RESEARCH

Mitochondrial Disease Community Registry: First look at the data, perspectives from patients and families

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ABSTRACT

Patient-populated registries are an important component of rare disease communities for many reasons, including their use as a tool for gathering opinions on specific topics. The Mitochondrial Disease Community Registry (MDCR) was launched in 2014 for this purpose as well as to identify and characterize mitochondrial disease patients *from the patient perspective*. Data collected over a four year period and provided by adult mitochondrial disease patients and caregivers of pediatric mitochondrial disease patients in response to a single survey are presented. Primary findings include the importance of clinician-patient communication, need for treatment and cure, impact of the disease on the entire life of a person, and quality of life as top issues as described by patients. Despite multiple challenges, patients are hopeful about the future and thankful for the survey. Efforts should be made to identify ways to better support patients, improve communication, and create more trusting and healing relationships between patients and doctors. Additionally, data quality checks showed that more clear and simple questions and shorter more-targeted surveys are needed in order to get accurate and meaningful data that can be used for analysis and research in the future.

KEYWORDS: mitochondrial disease, united mitochondrial disease foundation, UMDF, patient registry, genetics, doctor-patient communication, doctor-patient relationship, empathy, healing, hope, resiliency

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Introduction

Mitochondrial disease is a collection of rare disorders that result from inherited genetic defects that affect the electron transport chain responsible for generating cellular energy (Chinnery, 2014). Primary inherited mitochondrial diseases encompass hundreds of individual genetic disorders that are heterogeneous and frequently multisystemic. Organs with the highest energy demand are typically affected, although virtually any organ or tissue can be involved. Variability in the presentation of mitochondrial disease in infants, young children and adults often complicates clinical diagnosis (Parikh et al., 2015). Currently, there are no FDA-approved preventative or restorative agents for any mitochondrial disease or for these disorders as a whole (Weissig, 2019). The standard of care of mitochondrial disease is management of symptoms and non-specific supportive care. As in any rare disease, impact on the quality of life of patients and families is devastating and unpredictable, with lifelong and significant physical, emotional, social and financial implications (Pelentsov et al., 2016; Angelis et al., 2014).

Since 2014, the mitochondrial disease patient community has been actively sharing health information and personal opinions via the Mitochondrial Disease Community Registry (MDCR), stewarded by the United Mitochondrial Disease Foundation (UMDF). The primary goals of the patient registry are to identify and characterize mitochondrial disease *from the patient perspective*, in hope of facilitating improved diagnoses, developing treatments and cures, and optimizing clinical care. The data collected are meant to be complementary to clinician-derived data captured in other initiatives such as the North American Mitochondrial Disease Consortium (NAMDC) (https://www.rarediseasesnetwork.org/cms/namdc).

In this paper we will summarize the key findings of the primary survey completed by participants in the registry in order to better understand the patient and family perspective on diagnosis and clinical care of mitochondrial disease, while also assessing the registry design and quality of the data collected to date. Oftentimes living with a rare disease is characterized as a lonely, isolating process with a difficult road to diagnosis (Pelentsov et al., 2016; Grier et al., 2018). Our findings support this hypothesis and underscore the importance of patient education on disease, and for clinicians to speak openly and honestly with the patients for whom they are providing care (Awdish and Berry, 2019; Coulehan et al., 2001; Emanuel EJ and Emanuel EL, 1992; Back et al., 2019).

Methods

Participants were recruited to join MDCR through a variety of communications channels, including information on the UMDF website (http://www.umdf.org/registry), communication via the UMDF email list, social media (Facebook, Twitter) and direct communication at UMDF-sponsored meetings. After joining the registry, participants are presented surveys to complete within the registry software. This survey was developed by UMDF in conjunction with mitochondrial disease clinician experts because in the current literature there is not an existing survey that met our needs. As such, this survey is completely new and has not been validated in any way. The survey was filled out online by first registering and creating an account in the Platform

for Engaging Everyone Responsibly (PEER) software owned and operated by Genetic Alliance. Participants could register as "self, parent, or spouse/partner". The survey consisted of approximately 150 questions and is divided into sections including demographics, mitochondrial disease diagnosis information, general health, insurance coverage, interest in research or clinical trials, biospecimen availability, and thoughts about being a mitochondrial disease patient. Those who indicated caregiver status were asked an additional set of questions. Both the PEER platform and the survey were IRB-approved by Western Institutional Review Board.

This analysis involved data collected from August 2014 through September 2018, which included 2,223 participants. Participants in MDCR are able to dynamically control sharing preferences with respect to who can see or export their de-identified data and potentially contact them regarding research opportunities. Participants could select one of three privacy settings. Options were "allow" – UMDF could view and use their data, "ask" – UMDF would have to contact participants and ask prior to being able to use the data and "deny" – data would not be available to UMDF. At the time of this analysis in September 2018, a total of 1428 respondents had data available for UMDF to use, and therefore were included in the analysis. Others (N=795 in total) were not included due to being enrolled in the registry but never having started the survey (N=458), having selected more restrictive privacy setting (N=263), and a technical issue at the time of data export (N=74). Summary of participants' enrollment is shown in Figure 1.

Information collected in the survey about mitochondrial disease consisted of a series of branching questions. Contrary to a clinician-populated registry, and in an effort to cast a wide net across the disease community, participants in MDCR were not asked if they have a genetic confirmation of their diagnosis. Instead participants were asked how their diagnosis was classified by their medical doctors: definite, probable, possible, unlikely, or not yet classified. A detailed breakdown of diagnosis and classification is shown in Supplement Table 1. Specific diagnosis options included mitochondrial DNA point mutation, mitochondrial DNA deletion, nuclear DNA mutation, biochemical disorders, system disorders, and other (free text). Participants could select multiple diagnoses or fill in any number of free text fields.

