ASSESSMENT OF ONLINE EDUCATIONAL RESOURCES REGARDING MITOCHONDRIAL DISEASE GENETICS

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ABSTRACT

The internet has become the primary resource for the public to access information about rare diseases. Patients and families have acknowledged the need for readable and up-to-date resources. Mitochondrial diseases are a group of rare disorders that illustrate the need for improved patient educational material (PEM). This diverse group of conditions is characterized by a high degree of genetic and clinical heterogeneity. Genetics of mitochondrial disease are complex resulting from pathogenic variants within nuclear DNA or mitochondrial DNA. Next Generation Sequencing (NGS) tests are becoming the standard genetic testing platform for cases of suspected mitochondrial disease given its high diagnostic yield. NGS tests are complex, yielding ambiguous results (VUS) and incidental findings. Educational resources are therefore essential.

Online PEMs regarding mitochondrial disease genetics were analyzed for readability. A survey was developed to assess patient/caregiver use, perception of material readability, and views on topics for inclusion on PEMs for genetic testing. The survey was distributed through the Mitochondrial Disease Community Registry (MDCR), a health information registry comprised of individuals affected with mitochondrial disease and caregivers sponsored by the United Mitochondrial Disease Foundation (UMDF).

A total 60 participants completed the survey. In general, online PEMs were written above a 6^{th}-8^{th} grade reading level. Flesch-Kincaid Readability Grade-level scores ranged from 7.6-15.9. The internet was the most frequently utilized resource (84%, n=48). Participants relied on

combinations of resources with 77% (n=44), reporting use of 2 or more resources including the internet, physicians, genetic counselors, and written material. Participants perceived a difference in knowledge about mitochondrial disease genetics, inheritance, and recurrence risk. Suggested topics for online genetic testing resources ranged from recommended tests, risks/benefits, VUS results, and insurance coverage.

Improving the readability of online PEMs is matter of public health significance given that members of the rare disease community rely on the internet for information. This study concludes that it is imperative for online PEMs to be up-to-date and written at a 6^{th}-8^{th} grade-level. Accessing multiple modalities of resources reflects a strong desire for information. This may be due to the perceived lack of resources and provider knowledge. Investigators recommend increasing provider education and awareness.

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PREFACE

Many people helped me get to this point. First, I want to thank Jodie Vento for her guidance throughout this project. From brainstorming ideas to the lengthy editing process, you have helped me carve out a meaningful and impactful project. Secondly, I want to thank Andrea Durst for all her feedback and keeping me on track. Thank you to Dr. Amy Goldstein for her support and expertise within the mitochondrial disease community. Many thanks to Dr. Elizabeth Felter for her expertise in health literacy and insight into the role this plays when considering patient educational materials. Phil Yeske and the United Mitochondrial Disease Foundation were instrumental to the project. Thank you for your enthusiasm and guidance in navigating the registry. Everyone's collective efforts have pushed me to reach a higher level and yielded document that I am proud of. I hope that my conclusions have a positive impact on the development of patient educational materials.

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1.0 INTRODUCTION

The internet has become the primary resource for patients and families to access information about genetic and rare conditions.[1] Definitions of a "rare disease" vary widely depending on region of the world; a rare disease is a condition that affects fewer than 200,000 people in the United States or no more than 1 of every 2,000 people in Europe.[2] Members of the rare disease community use internet resources as an educational tool to improve their knowledge so they can be better advocates for themselves, their loved ones, and the people for whom they take on the role of caregiver. Often patients, parents, or caregivers report transforming into the role of disease expert because the condition is so rare that physicians may not be well informed about diagnosis and treatment. Patient experiences with rare conditions emphasize the importance of education to this population. A growing sentiment within the rare disease community is the collective struggle for improved outcomes, information, and interventions.[3] The need for readable, accurate, up-to-date, and informative resources has been identified by patients and their families.[3,4] Improved educational materials can clarify recurrence risk and inheritance patterns. Better educational materials can also help patients and their families feel supported when advocating for themselves. It is crucial that online educational resources be written using patient centered language in an overall readable format targeted to the public.

