient engagement in research.

WHAT IS MISSING FROM THE ELLIS & KASS FRAMEWORK?

The claims made by Ellis & Kass that patient engagement can be relevant to the ethics of a study by potentially increasing its relevance and respectfulness are substantiated, as seen in the previous section, by other literature and will be taken here as reasonable claims. Their framework, however, is silent about whether and why it might matter *who* is engaged. Specifically, might it matter if the patients who participate in patient engagement initiatives differ from patients who do not participate? This is a critical question, because patient populations are heterogeneous, and patients who volunteer for patient engagement initiatives might systematically differ from other patients in any number of ways.

Studies have found that heterogeneity in patient populations might impact patients' views about research. For example, there is evidence that ethnoracial differences may affect knowledge and attitudes about genetic research for Alzheimer's disease³⁶; that more parents of children with autism would prioritize research to help

autistic children develop ‘neurotypical’ skills, while more adults with autism would not³⁷; that there are gender-based differences in attitudes to animal research³⁸; and that beliefs about appropriate ways to obtain research consent differ depending on the cultural backgrounds of the study populations in question^{34,39}

This dissertation project was motivated by the idea that the ability of patient engagement to best uphold its ethical underpinnings might depend on *which* patients researchers choose to engage in their work. This concern arose from the observation that many researchers engage patients by partnering with patients who are highly motivated, conveniently available or who already have specific expertise^{5,11}.

WHY MIGHT IT MATTER WHOM RESEARCHERS CHOOSE TO ENGAGE?

When addressing the question of how researchers should select patients to engage in research, the patient engagement literature often invokes the concept of representation or refers to patients who volunteer to be engaged in research as "representatives". For example, Workman et al. (2013) find representing the patient experience to be a challenging aspect of patient engagement in comparative effectiveness research; Hoffman et al. (2010) stress the importance of achieving balanced representation of different groups, including patients, in research engagement efforts, and Forsythe et al. (2015) cite the challenge of identifying patient representatives as a barrier to conducting patient engagement in PCORI research. In her work on the role of patient advocates in research ethics, Rebecca Dresser (2003) also identifies "uneven quality and legitimacy of representation"⁴⁰ as one pitfall of having patient advocates more involved in the research process without explicitly articulating what is morally at stake in such a shortcoming.

The suggestion that researchers should consider representativeness when embarking on patient engagement appears linked to an implicit, underlying argument that differences among engaged and non-engaged patients might matter with respect to the intrinsic and/or instrument value of patient engagement. To better understand the link between representativeness, patient differences, and the ethical value of patient engagement outlined above, it is helpful to clarify what the concept of "representativeness" means in relation to patient engagement in research, and whether "representation" in any sense ought to be a goal of patient engagement.

WHAT IS REPRESENTATION?

Political theory offers an extensive discourse on the topic of political representation. Much of this literature focuses on representation in the context of a democratic nation-state, in which individuals are asked to represent the interests of others by assuming roles in government institutions. Unlike a nation-state, the research enterprise is not a sovereign or political entity. As such, patients do not have rights or duties of citizenship related to the research enterprise. The political theory literature is nonetheless useful in clarifying the meaning of the concept of representation.

Representation is a complex concept including multiple elements. In political theory, debates about the nature of political representation often focus on the degree to which it is formalistic (institutionally shaped), symbolic (based on the meanings representatives have for their constituents), descriptive (based on the degree of similarity between representatives and their constituents), or substantive (based on the expression of substantive interests of a group by representative members of that group)⁴¹.

Another fissure in the literature concerns whether representatives should act as delegates (who follow the expressed preferences of their constituents) or trustees (who follow their own judgment about a proper course of action)⁴², though some authors consider this to be a false dichotomy. To reconcile these two ideas, Iris Marion Young conceives of representation as a relationship in which representatives are considered separate from their constituents but are connected to them in determinate ways, moving from "moments of authorization to moments of accountability"⁴³. Hanna Pitkin puts forth a similar idea, arguing that the specific function of representation is to exercise independent judgment but with credible knowledge about what constituents want⁴¹.

In his analysis of representation related to citizen panels, Mark Brown organizes conceptual literature on representation into five domains. The five elements distilled by Brown are: authorization, accountability, participation, knowledge, and resemblance⁴⁴. In the section that follows, I will highlight these dimensions of the concept of representation, drawing upon additional work from political theory literature. I will argue that if representation is understood using these five parameters, then patient engagement in research should be considered a representative exercise in only a very narrow sense. Understanding this relatively narrow sense of representation will later help me to clarify precisely when and how differences between engaged and non-engaged patients might matter ethically.

Authorization.

Brown describes authorization as the process of selection that determines who undertakes the job of representing a group. According to Hanna Pitkin (1967),

authorization is a formal feature of representation that says nothing substantive about the act of representing, or whether representatives should act as delegates or trustees. It logically precedes representation, making representation possible⁴¹. Representatives may be authorized to represent a group through a selection process such as nomination, appointment, popular vote, or random selection. There is some disagreement about whether the authorization of representatives via random selection confers authority on them in the same ways as an election or appointment would⁴⁵; however, there is general agreement that by instituting some technical or formal process of appointment, institution can recognize and therefore legitimize a representative's claim to speak on behalf of a group⁴⁵.

Accountability.

When a community has authorized someone to represent it, according to Brown, accountability requires a mechanism allowing members of that group to ensure that their representatives act in conformity with promises they have made. In Pitkin's view, while authorization makes representation possible, accountability logically follows it⁴¹. In the deliberative democracy literature, accountability is understood as a process of transparently justifying controversial decisions by invoking reasons that a representative's fellow group members endorse as relevant⁴⁶. These accounts share the notion that accountability involves a relationship between the members of a group and their representative, in which group members constrain and communicate with a representative in some way.

The concept of accountability in this context makes the most sense in reference to actions taken by representatives who are authorized to act on behalf of others. However, in situations where an individual has no such authorization, Jane Mansbridge argues that representatives can still be held accountable for what they have promised members of a group they will do⁴⁷. Without a formal process for selecting and re-authorizing representatives at periodic intervals, however, this softer form of accountability may be practically difficult to accomplish.

Participation.

Brown views increased public participation in policy decisions to be a core component of representative democracy and describes openness to participation as a central feature of representation. He acknowledges that some theorists view the concept of representation as antithetical to public participation, because by some accounts the purpose of representation is to render it unnecessary for citizens to participate directly in complex policy decisions. However, to the extent that representative roles are open to a diverse range of group members, representation can be said to have a participatory dimension.

In a political context, a decision-making body can be said to be more or less representative based on its degree of openness to the participation of marginalized or disempowered groups. In particular, so-called "difference theorists" including Iris Marion Young and Anne Phillips have argued that formal and informal barriers to political participation correlate with the systematic disadvantage of some groups that have been historically excluded from democratic institution-building and decision-

making^{48,49}. They use this argument to justify measures that encourage the inclusion of these marginalized groups in representative political processes using quotas and other affirmative action policies.

Knowledge and Expertise.

In Brown's view, the knowledge and expertise component of representation is related to the idea that representative institutions exist to advance the best interests of their constituents. While it may never be possible for members of a group to agree about what is right and wrong in a pluralistic society, Brown argues that some measure of expertise, or knowledge, is required to distinguish between a group's reflective collective interests and their mere impulsive desires.

The uncertainty surrounding many complex policy topics means that competing interest groups can find evidence in support of their opposing views⁵⁰. As such, there is ample scope for members of an overall group to disagree about what constitutes relevant or legitimate expertise. Furthermore, knowledge and expertise can be construed broadly, as either the products of formal, skill-based training or informal personal experience.

Resemblance.