Participants could indicate if they are personally affected, are a caregiver, or both.

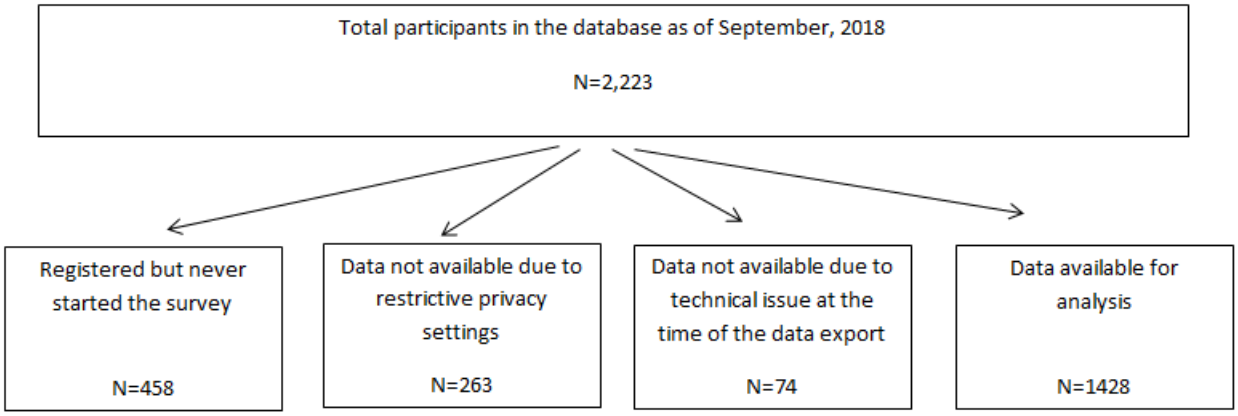
Age was calculated based on reported date of birth and date when the survey was completed, generated automatically by the survey based on account creation data.

Free text responses were grouped into categories to facilitate analysis. Both of the authors read all of the responses and agreed on the categories in order to reduce bias. A response could be categorized into more than 1 category. Invalid responses such as "n/a", "don't know", "none" or those that didn't answer the question were not considered.

Missing or invalid data was not included in the analysis.

Results

Figure 1: Summary of Participants' Enrollment



This analysis includes data on 1428 participants in the survey. Participant characteristics are shown in Table 1. The majority were female (63.2%) and white (88.2%). A majority of the participants were born in the US (86.2%), however the participation was international with at least 13 different places of birth represented. At least 26 languages were reported to be spoken at home, with English being the primary language for 91% of participants.

Age was calculated for 1037 respondents. 7 participants are not represented in the age calculation in Table 1 due to incorrect ages (3 had a calculated negative age, 2 had an age over 100 years old, and 2 reported date of birth to be the same as the date the survey was completed). Of the remaining 1030 the mean age was 31.5 years old, the minimum was 11 days and the maximum age was 94 years old.

Table 1. Demographic Characteristics of MDCR Survey Participants.

Category	n[b] (%)
Biological Sex (Genotype) (N[a]=905)	
Female (XX)	572 (63.20)
Male (XY)	328 (36.24)
Neither XX nor XY	5 (0.55)
Race (N[a]=974)	
White	859 (88.19)
Hispanic, Latino, or Spanish origin	35 (3.59)
American Indian or Alaskan Native	25 (2.57)
Asian	19 (1.95)
Black or African American	17 (1.75)
Other race or origin	17 (1.75)

Native Hawaiian or Other Pacific Islander	2 (0.21)
Location of origin (N[a]=934)	
United States	805 (86.19)
Other European Countries (other than UK)	32 (3.43)
Canada	27 (2.89)
Other	17 (1.82)
United Kingdom	17 (1.82)
Asia	9 (0.96)
South America	7 (0.75)
Middle East	6 (0.64)
Mexico	4 (0.43)
Africa	3 (0.32)
Caribbean	3 (0.32)
South Pacific	3 (0.32)
Central America	1 (0.11)
Age[c] (years, at time of survey completion)	
N[a]	1030
Mean ± Standard Deviation	31.5±21.4
Median	31
Q1 – Q3	11 – 49
Min – Max	<1[d] – 94

a. N = number of subjects with valid data for a specified category. This value is used as the denominator for the percentage calculations.
b. n = number of subjects with a specific characteristic.
c. In some cases, participants made updates to their profile several times. In that case only earliest instance was used for age calculation.
d. Youngest subject was 11 days old.

A total of 775 patients reported being a caregiver, affected by the disease, or both (Table 2). Of that total, 573 (73.9%) said that they are affected, 139 (17.9%) are caregivers, and 63 (8.1%) are both a caregiver and personally affected.

Table 2. Status of MDCR Survey Participants.

Affected/Caregiver (N[a]=775)	n[b] (%)
Affected	573 (73.94)
Caregiver	139 (17.94)
Both	(8.13)

a. N = number of subjects with valid data for a specified category. This value is used as the denominator for the percentage calculations.
b. n = number of subjects with a specific characteristic.

Table 3 summarizes mitochondrial disease diagnoses as reported by the participants of the survey. The top diagnosis was "Other" with 172 patients (41.2%) while all other individual diagnoses (29 types) had significantly lower counts (12% of patients or less).

Table 3. Mitochondrial Disease Diagnosis Reported by MDCR Survey Participants.