Mitochondrial diseases are a group of rare disorders that illustrate the need for improved patient educational resources. This diverse class of conditions is unique because they are characterized by a high degree of genetic and clinical heterogeneity.[5] As of 2017, MitoCarta, a curated catalogue of genes, lists 1,158 nuclear and mtDNA genes encoding proteins strongly implicated with mitochondrial function.[6] Individually, mitochondrial diseases are rare however they are more common as a collective group with

an estimated prevalence of 1 in 5,000.[7] Although mitochondrial diseases demonstrate a wide range of symptoms, dysfunction is typically observed in body systems requiring high amounts of energy such as the central nervous system, gastrointestinal system, musculoskeletal system, and cardiovascular system. Symptoms can include low muscle tone, developmental delay, seizures, stroke, hearing loss, ophthalmologic manifestations, and gastrointestinal issues. Symptom onset typically occurs in childhood however onset can occur over a wide range of ages from neonatal to adulthood. Disease and symptom severity are also variable, ranging from severe to mild within and between families with the same disease.[5] The genetics of mitochondrial disease are complex. Mitochondrial dysfunction can result from pathogenic variants within the nuclear DNA (nDNA), or within the mitochondrial DNA (mtDNA) which are necessary for energy production.[8,9] The combination of clinical and genetic heterogeneity makes diagnosing mitochondrial diseases difficult even for the most experienced clinician. Next Generation Sequencing (NGS) technologies are becoming the standard platform for genetic testing in cases of a suspected mitochondrial disease given its high diagnostic yield.[10] NGS tests allow for concurrent analysis of many genes, thus it is faster and more cost-effective than traditional sequencing methods. NGS technologies can include exome sequencing, mtDNA sequencing, and multigene panels. The exome consists of all the genome's exons, which are the coding portions of genes. It makes up roughly 1% of the entire human genome or 22,000 genes.[11] It has been estimated that 85% of pathogenic variants can be found in the exome.[12] Exome sequencing is typically more cost effective than testing 2 or more genes via sanger sequencing.[13,14] As a clinical tool, NGS technologies are superior to traditional sequencing because they cast a wide net such that testing is not limited to genes known to be associated with the patient's manifestations. By casting a wide net, clinicians can diagnose genetic conditions with overlapping phenotypes that mimic mitochondrial disease. [15,16]

NGS tests are complex and can yield ambiguous results known as variants of uncertain significance (VUS). VUS represents a change within a gene that may be novel and unique to an individual. It can also represent a rare population variant that has yet to be characterized. A VUS may or may not explain a patient's phenotype. Geneticists use a set of guidelines to determine if a VUS may be

pathogenic including MSeqDR, an annotated database of pathogenic DNA mutations known to cause mitochondrial diseases. VUS results can be reclassified over time as benign or pathogenic as more clinical and genomic data is gathered. The probability of getting a VUS result increases with the number of genes sequenced. The probability of finding this type of result with NGS testing is high as multiple genes are simultaneously sequenced. Exome sequencing also has the potential to yield results known as incidental or secondary findings which are unrelated to the patient's symptoms but have serious health implications for the patient and their family. The breast cancer genes, BRCA1/2, are examples of secondary findings that can be identified by exome and can have risk implications for breast and other cancers within a family.

Online educational materials about genetic testing are limited, difficult for patients to read due to technical language, and often may be outdated due the rapid pace of developing technologies. This limited availability is particularly problematic in the context of rare conditions such as mitochondrial diseases where the patient and/or their love ones primarily use online educational materials as a resource. Due to potential for ambiguous and incidental results of genetic testing, it is crucial that material about the genetics of mitochondrial disease and genetic testing be written in clear, concise, and patient-centered language. It is vital that patients be well informed before consenting to genetic testing about the benefits, limitations, and types of results that NGS technologies can provide before they pursue genetic testing. In addition to promoting informed consent, developing educational material specific to genetic testing for mitochondrial disease would enable patients to feel more empowered and better able to advocate for their care.