The final component of representation that Brown points to is descriptive representation, which construes representation as a function of the degree of similarity (resemblance) between the representative and those she represents. This type of representation has been resoundingly unpopular with normative political theorists owing to its lack of substantive content. Descriptive representation is fundamentally concerned

with who the representative is, not what he or she wants or does. As Jane Mansbridge describes it, it is an "essentialist model in which representatives are viewed as 'typical' of their constituents by virtue of sharing some discernible characteristic"⁵¹.

In any context, descriptive representation is problematic because individuals belong to multiple statistical categories and define themselves and the groups they belong to in variable ways. However, there is some sense in which shared characteristics (such as ethnicity or gender) may correlate with what Iris Marion Young calls "social perspectives", defined as shared experiences that give rise to shared questions and concerns, if not interests or preferences⁴³. Social perspective, in Young's view, does not contain determinate content (and thus is different from an interest or substantive opinion on an issue).

IN WHAT SENSES SHOULD PATIENT ENGAGEMENT BE CONSIDERED A REPRESENTATIVE ACTIVITY?

In considering whether representation should be considered a goal of patient engagement, it is important to remember two of the reasons that patient engagement has ethical value in the first place: First, patient engagement has potential to make research more relevant to patients and second, it has potential to make research more respectful to patients. As argued earlier in this paper, patient engagement in research can make research more respectful because listening to patients is an intrinsic act of respect and because patient engagement can teach researchers how to express respect to patients through specific words, actions, and behaviors.

There is most obviously a link between the knowledge/expertise dimension of representation and these ethical goals of patient engagement. Here, "knowledge" is

construed broadly to include the experiences, perspectives, and values patients have regarding their health condition. If patient engagement is intended to teach researchers about what matters to patients, then it follows that it will be a more successful exercise if patients who volunteer to give researchers their input are familiar with the experiences and views of a wide range of patients. Since another ethically important goal of patient engagement is for researchers to learn how to demonstrate respect to patients by being culturally competent, it also matters how much engaged patients know about the range of values and cultural practices among patients in a given patient group.

Yet incorporating the full range of experiences, values, and perspectives that patients have with respect to research can be challenging because patients with the same disease often differ from one another with respect to certain sociocultural and disease-related experiences. Health conditions affect patients in varied ways, and socioeconomic, cultural, geographical, or educational differences can affect how patients form views about research priorities relevant to their disorder. For example, an early-stage patient with muscular dystrophy who lives in New York City may face very different mobility challenges than an advanced stage muscular dystrophy patient who lives in rural Wyoming, and as such, different mobility-related research questions might be relevant to each of them. While some patients interact with other affected families and are exposed to many impacts a condition has, others experience their health condition in relative isolation and may only be able to share their own sociocultural or disease-related point of view.

When a patient volunteers to give researchers input about research questions or study instruments, it matters from an ethical perspective whether she can credibly convey

the experiential knowledge and values of other patients with the same disease. If she cannot, then patient engagement may be limited in its ability to do its morally important work of making research questions, instruments, and outcomes more relevant to a heterogeneous group of patients. Furthermore, if engaged patients are only able to convey experiences and views of affluent or formally-educated patients, their engagement in research could pose justice concerns because their input could lead researchers to systematically ignore issues that matter to patients who are marginalized or disadvantaged.

Representing diverse patient experiences and views may be especially important when researchers are studying a disease with a progressive or variable disease course, or if a patient group is internally diverse in ways that could affect views about research among its members, such as religious affiliation. Evidence suggests that patients with different manifestations of a disease, or different ideological influences, can have different ideas about research. As data from my study showed, patients with the same disease may disagree about research priorities if they have experienced a disease differently.

The *resemblance* of engaged patients to non-engaged patients is also directly relevant to the ethical goal of enhancing the respectfulness of research to patients. Resemblance matters for two reasons: First, engaging a sample of patients that resembles the broader patient group may be viewed as an act of respect to members of the different demographic or sociocultural constituencies within that patient group. To varying degrees, patients who share similar demographic or sociocultural attributes might identify with each other and feel connected. In other words, those who view religion to be a

meaningful aspect of personal identity might feel respected knowing that another person from their religious background has been listened to by researchers, irrespective of any similarities or differences in their substantive beliefs related to research.

Importantly, individuals from a sociocultural group are not guaranteed to feel respected just because someone who shares that aspect of their identity has been listened to by researchers. However, Young's concept of social perspective helps us see that some characteristics (such as socioeconomic status, gender, age, or disability) are correlated with shared experiences that give rise to shared questions or spheres of relevance. By providing a way of listening to and demonstrating concern for the social perspectives of diverse patients, patient engagement can be considered an intrinsic act of respect for diverse patients, by proxy.

The second reason that the resemblance of engaged patients to non-engaged patients matters is because researchers are more likely to learn about a wide range of patient experiences and attitudes if they engage a subset of patients that reflect the true heterogeneity of that group. For example, if researchers wish to study a treatment for metastatic breast cancer in young women, they might wish to consult a group of patients that includes a large percentage of young African American women, because evidence suggests that these women bear a disproportionate burden of breast cancer at young ages⁵². Evidence also suggests that African American breast cancer patients may have different views about research and cancer treatment compared to women from other ethnic groups⁵³. By failing to engage a sample of patients that truly reflects the ethnic and cultural composition of this patient group, researchers might miss out on important

insights about young breast cancer patients' attitudes and values related to breast cancer research.

Thus far, I have argued that researchers should attempt to engage patients who know about the experiences and values of patients from diverse backgrounds if they are seriously committed to making their research more relevant to an internally heterogeneous patient group. I have also argued that by engaging a group of patients that resembles the demographic and sociocultural composition of a broader patient group, researchers stand a better chance of demonstrating respect to members of that group. Although these dimensions of representation cannot be substituted for one another, it stands to reason that if a small handful of engaged patients is very knowledgeable about a full range of patient experiences, it may be less imperative to engage a descriptively representative sample of patients. Conversely, engaging a descriptively representative sample of patients may alleviate the need for any single engaged patient to have extensive knowledge of other patients' experiences and beliefs. The point is that these two dimensions of representation - knowledge/expertise and resemblance - are direct shapers of how effectively patient engagement can function as a means to achieving ethically important ends.

What about authorization, accountability, and participation? Patients who become engaged in research are often chosen because they are already known to researchers, they are conveniently available, or they have the motivation and ability to devote time to such involvement⁵. Thus, patients engaged in research are not generally described as being "authorized" in any formal sense to speak for, or make decisions on behalf of, other patients. Owing to the logical relationship between the authorization and

accountability components of representation, there is currently little emphasis on holding engaged patients formally accountable to other patients, because they are not formally authorized to speak on behalf of those patients in the first place.

However, the fact that this is the case says nothing about whether engaged patients *should* be chosen based on explicit criteria. Since it matters from an ethical perspective whether the knowledge/experience and descriptive characteristics of engaged patients reflect those of the broader patient group they belong to, it follows that the selection process used to engage patients in research might matter as well. In a research context, where the goals of selecting patient representatives is highly focused, the use of formal elections would be an impractical way to select the appropriate patients to be engaged. Furthermore, formal elections would still not guarantee that engaged patients could provide input about a broad range of patient experiences and values.

Rather, having researchers publicize an explicit set of reasons for seeking broad patient input about research might encourage engaged patients to develop the depth and breadth of knowledge that researchers are asking for. It might also justify the selection of certain patients with specific knowledge or expertise for the job. For example, if researchers wish to engage patients to learn about all the possible side effects of a pain medication for sickle cell disease, it might benefit them to state explicitly that they wish to learn about impacts of that medication for patients across the lifespan, at all dosage levels. Any patient who could not demonstrate an understanding of other patients' experiences with the pain medication would clearly fall short of meeting the needs of the engagement exercise. The public statement of intent would help researchers stay accountable to the goals of their engagement exercise and would signal that patient

volunteers need to either develop the requisite knowledge or have their input replaced/supplemented by the input of other patients. By making public researchers' intentions to seek diverse or descriptively representative patient input, patient engagement efforts would also be more transparent and accountable to broader patient groups.