	All patients (N[a]=418)	Patients with self-reported "definite" diagnosis (N[a]=301)
Diagnosis	n[b] (%)	n[b] (%)
Other	172 (41.15)	123 (40.86)
MELAS (Mitochondrial Encephalomyopathy Lactic Acidosis with Stroke-like Episodes)	52 (12.44)	34 (11.30)
CPEO (Chronic Progressive External Ophthalmoplegia)	46 (11.00)	41 (13.62)
Complex I Deficiency	39 (9.33)	29 (9.63)
CoQ Deficiency	38 (9.09)	22 (7.31)
KSS (Kearns-Sayre Syndrome)	30 (7.18)	26 (8.64)
Mitochondrial DNA Depletion Syndrome	29 (6.94)	20 (6.64)
Complex IV Deficiency	27 (6.46)	19 (6.31)
Complex III Deficiency	25 (5.98)	20 (6.64)
Encephalopathy	24 (5.74)	11 (3.65)
Multiple Respiratory Chain Enzyme Deficiencies	21 (5.02)	14 (4.65)
MNGIE (Mitochondrial Neurogastrointestinal Encephalomyopathy)	19 (4.55)	10 (3.32)
LHON (Leber's Hereditary Optic Neuropathy)	18 (4.31)	15 (4.98)
MERRF (Myoclonus Epilepsy Ragged-red Fibers)	14 (3.35)	7 (2.33)
Encephalomyopathy	12 (2.87)	6 (1.99)
MILS (Maternally Inherited Leigh Syndrome)	12 (2.87)	9 (2.99)
NARP (Neuropathy, Ataxia and Retinitis Pigmentosa)	12 (2.87)	5 (1.66)
Sensory Ataxia Neuropathy	12 (2.87)	10 (3.32)
Complex V Deficiency	7 (1.67)	4 (1.33)
SANDO (Sensory Ataxia, Neuropathy, Dysarthria, Ophthalmoplegia)	7 (1.67)	6 (1.99)
Complex II (SDH) Deficiency	6 (1.44)	5 (1.66)
LHON-Plus (Leber's Heredity Optic Neuropathy Plus)	6 (1.44)	3 (1.00)
Alpers syndrome	5 (1.20)	4 (1.33)
MIDD (Maternally Inherited Diabetes and Deafness)	5 (1.20)	4 (1.33)
Dysarthria Ophthalmoplegia	4 (0.96)	3 (1.00)
Pearson syndrome	4 (0.96)	2 (0.66)
FBSN (Familial Bilateral Striatal Necrosis)	1 (0.24)	1 (0.33)
Hepatocerebral disease	1 (0.24)	1 (0.33)

Leukoencephalopathy	1 (0.24)	1 (0.33)

Note: Participants could select more than one diagnosis. 27% of all patients are counted in more than 1 category. 25% of subjects who responded as having "definite" diagnosis are counted in more than 1 category.

Note: Responses to ten multiple choice survey questions, where multiple responses could be selected, where used for this table. Additional responses, where diagnosis was specified in free text field, were not considered.

a. N = number of subjects with valid data for a specified category. This value is used as the denominator for the percentage calculations.

n = number of subjects with a specific characteristic.

Table 4 shows participants' willingness to update their health profile on a regular basis and participate in research. Most are willing to update their health profile with 420 (51.8%) and 259 (31.9%) definitely and very likely, respectively. Similarly 159 (53.2%) and 79 (26.4%) are definitely or very likely willing to participate in research.

Table 4. Participants' Willingness to Update Profile or Participate in Research.

Category	n[c] (%)
Willing to update health profile on a regular basis[a] (N[b]=811)	
Definitely would want to do this	420 (51.79)
Very likely	259 (31.94)
Somewhat likely	88 (10.85)
Uncertain	30 (3.7)
Very unlikely	7 (0.86)
Somewhat unlikely	6 (0.74)
Definitely not	1 (0.12)
Willing to participate in research (N[b]=299)	
Definitely would want to do this	159 (53.18)
Very likely	79 (26.42)
Somewhat likely	37 (12.37)
Uncertain	20 (6.69)
Very unlikely	2 (0.67)
Definitely not	1 (0.33)
Somewhat unlikely	1 (0.33)

a. 6 subjects had 2 different responses to this question. In these cases, their latest response was used.

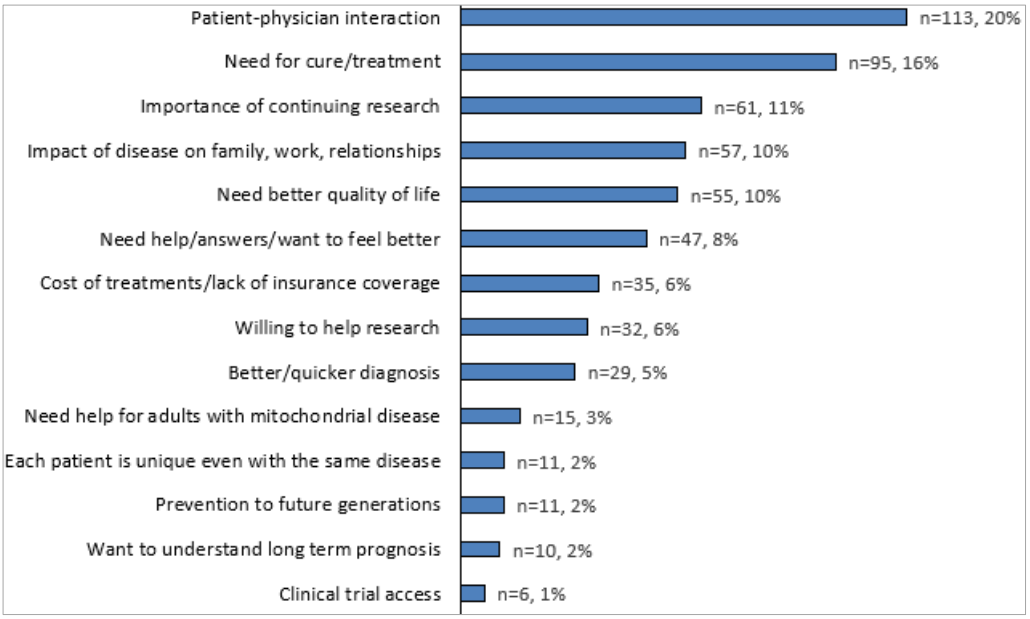
b. N = number of subjects with valid data for a specified category. This value is used as the denominator for the percentage calculations.

n = number of subjects with a specific characteristic.