The rationale for the current study derived from initial observations of patient online educational materials regarding the genetics of mitochondrial disease. Overall, online educational materials are written in language above the recommended 6th-8th grade level and were low in readability. Online patient resources vary in what information about mitochondrial disease genetics is included. For example, many online resources include information about genes and chromosomes, and the difference between

nDNA and mtDNA. However, a number are lacking in concepts that can complicate mitochondrial disease inheritance and predicting severity, such as heteroplasmy, bottleneck, threshold, and mutation load. Some resources are easy to locate on an organization's website while others were not. Online content regarding genetic testing for mitochondrial disease is present on some websites but not others and vary greatly. These observations prompted the author to explore patient perception of educational material found online, specifically looking at ease of reading and understandability, ease in finding patient resources online, and perceptions about the content included in online resources regarding mitochondrial disease genetics. Through the development and distribution of a patient survey, information and results were obtained for this study. Given the observed lack of online patient resources for genetic testing and the importance of such testing to diagnosing mitochondrial diseases, patients were also asked what information about genetic testing they would find helpful if such resources were developed.

1.1 SPECIFIC AIM I

Assess the degree to which online educational literature and resources for mitochondrial genetics and the available genetic tests meets the health literacy needs of a general audience.

1.2 SPECIFIC AIM 2

Improve understanding of overall patient, family member, and/or caregiver perception of current online educational resources for mitochondrial genetics and genetic testing options. This aim will be accomplished by surveying patients, families, and caregivers enrolled in the Mitochondrial Disease Community Registry (MDCR), which is maintained by the United Mitochondrial Disease Foundation (UMDF).

1.3 SPECIFC AIM 3

Develop recommendations for educational material development based on the findings of the survey from Specific Aim 2.

2.0 LITERATURE REVIEW

Mitochondria are double membrane bound organelles found in eukaryotic cells. Mitochondria are responsible for the production of energy in the form of adenosine triphosphate (ATP) through the process of oxidative phosphorylation. Embedded in the inner cristae is the electron transport chain, a series of protein complexes that carry out a sequential set of redox reactions to produce ATP. Roughly 90% of a cell's energy is produced during this process. Mitochondria also play a role in the production and removal of reactive oxidative species, initiation of cellular apoptosis, steroid synthesis, thermogenesis, and the regulation of calcium signaling.[17,18] A single cell can carry hundreds to thousands of mitochondria. Mitochondria are unique from other organelles because they carry their own DNA (mtDNA),16.5kb in size.[19] A single mitochondrion carries multiple copies of mtDNA. There are 37 genes in the mitochondrial genome that encode 13 mitochondrial proteins, 22 transfer RNAs, and 2 ribosomal RNA units involved in the formation of respiratory complexes I, III, IV, and V.[18] Nuclear DNA (nDNA) encode the protein products that make up the respiratory complexes and the enzyme polymerase gamma, the DNA polymerase responsible for mtDNA replication and repair. [19]

2.1 GENETICS OF MITOCHONDRIAL DISEASES

Mitochondrial disease inheritance is significantly more complex than single gene disorders given the possibility of nDNA and/or mtDNA pathogenic variants. Nuclear genes encode components of the respiratory chain including structural subunits and translation factors. Pathogenic variants can occur

within mtDNA encoded proteins, tRNAs, and rRNAs.[20,10] Deletions and duplications to the genome can also cause mitochondrial diseases. mtDNA is maternally inherited being passed through generations by women in a family.[21] Unlike sperm, egg cells retain cytoplasm containing multiple copies of mitochondria to pass onto future offspring. Recurrence risk can range from 1% or less to virtually 100% depending on the disease. Some examples of mitochondrial disorders caused by alterations in the mtDNA include: Leber hereditary optic neuropathy (LHON), mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), and myoclonic epilepsy with ragged-red fibers (MERRF). This contrasts with nDNA pathogenic variants, which follow Mendelian inheritance patterns.