Regarding the participation aspect of representation, it is true that in some sense patient engagement is designed to increase the participation of patients in multiple aspects of research. However, increased patient participation in decision-making about research is not an end unto itself. Rather, it is a means through which researchers can learn about how to make research more relevant and respectful to patients. Increased participation without any demonstrable effect on these ethically-important outcomes has no moral value in and of itself.

GIVEN REAL-WORLD CONSTRAINTS, HOW SHOULD RESEARCHERS ENGAGE PATIENTS?

In practice, there are three reasons why it may be difficult or undesirable for researchers to engage a diverse or representative sample of patients in research. First, researchers have finite time and resources available for patient engagement and a primary fiduciary duty to contribute to generalizable knowledge about health. In many instances, it may be challenging for researchers to execute their study in a timely fashion and conduct representative patient engagement. In some cases, engaging a more representative sample of patients may be ethically unsupportable if it diverts resources from the pursuit of research itself. Furthermore, researchers may need additional training

and support to help them design patient engagement efforts, and these resources are not always available.

Second, experiential differences between patients need not *always* undermine the instrumental value of patient engagement; it is merely possible that differences between engaged and un-engaged patients *could* do so. For example, my study did not identify any substantive differences in beliefs about biorepository research when I compared the views of parents who have advocacy experience and parents who do not. Whether engaged patients' views about research differ from those of non-engaged patients is an empirical question that researchers can explore from time to time by polling broader patient groups for feedback about the relevance and value of the patient input they have incorporated into their research plans and around particular topics.

Third, there is evidence that the expertise and motivation of patient advocates can be assets in bridging divides between patients and formally-trained scientists^{56,57}. Furthermore, patient advocates may bring research-related expertise to the table and may be in a strong position to reach out and contact other patients by virtue of their roles in advocacy networks. Evidence from my study also suggests patient advocates may be strongly motivated to be engaged in research as part of their advocacy work. This suggests that there might be tradeoffs involved in engaging a diverse or representative group of patients as opposed to partnering with a potentially less diverse or representative group of advocates who are well-equipped to have meaningful and sustained involvement in a research project.

With these considerations in mind, to the best of their practical abilities researchers should employ a mixture of patient engagement methodologies. Doing this

will help them balance the benefits of involving patient advocates (and other available, motivated patient volunteers) with input from a more representative group of patients using surveys, webinars, or town hall meetings. Where researchers have only one patient on a planning committee or data analysis team, they might consider inviting three or four patients from different cultural backgrounds to participate, with the goal of demonstrating respect for a variety of social perspectives related to their research. If possible, researchers should be explicit about the type of information they wish to learn by engaging patients in research, so they can later evaluate whether patient engagement efforts have fulfilled their intended purpose. By paying attention to the of variability within a patient group and the natural progression of the disease they wish to study, researchers can be more attuned to potential gaps in the experiential knowledge and social perspectives of the patients they engage.

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Table 1.0: Characteristics of the Three Diseases Affecting Children of Parents in this Study

	Inheritance	Incidence	Symptoms	Disease Course	Life Expectancy	Treatments	Research Opportunities
Childhood Cerebral Adrenoleukodystrophy (CALD)	X-linked	1/17,000	Personality changes, loss of vision, cognitive decline, seizures	Rapidly progressive	7-15 years	Hematopoietic stem cell transplant	Few (<10)
Duchenne Muscular Dystrophy (DMD)	X-linked	1/3,500	Skeletal weakness, cardiomyopathy, respiratory failure	Progressive	30s	Corticosteroids, cardioprotective agents, respiratory therapy	Many (>50)
Sickle Cell Disease (SCD)	Autosomal Recessive	Unknown; (1/500 African Americans)	Pain crises, infections, pulmonary hypertension, ischemic stroke	Chronic	40s-50s	Hydroxyurea, blood transfusions, opioid therapy, hematopoietic stem cell transplantation	Some (>15)

Sources: www.genereviews.com; www.clinicaltrials.gov

Table 1.1: Participants' Background Characteristics

	CALD (n=12)	DMD (n=12)	SCD (n=10)	Total (N=34)
Parent Type				
Mother	10	9	9	28
Father	1	3	0	4
Legal Guardian	1	0	1	2
Median Age	46	39	45	n/a
Race				
White Non-Hispanic	9	11	1	21
Black	1	0	9	10
Hispanic	2	0	0	2
Other	0	1	0	1
Educational Status				
HS Diploma Only	0	0	0	0
Some college	6	3	1	10
College Degree	3	6	3	12
Graduate Degree	3	3	5	11
Military	0	0	1	1
Forms of Research Participation for Child*				
Randomized Clinical Trial	0	5	0	5
Other Clinical Trial	3	0	1	4
Observational Research	4	8	1	13
Social Science Research	0	1	1	2
None	5	1	7	13
Deceased Status of Child				
1 or more deceased children	6	1	0	7

No deceased children	6	11	10	27
Time Since Child's Diagnosis				
1-3 years	4	4	0	8
3-10 years	5	6	6	17
10+ years	3	2	4	9
Geographical Region**				
Northeast	5	4	8	16
Midwest	1	3	1	5
South	4	1	1	6
West	2	4	0	6

*Parents may have reported enrolling their child in more than one type of study

**According to U.S. Census categories

Table 1.2: Characteristics of Parent Advocates and Non-Advocate Parents

	Parents in Formal Advocacy Roles (n=16)	Parents Not in Formal Advocacy Roles (n=18)	Total (N=34)
Parent Type			
Mother	14	14	28
Father	2	2	4
Legal Guardian	0	2	2
Median Age	50	43	n/a
Race			
White Non-Hispanic	10	11	21
Black	5	5	10
Hispanic	0	2	2
Other	1	0	1
Educational Status			
HS Diploma Only	0	0	0
Some college	4	7	11

College Degree	5	6	12
Graduate Degree	7	4	11
Military	0	1	1
Forms of Research Participation for Child*			
Randomized Clinical Trial	2	3	5
Other Clinical Trial	2	2	4
Observational Research	9	4	13
Social Science Research	2	0	2
None	4	9	13
Deceased Status of Child			
1+ deceased children	5	2	7
Child(ren) living	11	16	27
Time Since Child's Diagnosis			
1-3 years	1	7	8
3-10 years	9	8	17
10+ years	6	3	9
Geographical Region**			
Northeast	6	11	17
Midwest	4	1	5
South	4	2	6
West	2	4	6

*Parents may have reported enrolling their child in more than one type of study

**According to U.S. Census categories

Table 1.3: Advocacy Roles of Parent Advocates

	CALD	DMD	SCD
Advocacy Group Leader/Founder	3	0	4
Newborn Screening Advocate	2	0	0
Public Relations Officer	0	1	0
Board Member	1	2	0
Scientific Reviewer	0	1	0
Conference Organizer/Fundraiser	0	2	0

APPENDIX 1: IRB APPROVAL NOTICE



FWA #00000287

Institutional Review Board Office

615 N. Wolfe Street / Room E1100
 Baltimore, Maryland 21205-2179
 Phone: 410-955-3193
 Toll Free: 1-888-262-3242
 Fax: 410-502-0584
 Email: jacob.lidoff@jhup.edu
 Website: www.jhsph.edu/irb

**INITIAL APPLICATION
 APPROVAL NOTICE**

Date: August 3, 2015

To: Nancy Kass, ScD
 (Lella Jamal)
 Department of Health Policy and Management

From: Luke C. Mullany, PhD, MHS
 Chair, IRB-X

Re: **Study Title:** "Exploring Parental Involvement in Research on Rare Pediatric Diseases"
IRB No: 00006316

The JHSPH IRB-X voted to approve the above referenced application at its meeting on July 9, 2015. The Board made the following determinations:

Approval of the research is for the period of July 9, 2015 to July 8, 2016. Please submit a progress report no later than 6 weeks before the approval lapse date. We recommend that YOU USE YOUR OUTLOOK CALENDAR, OR OTHER ELECTRONIC REMINDER CALENDAR TOOL, to set a timely reminder notification for this submission to avoid a lapse in approval.