Figure 2 summarizes responses to the question: "What is the most important thing that patients want scientists and physicians engaged in research for mitochondrial disease, as well as drug approval agencies such as the FDA, to know". A total of 534 participants responded to this question, which was classified to 630 responses due to responses being free text and some survey participants covering more than one

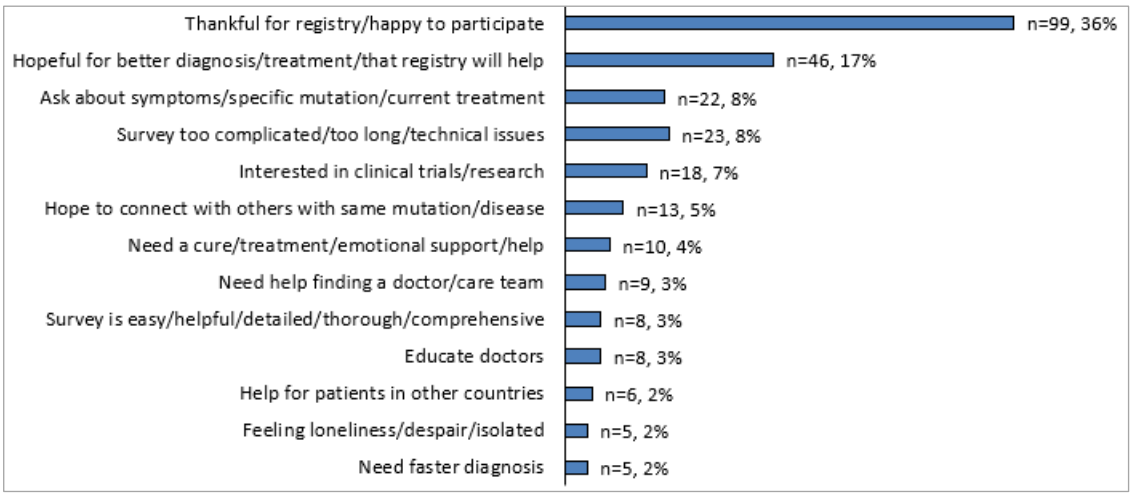
topic in the same response. We were unable to categorize 53 responses. Overall, the figure shows 577 responses from 481 participants. The top category was patient-physician interaction – 113 responses (20%). The next category was need for cure/treatment with 95 responses (16%).

Figure 2: Most Important Thing Survey Participants Want Scientists and Physicians to Know

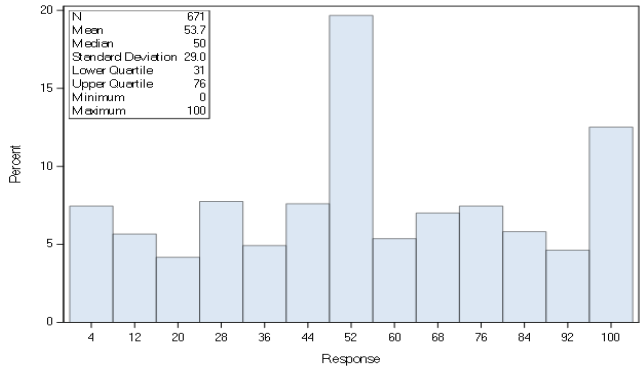
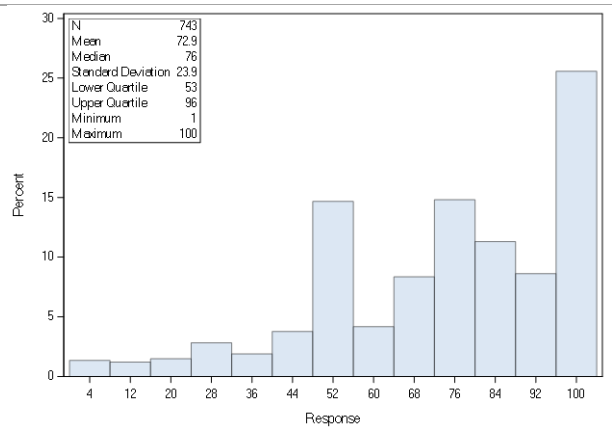


In Figure 3 we summarize participants' thoughts about this registry and survey. A total of 298 individuals responded to this question, which was classified to 315 responses. In total, 278 responses (from 261 participants) were categorized and 37 responses were not. The top categories were patients being thankful and excited about the registry with 99 responses (36%) followed by being hopeful about a future cure and that this registry will help doctors and others with 46 responses (17%).

Figure 3: Participants Thoughts About This Registry and Survey



Figures 4 and 5 show participants' level of optimism regarding treatment being available in time to be of benefit for themselves vs. available for others in the foreseeable future respectively by choosing a number from 0 to 100 (0 being most pessimistic). Figure 4 shows responses from 671 participants with a median of 50. Figure 5 shows responses from 743 participants with a median of 76. These figures are discussed in more detail in the discussion section.

Figure 4: Participant Level of Optimism- Personal Benefit	Figure 5: Participant Level of Optimism- Benefit to Others in the Future
	
Regarding myself I feel (0=Pessimistic anything can be done in time to address my needs; 100=Optimistic a treatment will be available in time to address my needs)	Regarding those affected in the future I feel (0=Pessimistic anything learned from my experiences could be meaningful to helping others in the foreseeable future; 100=Optimistic my participation in research may make a meaningful contribution to helping others in the foreseeable future)

Tables 5-9 show sample quotes from participants that correspond to the top 5 themes that patients want doctors and researchers to know the most (Figure 2). Tables 5 corresponds to the top category, patient-physician interaction (113 responses, 20%). Responses in that category related to doctor-patient communication and insufficient medical knowledge about the disease.

Table 5. Most Important Thing Survey Participants Want Scientists and Physicians to Know - "Physician-Patient Interaction"	
Theme	Quote
Insufficient medical knowledge of the disease	Every health care professional I have seen, I have had to educate about my disease and Mito in general. That's not an exaggeration.
	Eleven years of suffering and many, many visits to doctors who have no idea what's wrong across the country is unacceptable.
	I have mentioned symptoms to doctors before and many of them are very... I'm not sure if confused or uneducated are the right words but something like that. I explain the history and several doctors have no clue what I'm talking about and have little idea of what to tell me.

	It sucks when your symptoms don't fit the textbook idea of what is wrong with you and no one seems to be able to help. For some reason helping me is not profitable so therefore I suffer? HELP!!!!!
	Most of us feel that a lot of doctors think we make our symptoms up and do not believe us. We feel isolated and alone to deal with our disease. More education on the disease to doctors and the general community.
Doctor-patient communication	I feel my daughter has been seen too many times as merely a subject to experiment on. I want more for her than that- she is a living, breathing, human being first and foremost!
	... so many physicians don't listen and are so unkind I believe, not because they don't care but because they don't know and that's hard to be someone who cures not to be able to have an answer
	Be respectful and don't put a patient through the roller coaster of hope and disappointment if it is not worth the ride.
	those suffering with mito deserve to be treated with dignity & compassion.
	It was really hard to get help and for people to listen. It was extremely frustrating and it felt like nobody cared.

Table 6 shows selected participant quotes from MDCR survey emphasizing need for a cure or treatment as the most important thing patients want scientists and physicians to know, which was the 2nd most common response category in Figure 2 with 95 responses, 16%.

Table 6. Most Important Thing Survey Participants Want Scientists and Physicians to Know- "Need for a Cure or Treatment".

Quote
That people who suffer from mitochondrial disease are really desperate. Hopefully you will be able to find a treatment and save our lives. We pray for the cure. Thank you all for your support.
We are desperate for a cure or treatment to this horrible disease stripping the health and lives of so many. It is heart wrenching to watch your child's health deteriorate with no treatment.
We don't have a lot of time. Let's get drugs and therapies in the hands of patients ASAP
Time is running out. Quickly. Let us try some of the new drugs sooner rather than later. We have nothing to lose.
We can't wait years for viable treatments, we need real time clinical outcomes charted and assessed and then rapidly communicated. This community needs some sort of "model" for care as well. Please do not waste time on developing aps (sic) or tools to track your symptoms or your meds.... Nor support group efforts. We need real time data in clinics. Doctors need to work together to develop protocols that ALL patients would have access to.

Table 7 shows selected participant quotes from MDCR survey emphasizing importance of continuing research as the most important thing patients want scientists and physicians to know, which was the 3rd most common response category with 61 responses, 11%.

Table 7. Most Important Thing Survey Participants Want Scientists and Physicians to Know- "Importance of Continuing Research".

Quote
Do not stop researching! So many people appreciate what you do and so many people can potentially benefit from

your efforts.
Please keep trying and working hard for this, you are our only hope.
More progress needs to be made/research done on the types of mitochondrial disease that do not fit the currently established phenotypes, and as well as progress on improving diagnostic accuracy, specificity and sensitivity.
Please keep working for us! Please give us hope!
We are so grateful for doctors who are tirelessly working to better the lives of individuals with MD. Thank you for your commitment…

Table 8 shows selected participant quotes from MDCR survey emphasizing impact of disease on their entire life and quality of life as the most important thing patients want scientists and physicians to know. These categories were 4th and 5th most common themes with 57 and 55 responses respectively, both around 10%.

Table 8. Most Important Thing Survey Participants Want Scientists and Physicians to Know- "Impact of Disease on Their Entire Life and Quality of Life".

Theme	Quote
Impact of disease	It's important to realize these are real people with real lives and families. Testing and data collection takes a lot of time and resources, and young kids don't have that capacity, especially when they are already dealing with so many doctors and tests.
	…mitochondrial disease affects every area of my life: my education, my family, my activities, my commitments, my quality of life and my ability to care for myself and my family.
	It has bankrupted me financially, emotionally, spiritually and mentally It has robbed me of my virility which may the worst of all.
Quality of life	Patients with any form of mitochondrial disease are suffering–the quality of life is abysmal.
	My priority is balancing quality of life with research and medical testing.
	Quality of life is the most important thing for affected individuals.

Sample responses from less common categories are also shown below in Table 9.

Table 9. Most Important Thing Survey Participants Want Scientists and Physicians to Know - Other Topics.