Single Reviewer <input type="checkbox"/> Convened <input checked="" type="checkbox"/> DHHS 46.110 <input checked="" type="checkbox"/> DHHS <input type="checkbox"/> FDA 56.110 <input type="checkbox"/> FDA <input type="checkbox"/> Category: 6 & 7 GWAS <input type="checkbox"/>	Consent/Parental Permission Required From: Adult Participant <input checked="" type="checkbox"/> LAR <input type="checkbox"/> One Parent <input type="checkbox"/> Two Parents <input type="checkbox"/> Legal Guardian <input type="checkbox"/> (Foster Care Children)	Form of Consent/Permission: Written Consent <input type="checkbox"/> Waiver of Signature <input checked="" type="checkbox"/> (Oral Script) Waiver of Informed Consent <input type="checkbox"/> HIPAA Authorization <input type="checkbox"/> HIPAA Waiver <input type="checkbox"/> No Longer Enrolling <input type="checkbox"/>	Study Site(s): U.S. <input checked="" type="checkbox"/> International <input type="checkbox"/> List Country(ies):
Vulnerable Populations: Children <input type="checkbox"/> Foster Care Children <input type="checkbox"/>	Assent Required From: No children (waived) <input type="checkbox"/> Children aged: <input type="checkbox"/>	Pregnant Women/Fetuses 46.204 <input type="checkbox"/> Neonates 46.205 <input type="checkbox"/>	Sample Size: (screened plus enrolled) 42 Final Enrollment:

DHHS 46.404 <input type="checkbox"/>	FDA 30.51 <input type="checkbox"/>	Form of Assent: Written <input type="checkbox"/>	Prisoners 46.305 <input type="checkbox"/>	Secondary Data Analysis: (# specimens/participants)
46.405 <input type="checkbox"/>	30.52 <input type="checkbox"/>	Oral <input type="checkbox"/>	46.306 <input type="checkbox"/>	
46.406 <input type="checkbox"/>	30.53 <input type="checkbox"/>	Assent Statement in Parent Permission <input type="checkbox"/>	Epidemiological Research... <input type="checkbox"/>	

This approval is inclusive of the following documentation:

Research Plan (Version #1, 7-17-15)

Electronic Informed Consent for Screening Questionnaire (Version #1, 7-9-15)

Oral Consent Script (Version #1, 7-9-15)

Screening Questionnaire (Version #1, 7-17-15)

Interview Guide (Version #1, 7-7-15)

Flyer (Version #1, 7-17-15)

Initial Contact Note to Referral Liasons (Version # 1, 7-7-15)

As principal investigator of the research, you are responsible for fulfilling the following requirements of approval:

- 1) The co-investigators listed on the application should be kept informed of the status of the research.
- 2) Submit an Amendment Request Form for any changes in research. These changes in research are required to be reviewed and approved prior to the activation of the changes, with the following exceptions:
 - a) changes made to eliminate an apparent immediate hazard to the research participant may be instituted immediately and the JHSPH IRB should be informed of such changes promptly; and
 - b) changes to IRB Approved questionnaires, interview or focus group guides, other data collection or recruitment materials – limited to rewording to clarify meaning, correcting grammatical or typographical errors, or removing items that will not be used in the research.
- 3) Unanticipated problems involving risk of harm to participants or others that are related to the study procedures must be reported to the JHSPH IRB within 10 days of the time that the PI learns of such problems. A Problem Event Report Form must be submitted to the IRB immediately.
- 4) Only consent forms with a valid JHSPH IRB approval stamp or logo, with the correct IRB Approved version number and approval date may be presented to participants. All consent forms signed by subjects enrolled in the study should be retained on file. The Office of Graduate Education and Research conducts periodic compliance monitoring of study records, and consent documentation is part of such monitoring.

- 5) Federal regulations require review of approved research not less than once a year, unless a shorter period is determined by the IRB. **Therefore, a Progress Report for continuing review must be submitted to the IRB Office no later than six weeks prior to the approval lapse date. This will allow sufficient time for review of the application to be completed prior to the approval lapse date.** Failure to submit a Progress Report prior to the approval lapse date will result in termination of the study, at which point new participants may not be enrolled and currently enrolled participants must discontinue participation in the study. All ongoing research activities must stop immediately, including data analysis.
- 6) If your research involves international travel, please don't forget to register with the International Travel Registry <https://apps4.jhsph.edu/ITR/Default.aspx> so that the School may locate you in the event of an emergency.

LCM/sro

APPENDIX 2: EXTENDED METHODS FOR EMPIRICAL STUDY

This qualitative study had two aims, 1) to explore the views that parents of children with rare diseases have about research and 2) to determine whether parents of children with rare diseases who are patient advocates have different views about research than parents who are not involved in advocacy work. To accomplish these aims, qualitative interviews were conducted with 34 parents of children with either childhood cerebral adrenoleukodystrophy (CALD), Duchenne muscular dystrophy (DMD), or sickle-cell disease (SCD). Eighteen of these parents had no prior patient advocacy experience, and 18 currently held formal roles in patient advocacy organizations.

DEVELOPMENT OF MATERIALS

The materials used for this study were 1) recruitment materials (Appendix 3); 2) informed consent forms (Appendix 4); 3) a screening questionnaire (Appendix 5), and 4) an interview guide (Appendix 6). The study materials were developed by the student investigator under the supervision of her faculty adviser; the protocol and all materials were approved by the JHSPH IRB.

In order to test the interview guides, two pilot interviews were conducted via phone. Pilot interview testing is a good way to obtain guidance about questionnaire design, development, and pre-testing sequence, through post-interview discussions with individuals who are similar to those who will be recruited into the study¹. The first pilot interview was conducted with a parent of a child with a rare neurological disease who is not involved in patient advocacy and the second pilot interview was conducted with a rare disease patient advocacy group leader who was not eligible for enrollment in this

study. The pilot interviews were audio-recorded but not transcribed. The student investigator took notes during the pilot interviews and used these notes to inform changes to the flow of the interview guide as well as the re-wording of some questions to make them more understandable.

STUDY SAMPLE

Parents were eligible for inclusion in this study if they were English-speaking and parents/legal guardians of at least one living or deceased child aged 0-18 years of age who is or was diagnosed with CALD, DMD, or SCD. Eligible parents also lived in the United States. Non-English speaking individuals, individuals under 18 years of age, and individuals whose child died less than a year ago were not eligible to participate.

The section below describes the features of the three diseases that affected children of parents in this study as well as how the student investigator recruited parents into this study.

Background Information About the Conditions Parents' Children Had

Childhood Cerebral Adrenoleukodystrophy (CALD)

Adrenoleukodystrophy is estimated to affect 1 in 20,000 male births worldwide and is caused by mutations in the *ABCD1* gene. The childhood cerebral form of the condition (CALD) affects roughly 35% of boys born with a mutation in *ABCD1*. CALD is a fatal condition that affects the nervous system, involving a breakdown of the nerve cells in the brain responsible for thinking and muscle control. Affected boys typically present with ADHD-like symptoms which progress rapidly, resulting in a loss of vision,

seizures, personality changes, cognitive decline, and eventually a vegetative state followed by death (usually in childhood between ages 7-15)². Currently, the only way of treating CALD is to initiate a hematopoietic stem cell transplant (HSCT) prior to the onset of disease symptoms.