Theme	Quote
Need help/answers/want to feel better	Please help us!!!
Cost of treatments/lack of insurance coverage	… some of us are spending tremendous amounts of money on supplements to keep us going without an FDA approved therapy. I personally spend 1000 dollars out of pocket for my supplements, which are not covered by insurance.
Willing to help research	we are here and willing to help. you just have to ask.
Better/quicker diagnosis	How difficult it is to get a definite diagnosis
More attention to adults with mitochondrial disease	That adults are also affected, and just because we are not specified with a named mitochondrial disease does not count us out. we are still in pain and struggling daily, but with less answers and hope.
Each patient is different even	Even though many of us have the same diagnosis, each of us still are still individuals

with the same disease	with varying reactions.
How to prevent disease transmission to future generations	Personally, my primary urgency in this area is for research to be approved for mitochondrial replacement therapy. I would like for the FDA to approve this procedure before it is too late for me to take advantage of IVF by this means.
Want to understand long term prognosis	the unknown progression or symptoms to expect because her mutation is so rare, is extremely frustrating and scary.
Clinical trial access	There needs to be a way to increase the number of participants in trials, decrease the age limitations and bring the drugs to market faster.

Table 10 shows sample patient quotes that corresponds to the top 2 categories reflecting participants' thoughts about this registry and survey (Figure 3). Top themes were thankful for the registry and happy to participate (99 responses, 36%), followed by being hopeful that this registry will help researchers, doctors, patients and lead to better diagnosis and treatment (46 responses, 17%).

Table 10. Participants Thoughts About This Registry and Survey - "Being Thankful and Hopeful".

Theme	Quote
Thankful	Thank you for all you do in an effort to give use some hope and help dealing with this disease
	Thank you for developing this Registry. I hope it will grow and we can come together to find a cure for Mito!
	Thank you for putting the time and effort into helping find a treatment/cure for our mito families! Our hope is that one day there will be a treatment/cure and more knowledge about the disease.
	Thank you so much for creating UMDF. I am so glad that I found you.
	I am thankful there is a registry and research and I am willing to help in any way needed!!!
Hopeful	Hopefully, this will assist in scientist and researchers working harder to find a cure, maybe not in my lifetime but in my children's lifetime who also suffer from this disease.
	I am hopeful that I can make useful contributions through my participation that will help others in the future. Otherwise my participation is in vain.
	I am hopeful that this will open avenues for expanded research programs, awareness in the medical community, and better treatment options for patients with mitochondrial disease.
	I am hoping that this registry will not only expose us to other medical professionals who may have experience with this mutation and can provide us with assistance but also that it will help others in similar circumstances.
	We are very hopeful that this registry will work and that as many mito patients as possible will participate so we can finally make some strides in the research

Discussion

Most important issues to patients

Patient-physician interactions were the top issue expressed by participants in our study when asked to describe the most important thing they want physicians and scientists to know (Figure 2). Responses can be split into two themes, one of which covers insufficient medical expertise regarding their disease and another deals with the human component of a doctor-patient relationship (Schmidt, 1996).

A prior study of 210 mitochondrial disease patients and their caregivers showed that patients face a long and difficult diagnostic journey, having to go through multiple consultations and conflicting diagnosis before receiving mitochondrial disease diagnosis (Grier et al., 2018). Our data confirms these findings and adds a human dimension by having direct quotes from the patients and families. Responses particularly emphasized a long diagnostic process, not being believed, and a struggle to find appropriate medical help. One patient commented, "Most of us feel that a lot of doctors think we make our symptoms up and do not believe us". Other sample quotes are shown in Table 5.

Responses regarding doctor-patient communication emphasized a need to be heard and seen as a real person and treated with respect and compassion. One participant commented: "Please hear and believe what the patients are telling you. Treat the health of the patient as [if] it was your own health". A desire to be seen as a person and not only as a patient was reflected in multiple comments such as "we are real people – not numbers" and "We as patients are people with families and friends". Some other sample quotes are shown in Table 5. As this was the top category, even surpassing the need for a cure or treatment, this shows how important doctor-patient interactions are for this patient population.

Research supports similar findings in other rare and common disease communities (Pelentsov et al., 2016; Tai et al., 2017; Down et al., 2019). For example, based on an online survey of around 300 parents of children with a rare disease, 54% of parents "felt that health professionals lacked the necessary knowledge and awareness to properly care for their child with a rare disease" (Pelentsov et al., 2016). Parents in this study experienced lack of overall support, poor communication from the medical community, and reported feeling isolated and alone. A qualitative study on the rare disease Behcet's syndrome included 8 patients who were interviewed in a 90-minute one-on-one interviews identified similar themes, revealing that patients valued being listened to and believed and ultimately that they most appreciated honest and clear communication (Tai et al., 2017). The authors highlighted that "acknowledgement of their struggles helped patients feel understood, which was emotionally therapeutic and enabled them to trust the doctor".

In another study, telephone interviews were conducted across 14 clinics with 192 patients who reported that being "empathetic", "humane", and "personal" were among the top 7 ideal physician behaviors (Bendapudi et al., 2016).

To our knowledge, our study is the first to demonstrate the impact of physician-patient communication specifically in mitochondrial disease. Responses show that even in the absence of a treatment or cure, the doctor's role is still tremendously impactful and can greatly affect and change the well-being of a patient and family (Awdish and Berry, 2019). Recognizing the therapeutic nature of the physician-patient relationship, particularly the role of empathy and kindness may improve health outcomes and help patients to better understand and manage physical and emotional aspects of living with their disease, as well as decrease physician's distress and burnout (Back et al., 2019; Berry et al., 2017; Doty, 2014; Fong Ha and Longnecker, 2010).

We believe that the comments described above should not be taken as a reflection of the medical system, general practitioners or clinicians who

specialize in the care of mitochondrial disease patients, but rather as the reality of a rare and not well understood disease. While patients are struggling to get answers, doctors may not be certain about the right thing to do medically or the right approach to take toward a patient who is going through traumatic experiences (Epstein and Back, 1995; Back et al., 2015; Weston, 2019). It is also important to recognize that this question didn't attempt to explore patients' experiences with doctors but rather asked to describe the most important thing survey participants want doctors to know, which likely resulted in a bias toward critical responses. Our hope is that bringing these issues and quotes to light may lead to improvements in communication and a better understanding between patients and doctors. Educational resources, both general (e.g., www.courageousparentsnetwork.org; www.empathetics.com) and specific to mitochondrial disease (e.g., www.mitosoc.org) are readily available to facilitate this process.

The category with the second-most responses was related to the need for a cure/treatment, with many comments emphasizing that cure or treatment is needed urgently, such as: "Time is running out. Quickly. Let us try some of the new drugs sooner rather than later. We have nothing to lose." Other quotes shown in Table 6.

It is interesting that the need for a cure or treatment was not the top category. Possibly, survey participants felt that doctors and scientists are already doing their best to find treatment or a cure and chose to focus on an issue which they hope to help change by sharing their thoughts. As one of the participants responded: "I/we could accept that there is no cure but what has been the worst is the way we have been treated and mistreated through the years!". It is also possible that participants were acknowledging the challenge of finding a treatment or cure for this complex disease. On the other hand, the fact that this was a close second does signal the importance of a finding a cure or treatment in the near future.

The third most-common category was the importance of continuing research. Many participants expressed that research that's going on gives them hope: "Please keep working for us! Please give us hope!". It is encouraging that many patient families are supportive of research moving forward. This relates to the importance of focusing on a cure/treatment and provides a measure of hope for the future for mitochondrial disease therapies. Some sample responses in this category are shown in Table 7.

The fourth and fifth most common response categories with nearly identical counts were impact of disease on the entire life of a person and quality of life. Responses in both categories emphasize that the disease and associated medical decisions go far beyond anyone's medical chart, but rather affect patient's quality of life, work, relationships, family, and more (Golics et al., 2013). One participant commented, "We feel isolated and alone to deal with our disease". Examples of other quotes from these categories are shown in Table 8.

These findings are supported by other studies. For example, a systematic review included 13 qualitative studies on feeding tube use in children with neurological diseases, and found that while this intervention is given for nutritional reasons it affects lives of the child, parents, family as a whole and relationship of a family with the outside world (Nelson et al., 2015). Additionally, a randomized control trial that included 91 clinicians and 278

patients with advanced cancer, showed that a clinician having a conversation with a patient about their values, goals, and preferences significantly reduced rates of anxiety symptoms in the intervention group within 2 weeks of conversation. This reduction lasted until at least 24 weeks after baseline, underscoring the long-lasting healing effect on patients when they feel that their life as a whole, and not just their disease, is considered (Bernacki et al., 2019; Paladino et al., 2019).

We have discussed the top five themes that emerged as the most important things patients want doctors and researchers to know. While it would be impossible to cover the rest in this paper, all responses are important and some selected responses from other categories can be seen in Table 9. We believe that everyone who responded to this question wanted to feel heard and understood. Indeed, one person commented, "I hope that something comes of this. I have done so many surveys and questionaires [sic] and NOTHING has ever come of it, NOTHING". We hope that it brings some relief to all who commented to know that all the responses were read and summarized in this paper.

Thoughts about the registry and the future

When participants were asked about their thoughts on this registry (Figure 3), the top 2 categories were being thankful and excited about the registry and hopeful about a cure, better diagnosis, and that this registry will help doctors, scientists, and other patients. One participant commented: "Thank you so much for creating UMDF. I am so glad that I found you", and another commented: "We are very hopeful that this registry will work and that as many mito patients as possible will participate so we can finally make some strides in the research ". Some other selected quotes are shown in Table 10.

Despite all the serious challenges described earlier, most participants are overwhelmingly thankful and hopeful; a conclusion also supported by a substantial increase in optimism in participants' thoughts regarding the likely success of mitochondrial disease therapy development now vs. in the future (Figures 4 and 5). That such opposite feelings can co-exist is thought provoking. It is known that hope can and does exist even in the most difficult of circumstances (Frankl V., 1946). For example, a study of parents of 32 children with relapsed or refractory cancer who were interviewed about their hopes and expectations found that parents were able to understand realistic expectations regarding their child's diagnosis and prognosis, yet still have hope (Kamihara et al., 2015). Most parents in the study initially expressed hopes for a cure or treatment, but later on expressed more realistic hopes, focused on the quality of life or minimal suffering. The authors concluded that "conversation [between a doctor and patient] about hopes, even impossible ones, can be a doorway toward talking about what is possible" and can help patients prepare for the future.

It is encouraging to see that mitochondrial disease patients and caregivers in MDCR have a significant level of hope. Possibly this means that patients want to be actively involved in making decisions about their own life and health as well as help advance research and contribute in other ways, as is also demonstrated by the fact that 84% of participants are definitely or very likely willing to update their health profile on a regular basis and 80% are definitely or very likely willing to participate in research (Table 4).

Data interpretation and registry design

Interpretation of reported age (Table 1) in this study is problematic due to the way the survey was designed. It is unclear whether the date of birth recorded by the participant represents the date of birth of a patient or a caregiver. This issue can also be demonstrated by the fact that out of 536 patients who had entered date of birth and identified themselves as affected or both (affected and caregiver), 74 (13.8%) reported an age of 12 or below, where we would expect affected patients to be adults.