Duchenne Muscular Dystrophy (DMD).

DMD is a progressive X-linked neuromuscular disorder that affects an estimated 1:3500 live births. The condition also typically affects boys, not girls, and is thought to be pan-ethnic although in the U.S. it is diagnosed most often in individuals with European or Latino ancestry³. DMD is characterized by worsening muscle weakness and wasting due to mutations in the *DMD* gene, which produces an essential component of healthy cardiac and muscle tissue. The average age at diagnosis is four years old, with most patients becoming wheelchair-dependent by age 10 and developing severe cardiomyopathy and pulmonary dysfunction between ages 10 and 20. Most affected boys die from cardiac or respiratory failure in their second or third decade of life⁴. The nature and speed of *DMD* progression can vary depending on the type of mutation a boy carries.

Sickle Cell Disease (SCD).

SCD is an autosomal recessive hematological disorder that occurs more commonly in individuals of Mediterranean, Asian, and Sub-Saharan African descent. Although the overall incidence of SCD is unknown, it is believed to affect approximately 100,000 individuals in the U.S. However, among individuals of African descent, approximately 1 in 365 babies is born with the condition per year, most of whom are

detected via newborn screening. Initially, affected babies may experience repeat blood infections and pain crises; these symptoms are often followed by acute pulmonary symptoms and a risk of stroke which peaks at around six years of age. Children also experience crises of bone pain, chronic leg ulceration, and in adolescent boys, priapism (painful sustained erection unassociated with sexual desire) may occur. Patients can live into their fourth or fifth decade of life⁵. In severe cases, SCD is treated with HSCT, usually in adulthood.

Recruitment Approach

Participants were recruited into this study via two avenues: 1) Recruitment announcement sent via e-mail by leaders of patient advocacy organizations (PAOs) identified via the website of the Genetic and Rare Diseases Information Center at NIH and 2) Recruitment flyers distributed via clinicians in clinics at Johns Hopkins Hospital and Kennedy Krieger Institute.

To recruit parents via PAOs, the student investigator e-mailed PAO personnel whose contact information was publicly available via a PAO website or the GARD patient advocacy group directory. The initial contact e-mail explained that a doctoral student in the Johns Hopkins School of Public Health was interested in recruiting parents of children with rare diseases into a qualitative phone interview study to learn about parents' attitudes to research and patient advocacy. If PAO personnel agreed to assist with recruitment for this study, they were provided with a copy of the study's recruitment announcement and were asked to distribute it to eligible parents in a manner they believed would be most effective. In total four PAOs for CALD agreed to assist with recruitment, two PAOs for DMD agreed to assist with recruitment, and two PAOs for

sickle-cell disease agreed to assist with recruitment. The PAOs that assisted with recruitment for CALD and DMD served patients across the United States; the PAOs that assisted with recruitment for SCD served patients in Maryland and Michigan.

To recruit PAOs via clinics, the student investigator contacted clinicians who see pediatric CALD, DMD, and SCD patients at Johns Hopkins Hospital and Kennedy Krieger Institute. The student investigator explained the aims of the study and provided clinicians and clinic staff with recruitment flyers. For CALD and DMD, recruitment flyers were distributed in clinics at Kennedy Krieger Institute; for SCD recruitment flyers were distributed in a clinic at Johns Hopkins.

Since it is not known how many recruitment e-mails were sent or how many recruitment flyers were distributed, it is not possible to calculate a response rate for this study. Furthermore, since the screening process for this study did not ask patients where they first heard about the study, it is not possible to calculate precisely how many study participants were recruited via which avenue.

Sampling Approach

This study adopted a purposive sampling approach. Purposive sampling allows a researcher to build a diverse and complete sample with respect to the dimensions of interest in a research project⁶. The specific type of purposive sampling used for this study was called intensity sampling, which aims to select information-rich cases for in-depth study.

The primary aim of purposive sampling for this study was to form two groups of parents to interview. One group consisted of parents with patient advocacy experience and one group consisted of parents who lacked patient advocacy experience. The

secondary aim of purposive sampling was to build a sample of parents that was as diverse as possible with respect to demographic characteristics, geographical location, education level, and time since their child's diagnosis.

To achieve purposive sampling, the recruitment flyers for this study included a link to a ten-item screening questionnaire administered by Google forms. The screening questionnaire was designed to assess the nature and degree of parents' prior patient advocacy experiences including whether they currently played a formal role in a PAO. The screening questionnaire also included questions about the nature and number of their child's prior research experiences, the amount of time that had passed since their child's diagnosis, and demographic information about them including their age, ethnicity, geographic location, educational status, and deceased status of their children.

To select parents to invite for interview, the student investigator first took into account the nature and degree of a parent's advocacy involvement. To form a group of parents with significant patient advocacy experience, the student investigator chose to interview parents with formal roles in PAOs who described being currently active in some aspect of advocacy. To form a group of parents with little to no patient advocacy experience, the student investigator chose to interview parents who said they had never been involved in advocacy work. As a secondary consideration, the student investigator tried to invite as demographically diverse a sample of parents to be interviewed as possible.

A subset of parents (n=12) interested in participating in the study volunteered for the interview and contacted the student investigator to be interviewed without filling out the screening questionnaire first. In these cases, the student investigator asked parents

the screening questionnaire questions verbally before proceeding with the interview to determine their eligibility for inclusion in one of the two groups of parents interviewed.

INTERVIEW PROCEDURES AND STRUCTURE

All interviews (n=34) were carried out by the student investigator via phone; all interviews were conducted between October 2015-April 2016. Participants were informed that the student investigator was a genetic counselor and PhD student conducting doctoral dissertation research about parents' attitudes to research and advocacy. Prior to the start of each interview, oral informed consent was obtained. All interviews were audio-recorded and transcribed either by the student investigator (n=4) or a professional transcription service (n=30).

The interview guide contained three principal domains related to parents' experiences and attitudes to research and advocacy for their child's condition. The overall interview structure was similar for all interviews, with some deviations in the portion of the interview that asked about parents' diagnostic journey with their children for different diseases. There was some variation in the interviews depending on the flow of conversation and which topics parents chose to elaborate on.

The specific domains included in the interview guide were as follows:

1) Perceptions and Experiences Related to Research: Questions included under this domain inquired about whether parents had previously enrolled their child in a research study and, if so, what that was like; if not, why not. Follow up questions and probes asked parents to describe their general perceptions of research for their child's condition,

including how they learn about such research. If they had enrolled their child in a research study, they were asked to describe what was good or bad about their experience.

2) Perceptions and Experiences Related to Patient Advocacy: Questions included under this domain asked parents to describe their experiences with and perceptions of patient advocacy and PAOs. This included asking about any prior interactions they had had with patient advocates, any prior experiences they had had performing work for PAOs, and any perceptions they had of patient advocates or PAOs with a specific focus on the role of PAOs in research.

3) Specific Views About Biorepository Research: The final section of the interview guide inquired about parents' opinions and beliefs regarding specific aspects of biorepository research involving their child's data. Using the hypothetical example of the National Institutes of Health's Precision Medicine Initiative (<https://www.whitehouse.gov/precision-medicine>) parents were asked to imagine that they were being asked to contribute their child's genomic and health record data to a research biorepository. They were then asked about their hypothetical preferences regarding a) data stewardship and the necessity of re-consent for secondary research uses of their child's data; b) appropriate ways to recruit parents to participate; c) how children's research data ought to be used and d) their view about what made biorepository researchers trustworthy.

DATA MANAGEMENT AND ANALYSIS

After each interview, the student investigator took detailed memos and filled out an interview summary sheet. Interview tapes were either transcribed by the student or by

a professional transcription service. Identifying information was redacted from all interview transcripts. Each transcript was proofread and checked for accuracy against the original tape. The content of each transcript was also reviewed with a view to how the student might improve the interviews and in order to identify emergent themes to probe in subsequent interviews. Interviews were conducted until informational redundancy was reached relative to this study's research questions.

The approach to data analysis followed a qualitative descriptive approach and proceeded in an iterative fashion⁷. The primary phase of analysis was mainly deductive, with the initial coding scheme informed by this study's research questions, the domains in the interview guide, and themes from the literature about biorepository research ethics. Inductive themes relevant to this study's research questions were identified subsequently as tapes and transcripts were reviewed. The initial coding scheme was applied to four transcripts, and the codes and code families were then further refined and re-applied before finalizing a coding scheme to use on all the remaining transcripts. Coded segments of text were then analyzed manually and using Atlas.ti (version 7) to identify patterns in the data.

To test the reliability of the coding scheme, a second coder who is also a PhD student in Bioethics and Health Policy at Johns Hopkins was trained on the coding scheme. The second coder independently applied codes to four transcripts. The double-coded transcripts were compared and any discrepancies between the codes were discussed and reconciled. All discrepancies involved the application of different sub-codes to the same chunks of text; there were no cases where the two coders applied codes from distinct code families to the same portions of text.

REFLEXIVITY

In addition to being a PhD student in bioethics and health policy, the student investigator is a board-certified genetic counselor who worked in the Division of Neurogenetics at Kennedy Krieger Institute for 2 years from 2012-2014. In that capacity, the student investigator clinically counseled pediatric patients with ALD and DMD, as well as their families. The student investigator also previously counseled patients with SCD as a trainee. Because the student developed an interest in this topic through her experiences as a clinician, epistemological reflexivity played a prominent role in all aspects of this research project.

Epistemological reflexivity is an approach in which a researcher must ask whether the desired knowledge could be obtained via other means instead of her own research project⁸. In asking questions like this, the researcher is forced to reflect on her own motivations and assumptions, and their implications for the research she is conducting. By considering reflexivity at each stage of the research process, an investigator must examine her methodological and analytical decisions and make these decisions explicit, taking into account the context of her study and her role in that context. Such considerations may add richness to qualitative research, particularly if that research is designed with a constructivist theoretical orientation which assumes that meanings are socially produced⁹.

This study used a combination of spontaneous journaling throughout the project and more structured memo-ing to document personal, relational, and contextual aspects of the student investigator's role in relation to each research question, each interview participant, and at each stage of data analysis.

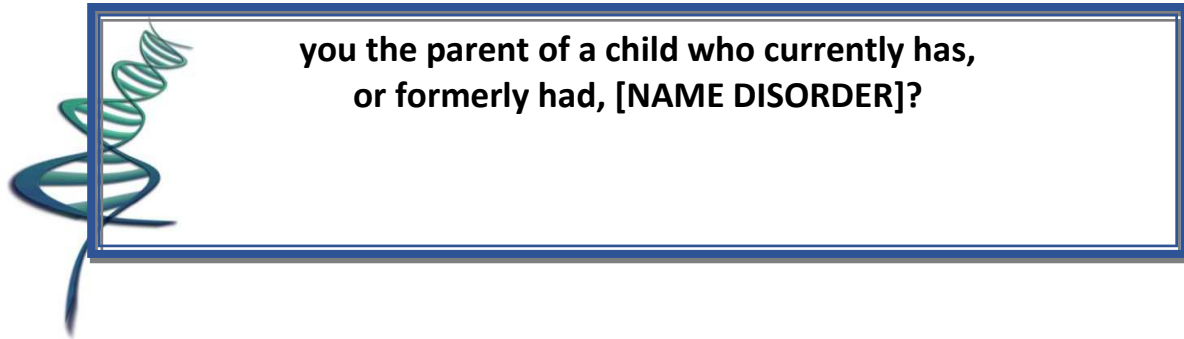
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APPENDIX 3: RECRUITMENT ANNOUNCEMENT

STUDY OF PARENTAL BELIEFS ABOUT RESEARCH

Are



- Does your child (aged 0-17) have a diagnosis of [NAME DISORDER]
- Are you the parent of a child who had a diagnosis of [NAME DISORDER] in the past?

We are asking you to participate in a study of parents' involvement in and beliefs about research on their child's condition.

You have a unique perspective — we would like to learn from your experience.

- Participation is completely voluntary.
- Participation involves a short online questionnaire and one 45-60 minute interview.
- Parents who are interested may find more information here, along with the online questionnaire: <http://bit.ly/1glLNtI>

For more information, please contact:

**Leila Jamal, ScM, CGC
(347) 327-0104; ljamal2@jhu.edu**

This research study was approved by the Johns Hopkins School of Public Health IRB, protocol # IRB00006316. The Principal Investigator for this study, Nancy Kass, ScD can be reached at nkass@jhu.edu.

APPENDIX 4: SCREENING QUESTIONNAIRE

****REMINDER:** If you have any questions about this study, you may call the Johns Hopkins School of Public Health Institutional Review Board at (410) 955-3193 or (888) 262-3242**

Questionnaire Content:

1. How old are you?
2. What disorder does your child have?
3. Which of the following best describes your relationship to a child with this disorder?
 - Mother
 - Father
 - Other primary caregiver or legal guardian
 - Other caregiver (not primary caregiver or legal guardian)
4. How long ago was your son or daughter diagnosed with this disorder?
 - Less than 1 year ago
 - 1-3 years ago
 - 4-5 years ago
 - More than 5 years ago
5. Have you been involved in any of the following? Please select all that apply:
 - Policy work related to this disorder (e.g. state or federal policy lobbying, legislative efforts)
 - Organizing or overseeing research for this disorder
 - Fundraising for this disorder
 - Educating the general public about this disorder
 - Other patient advocacy work (explain briefly in text box)
 - No, none of the above [IF NO, then SKIP to Q. 6]
6. Which of the following best describes about how often you are involved in any of the above activities:
 - About once per week
 - About once per month
 - A few times per year
 - Once per year or less
7. Has your child ever been enrolled in a research study?
Yes/No, then...(Optional free text field: If so, please describe your understanding of what the study was trying to learn:)
8. In what country or state do you live?
 - [Drop-down menu]
9. What is the highest level of education you've obtained?
 - High school or below
 - High school degree or GED

- Some college
- College/Undergraduate degree
- Graduate degree

10. What is your approximate household income (drop-down menu)?

- Less than \$100,000 per year
- More than \$100,000 per year

11. How would you describe your race/ethnicity?

- White Non-Hispanic
- African American
- Hispanic
- Native American
- Asian/Pacific Islander
- Other (Please specify) _____

12. Please tell me your name and how I can contact you to follow up about participating in an interview (i.e. please provide your phone number or email address) and what times of day are best to get in touch.

APPENDIX 5: VERBAL INFORMED CONSENT SCRIPT

ORAL CONSENT SCRIPT

You are being asked to take part in a research study. The purpose of this study is to understand your involvement in and beliefs about research on your child's rare condition. We hope to learn more about your prior experiences with research for your child's disorder and to learn more about your beliefs about how such research should be done. You are being asked to join this study because you are the parent of a child with a rare disorder. You expressed an interest in participating in the study when you completed our online questionnaire.

The interview portion of this study involves answering questions during one conversation which may occur via phone or Skype. The interview is expected to last between 45-60 minutes. We would like to audio record the interview, so we can note down your words accurately. If you do not want to have the interview audio recorded, you may still participate in the interview. Please let me know, and I will turn off the machine. If at any time you want to withdraw from this study please let me know, and will erase the tape of our conversation as well as your responses from the online questionnaire. The tape of our conversation, as well as all identifying information you provided to us, will be permanently erased at the conclusion of the study, approximately 18 months from now.