It is also unclear how to interpret the results about affected/caregiver numbers (Table 2). Based on known prevalence data, mitochondrial disease can affect people of any age (Schaefer et al., 2019). That said, a significant percentage of affected individuals are children and so it would be expected that a large percentage of participants would respond as caregivers while we see the opposite in the data. It's possible that caregivers unintentionally responded "affected" responding for their child or that most participants in this survey were adult patients. Additional efforts are needed to recruit more caregivers of affected children to join the registry.

Interpretation of specific mitochondrial disease diagnoses (Table 3) in this survey is challenging. Only 418 out of 1428 (29.3%) study participants provided information about a diagnosis. Questions were divided into mitochondrial DNA mutation, nuclear DNA mutation, and other categories. From analyzing responses it appears that respondents were not clear on their diagnosis category because 41% of participants reported having "Other" diagnosis, and 27% of respondents reported multiple diagnoses. This is even true for those who indicated having a "Definite" diagnosis. Of those who reported "Definite" diagnosis (N=301), the largest group (41%) reported having an "Other" diagnosis and 25% reported having multiple diagnosis. We have not included data entered in the free text diagnosis fields, but it was clear that responses in such fields often didn't belong to the selected response category. It appears that many participants did not know how to classify their diagnosis, emphasizing further the importance of education and patient-clinician communication. This also reflects the lack of unified and consistent diagnostic criteria in the field, in addition to the growing knowledge and improved ability to achieve a genetic diagnosis for many even in the past few years.

These issues and inconsistencies indicate the need to significantly simplify the way questions are asked in the future in order to improve the accuracy of data capture. It would be best to have separate surveys for adults vs. caregivers in order to reduce potential for data errors as well as make sure that date of birth entered correctly captures the date of birth of an affected individual, represented by the survey. Questions regarding diagnostic state (confirmed, probable, etc.) and specific diagnosis should preferably be asked in a simpler manner (e.g., reduced choices) and it would also be best to just have one free text diagnosis field to make it possible to clean and recode that data as necessary. At this time, we believe that age, caregiver status, and diagnosis are not reliable variables for analysis.

Strengths and Limitations

The main strength of this survey is that it is the largest study of patients with mitochondrial disease, and the first one to examine patients' opinions and perspectives described in their own words. Since the survey asked open-ended

questions and participants could respond with free text responses of any length, they were able to express all of their thoughts and feelings about their disease journey and about this registry. Reading those responses gave the authors a good understanding of the experiences that patients and families with self-reported mitochondrial disease are going through. However, the limitation of free text responses meant the need to categorize based on the authors' judgement, opening the potential for bias. In order to reduce the bias both of the authors read through each response and reached consensus with each other on the assigned categories.

Another limitation is that the survey did not require a genetic diagnosis to confirm mitochondrial disease and we can't be sure that all the participants have definite primary mitochondrial disease. Separately, one question asked about whether diagnosis was definite, possible, probable, or unlikely, and another question asked if genetic testing was done, but there was no consistency in the data in the responses to those two questions. In the future we will add data checks throughout the survey to get more consistent and complete responses.

Also, as described above, it appears to be difficult to interpret data regarding mitochondrial disease diagnosis, age, and affected or caregiver status. After reviewing this data in-depth, we now understand that we need to be much clearer and more precise in the way questions are asked in future versions of the survey in order to capture information as accurately as possible.

We were not able to use data for 263 participants as they had set more restrictive sharing preferences. Possibly, participants need to be informed that when they set sharing preferences to more restrictive settings their data may not always be used, such as the case in this analysis.

As most of the study participants were white, female, and living in the US, these results may not be generalizable to other populations.

All disorders were grouped together for this analysis due to the data limitations. In the future, it would be important to repeat similar analysis by splitting participants into those with adult and childhood-onset disease.

Though the entire survey didn't have to be filled out at once and questions could be skipped, length and level of detail required by the survey are problematic and likely made this survey difficult to fill out for those living with or taking care of someone with a severe disease. This should be accounted for in future surveys.

Finally, it should be noted that the survey itself has not been validated and that all data in this survey was self-reported with no data validation performed such as by requesting medical records or contacting patients to confirm any information.

Conclusion

This paper reviews the initial data collection of the first four years of the Mitochondrial Disease Community Registry (MDCR). Over 1000 free text responses from participants in the survey were reviewed and grouped into themes in order to understand as much as possible about the lives of patients with mitochondrial disease. We found that the most important issues to patients are those related to their difficulties interacting with doctors and the medical system, need of treatments and cures, impact of the disease on the entire life of a person, and quality of life. We also found that despite many challenges, patients are hopeful and

optimistic about the future, thankful for the survey, and want to help. It is important to increase education and awareness of mitochondrial disease among the general medical community, as well as identify ways to better support patients, improve communication, and create more trusting and healing relationships between patients and doctors.

Also, we have looked at the descriptive statistics of the data and consistency between various responses in order to understand if this data can be used for analysis and research. New survey should be created with updated design and questions and participants asked to re-enroll in order to get more accurate and meaningful data and so that more extensive data analysis can be done in the future. In this regard the use of shorter, more-targeted surveys on specific topics such as symptomology and quality of life issues will be developed. There will also be an emphasis placed on collecting data in a longitudinal manner when appropriate to facilitate the development of natural history data from the patient perspective.

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Conflict of interest

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Authors' contributions

Study concept and design: SZ and PY; data acquisition: PY; statistical analysis: SZ; interpretation of data: SZ and PY; writing and editing of manuscript: SZ and PY.

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