Use of your study information: We will not share the content of study interviews with individuals who are not on the study team. Your name will not be used in conjunction with any comments you share during the interview, but de-identified quotes and overall themes from the interviews may be shared in the study write-up and publications. After each interview is transcribed, a member of our study team will remove all individually identifying information from the transcript and assign a code to it. We will store all interview recordings and transcripts on a password-protected computer, separately from a spreadsheet containing links between the codes and the names of study participants.

Risks of participation: It is possible that you may feel distressed when asked to think about your child's condition or prior research experiences. There is also a slight chance that someone could find out about the content of our conversation due to a privacy breach.

Benefits of participation: There is no direct benefit to you for participating in this study. If you take part in this study, you may help others in the future. You will not be paid for being in this study.

You do not have to agree to be in this study. If you do not want to join the study, it will not affect your care at Johns Hopkins Medical Institutions or Kennedy Krieger Institute or any other medical institution.

If you have any questions about your rights as a research participant, or if you think you have not been treated fairly, you may call the Johns Hopkins Institutional Review Board (IRB) at (410) 955-3193.

Do you have any questions about me, the research, or our interview before we begin?
Yes___ No___

Do you agree to participate in this interview and to talk to me about your involvement in and beliefs about research for your child's condition? Yes___ No___

Date of Consent_____

Study ID_____

APPENDIX 6: INTERVIEW GUIDE

Thank you for your willingness to speak with me today. As a reminder, this interview is part of a study examining parents' involvement in research and advocacy for their child's condition. This project is part of my doctoral dissertation research for a PhD from the Johns Hopkins Bloomberg School of Public Health.

0. DOMAIN: INTRODUCTION, WARM-UP

To begin with, I'd like to get to know you a little bit better.

- 0.1) Tell me the story of how your child was diagnosed.
- 0.2) How are things going for you now?

1. DOMAIN: PERCEPTIONS AND EXPERIENCES OF RESEARCH

In this next part of the interview, I'm going to ask about your + your child's prior experiences with research.

EITHER: 1.1a) You mentioned in your survey responses that **your child has been** in a research study. Can you tell me a little bit about that experience?

Probes: *What was good about your experience? What was difficult about your experience? What did you learn from your experience?*

OR: 1.1b) You mentioned in your survey responses that **your child hasn't ever been** in a research study before. Can you help me understand why not?

1.2) Have you ever been involved in carrying out or fundraising for research on your child's condition? Tell me about that experience.

Probes: *What was good about your experience? What was difficult about your experience? What did you learn from your experience?*

1.3) Why do you think some parents get involved in orchestrating research, while other parents don't?

1.4) In your view, what are the pros and cons of having only some parents involved in orchestrating research?

1.5) Do you have any concerns about the safety of research your child might enroll in?

2. DOMAIN: PERCEPTIONS AND EXPERIENCES OF PATIENT ADVOCACY

Next, I'm going to ask you some questions about patient advocacy and patient advocacy organizations.

2.1) In general, what does the term "patient advocacy" mean to you?

2.2) Do you consider yourself to be a "patient advocate"? Explain why or why not.

2.3) Have you ever reached out to (or been part of) a patient advocacy organization? Tell me about that experience.

Probes: What were you looking for? What was good about that experience? What was difficult about that experience?

2.4) Sometimes, there is more than one patient advocacy organization serving people with the same disorder.

- Why do you think this happens?
- What do you think are the effects of this are?

2.5) Describe what role you think advocates and patient advocacy organizations should play in research on [disorder X].

2.6) What do you think are the effects of having advocates and patient advocacy organizations involved in [disorder x] research?

Probes: What are the benefits? What challenges can arise? Is there any difference having a patient advocate involved vs. an “average” patient with no advocacy experience?

2.7) When researchers want parents' input about research, they often get it from patient advocates and advocacy organizations. What are the pros and cons of this strategy?

3. DOMAIN: BELIEFS ABOUT RESEARCH

Now, I'm going to ask you about a specific scenario. As you may know, the federal government recently invested \$130 million dollars in building a national research database that will collect genetic and health record data from millions of people across the country. They are calling this the “Precision Medicine Initiative”

[Check for understanding, probe for prior knowledge, note this down. Explain more if needed]

The research database will be used by both government and industry researchers to study a wide variety of health problems. However, the project does not have infinite resources at its disposal. As such, some difficult decisions will need to be made about how this database is designed and used.

The Precision Medicine Initiative plans to consult members of the public about these decisions. In the final section of the interview, I'm going to ask you about some topics they might consult the public about.

Section i. Public Expertise/User-Specific Expertise

3.0) What aspects of this project do you think members of the public should have a say in. Why?

Section ii. Data Stewardship

3.1) Let's say a parent contributes his/her child's data to this research database. Some people think that no matter what, a parent should still be asked for permission every time their child's information is used in a new project. Others believe that when they contribute their child's data

for the first time, any researcher should be able to use that child's data in a future research project as long as that data does not include personal identifiers like name, date of birth etc.

- What do you think about this issue?
- What would your personal preference be?

Probes: Does it make a difference if the data is identifiable or not? What are the pros and cons of contributing de-identified data?

3.2) Some people believe there should be limits on how widely a child's health data is shared for research. Others believe that the more widely a child's data is shared among researchers, the better.

- What do you think about this issue?
- What would your personal preferences be?

3.3) Some people feel uncomfortable allowing certain types of organizations to access to their child's health data (eg. the government, for-profit organizations). Others don't have strong opinions about this.

- What do you think about this issue?
- What would your personal preference be?

Section iii. Research Priorities

3.4) Describe some high-priority research topics you'd like to see this database used for.

Probes: Topics related to your child's condition? Topics unrelated to your child's condition? How would you rank these?

3.5) As you may be aware, there are different opinions about which research topics are most important. For example, some people believe research should focus on preventing the birth of children with genetic conditions. Others believe research should focus on treating symptoms. Still others think the most important goal is to find a cure.

- Have you come across any differences of opinion about research priorities in the context of research on [disease X]? Tell me more.
- What are your personal opinions about this issue?
- How do you think differences of opinion about research priorities should be handled by researchers? By patient advocacy organizations?

Section iv. Recruitment

3.6) What are some acceptable ways for a Research Program like this to recruit parents to contribute their child's data to research?

3.7) What recruitment method would be most acceptable to you, personally?

Section v. Trustworthiness

3.8) What would a researcher need to do to earn your trust? To lose your trust?

Probes: What features, attributes, or behaviors do trustworthy researchers have?

CURRICULUM VITAE

Leila Jamal, Sc.M., C.G.C.
2502 Foster Avenue,
Baltimore, MD 21224
ljamal2@jhu.edu | (347) 327-0104

Current Positions

2014-present	Research Associate (50% effort)	Center for Medical Ethics and Health Policy, Baylor College of Medicine
2016-present	Adult and Pediatric Cancer Genetic Counselor (40% effort)	University of Maryland

Education

Expected in 12/2016	Bioethics and Health Policy	Ph.D.	Johns Hopkins Bloomberg School of Public Health
2012	Genetic Counseling	Sc.M.	National Human Genome Research Institute/Johns Hopkins University
2003	Philosophy, Politics, and Economics	B.A./M.A. (Oxon)	St. Johns College, University of Oxford

Professional Certifications

2013-present - American Board of Genetic Counseling

Honors and Awards

2016 - Dissertation Award, Center for Qualitative Studies in Health and Medicine at Johns Hopkins University

2015 - Scholarship to attend Oxford University's Translation in Healthcare Conference, Center for Health, Law, and Emerging Technologies at Oxford University

2014 - Scholarship to attend the National Society of Genetic Counselors' Annual Education Meeting, Invitae Corporation

2011-2013 - Sir Arthur Newsholme Doctoral Scholarship, Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health

2012 - Young Investigator Award, Sage Bionetworks

2011 - Best Student Abstract Award, National Society of Genetic Counselors

2009-2011 - Intramural Research Training Award, National Human Genome Research Institute

Work Experience

2012-2014 Genetic Counselor, Division of Neurogenetics Kennedy Krieger Institute

2007-2009 Research Associate Harvard Business School

2004-2007 Associate Consultant Orion Consultants

Selected Peer-Reviewed Research Articles and Commentaries

Published

Jamal L, Robinson JO, Christensen KD, Blumenthal-Barby JA, Slashinski MJ, Vassy JL, Perry, DL, Wycliff J, Green RC, and McGuire AL for the MedSeq Project “When bins blur: Patient perspectives on returnable results from clinical whole genome sequencing” (accepted for publication by *AJOB Empirical Bioethics*)

Winickoff DE, **Jamal L**, and Anderson, NR. “New Modes of Engagement for Big Data Research.” *Journal of Responsible Innovation* 0, no. 0 (June 28, 2016): 1–9. doi:10.1080/23299460.2016.1190443.

Hercher L and **Jamal L**. “An Old Problem in a New Age: Revisiting the Clinical Dilemma of Misattributed Paternity.” *Applied & Translational Genomics* 8 (March 2016): 36–39. doi:10.1016/j.atg.2016.01.004.

Christensen KD, Vassy JL, **Jamal L**, Lehmann LS, Slashinski MH, Perry DL et al. “Are Physicians Prepared for Whole Genome Sequencing? A Qualitative Analysis.” *Clinical Genetics*, June 17, 2015. doi:10.1111/cge.12626.

Angrist M and **Jamal L**. “Living Laboratory: Whole-Genome Sequencing as a Learning Healthcare Enterprise.” *Clinical Genetics* 87, no. 4 (April 2015): 311–18. doi:10.1111/cge.12461.

Mathews DJH and **Jamal L**. “Revisiting Respect for Persons in Genomic Research.” *Genes* 5, no. 1 (2014): 1–12. doi:10.3390/genes5010001.

Jamal L, Sapp JC, Lewis K, Yanes T, Facio F, Biesecker LG and Biesecker BB. “Research Participants’ Attitudes towards the Confidentiality of Genomic Sequence

Information.” *European Journal of Human Genetics*, no. 8 (August 2014): 964–68. doi:10.1038/ejhg.2013.276.

Peer-Reviewed Case Reports/Series

Tunovic S, Barañano KW, Barkovich JA, Strober JB, **Jamal L**, Slavotinek AM. “Novel KIF7 Missense Substitutions in Two Patients Presenting with Multiple Malformations and Features of Acrocallosal Syndrome.” *American Journal of Medical Genetics. Part A*, July 14, 2015. doi:10.1002/ajmg.a.37249.

Srivastava S, Cohen JS, Vernon H, Barañano K, McClellan R, **Jamal L**, et al. “Clinical Whole Exome Sequencing in Child Neurology Practice.” *Annals of Neurology* 76, no. 4 (October 2014): 473–83. doi:10.1002/ana.24251.

Gonzaga-Jauregui C, Lotze T, **Jamal L**, Penney S, Campbell IM, Pehlivan D, et al. “Mutations in VRK1 Associated with Complex Motor and Sensory Axonal Neuropathy plus Microcephaly.” *JAMA Neurology* 70, no. 12 (December 2013): 1491–98. doi:10.1001/jamaneurol.2013.4598.

Additional Writing

2015 - Chapter 13. Ethical and Policy Issues in Clinical Genetics and Genomics in *Lashley’s Essentials of Clinical Genetics in Nursing Practice 3rd Edition*

2014 - "What Do We Gain or Lose by Regulating 23andMe?", Berman Institute Bioethics Bulletin, available at: <http://bioethicsbulletin.org/archive/what-do-we-gain-or-lose-by-regulating-23andme/>

2013 - "An Education in Re-Identification", The DNA Exchange, available at: <http://thednaexchange.com/2013/06/07/guest-post-an-education-in-re-identification-learning-from-the-personal-genome-project/>

2013 - "Genetic Risk for Hereditary Cancer", Berman Institute Bioethics Bulletin, available at: <http://bioethicsbulletin.org/archive/preventing-breast-cancer/>

Selected First Author Abstracts & Invited Talks

2016 – “Exploring the Role of Patient Advocacy Organizations in Research” (Office of Human Research Protections, National Institutes of Health)

2015 - "The Crisis of Converging Disparities in Genomic Medicine" (American Society for Bioethics and Humanities Annual Meeting)

2014 - "Patient Perceptions of Whole Genome Sequencing Results and Intentions to Use Non-Actionable Findings" (American Society for Bioethics and Humanities Annual Meeting)

2014 - "Teaching and Learning Empirical Bioethics: Resources from the Presidential Bioethics Commission" (Association for Practical and Professional Ethics Annual Meeting)

2013 - "Genomic Research in Children with Neurodevelopmental Disabilities: Consent and Assent Issues" (American Academy for Cerebral Palsy and Developmental Medicine Annual Meeting)

2013 - "Implementing the Affordable Care Act in the NYMAC Region: Considerations for Families with Heritable Conditions" (New York Mid-Atlantic Newborn Screening Regional Collaborative Board Meeting)

2011 - "Does Family History Influence Anxiety/Depression in Arrhythmogenic Right Ventricular Dysplasia Patients?" (National Society of Genetic Counselors Annual Education Conference)

Professional Service

2014-present Public Policy Committee, National Society of Genetic Counselors

- Chair, Position Statement Task Force on Clinical Genome Data Sharing
- Co-chair, Position Statement Task Force on Human Germline Editing
- Member, Task Force on FDA Regulation of Genomic Testing

Selected Teaching Experience

2016 – Graduate Lecturer “Research Designs for Genetic Counseling Research”; University of Maryland Genetic Counseling Training Program

2014 and 2015 – Graduate Guest Lecturer: “Genomics in Public Health: An Overview of Issues in Newborn Screening”; Johns Hopkins Bloomberg School of Public Health

2014 and 2015 - Graduate Guest Lecturer: "Contemporary Issues in Genome Research Ethics"; Johns Hopkins Berman Institute of Bioethics

2014 - Undergraduate Guest Lecturer: "Practical and Ethical Issues in Genetic Counseling"; Duke University Course on the Past and Future of the Human Genome

2013 and 2014 - Undergraduate Guest Lecturer: "Genomic Counseling: Around the Field in 60 minutes"; Johns Hopkins University

2012 - Graduate Guest Lecturer: “The Complexities of Communicating Genetic Risk”; Duke University Forums on Genomics & Personalized Medicine

Teaching Assistantships

2014 - Graduate Teaching Assistant: "Ethical Issues in Public Health Policy"; Johns Hopkins Bloomberg School of Public Health

2014 - Graduate Teaching Assistant: "Ethical Issues in Public Health Practice in Developing Countries"; Johns Hopkins Bloomberg School of Public Health

2014 - Graduate Teaching Assistant: "Ethical Issues in Public Health"; Johns Hopkins Bloomberg School of Public Health

Non-Didactic Mentoring

Student Supervisor, University of Maryland Genetic Counseling Training Program

Thesis Committee Member – Jenn Kohler, Genetic Counseling Sc.M. Candidate 2016

Funding

2017 - ELSI Supplement to the Centers for Mendelian Genomics, NIH Grant number: 3UM1HG006542 - 05S1 (Co-Investigator, 100% effort)

Skills

Statistical analysis (using STATA and SPSS)

Qualitative data analysis (using NVivo and Atlas.ti)

Grant Writers' Seminars and Workshops - NIH Version (2014)

Professional Societies and Memberships

National Society of Genetic Counselors

American Society of Human Genetics

American Society for Bioethics and Humanities

Personal Information

Citizenship: United States and United Kingdom