In autosomal dominant inheritance, one pathogenic copy of a gene is necessary for an individual to be affected with a disorder. An affected individual may inherit the pathogenic variant from an affected parent. Alternatively, the condition may be caused by a new pathogenic variant occurring in an individual with no family history of that condition. Individuals carrying one copy of an autosomal dominant pathogenic variant have a 50% chance to pass the change onto their children. For example, autosomal Dominant Progressive External Ophthalmoplegia (adPEO) can be caused by a pathogenic variant in one of the following genes: *SLC25A4*, *TWNK*, *OPA1*, *POLG2*, *POLG*.[22,23,24,25]

In autosomal recessive inheritance, two pathogenic copies of a gene are necessary for an individual to be affected. The parents of an individual affected with this type of condition each carry one copy of the pathogenic variant; however, they typically will not show signs and symptoms of the condition. A couple who are both carriers for an autosomal recessive disorder have a 25% chance of having an affected offspring and 50% chance of having an offspring who carries a disease-causing allele. For example, pathogenic variants of the nuclear genes *TYMP*, *COQ2*, and *DGUOK* can cause a variety of nuclear inherited mitochondrial diseases including; Mitochondrial Neurogastrointestinal Encephalomyopathy (MNIGE), Coenzyme Q_{10} deficiency, and encephalomyopathy and liver failure, respectively.[26–28]

Some other mitochondrial diseases caused by nDNA pathogenic variants demonstrate X-linked inheritance. Rarely, women who carry an X-linked recessive pathogenic variant have a 50% chance of

having an affected son and a 50% chance of having a daughter who is also a carrier. Daughters of an affected man have a 100% chance to carry the same variant. Women will be affected when they inherit two pathogenic copies of the gene. Women who carry an X-linked dominant pathogenic variant have a 50% chance of having an affected child. Men cannot pass an X-linked pathogenic variant onto their sons. Some forms of Leigh syndrome can be inherited in an X-linked manner.

De novo or new pathogenic variants can occur as novel events within an individual. In some cases, this is the result of a genetic change present in a person's egg or sperm cell but not in the person's other cells. The pathogenic variant would be present in every cell of an embryo resulting from fertilization of either gamete carrying the variant. *De novo* pathogenic variants can also occur after fertilization. Cells present in the developing embryo could contain the pathogenic variant in this scenario. Mosaicism describes when an individual has a mixture of cells with the pathogenic variant and normal cells. Pathogenic variants that arise in a *de novo* manner may explain genetic conditions in individuals with unaffected parents and no family history of the condition. There is a 1% chance of recurrence for a couple who has a child affected with a mitochondrial disease caused by a *de novo* nDNA pathogenic variant. This chance is due to the possibility of gonadal mosaicism. A person with a sporadic or *de novo* nDNA pathogenic variant has the chance to pass that same change onto their future offspring. There is a 1 in 24 recurrence risk when a *de novo* mtDNA deletion occurs in one family member.[29]

Some mitochondrial disorders have multiple genetic etiologies. Leigh syndrome is an example of a disease with multiple modes of inheritance including autosomal recessive, X-linked inheritance or maternal inheritance. The inheritance pattern depends on the gene involved. For example, Leigh syndrome due to *SURF1, LRPPRC,* or complex I deficiency (*NDUFS1, NDUFS4, NDUFS7, NDUFS8, NDUFV1*) are all autosomal recessive.[30–32] PDH Deficiency (*PDHA1)* is a form of Leigh syndrome inherited in an X-linked fashion.[33] A variety of mitochondrial encoded genes including *MT-ATP6*, *MT-TL1*, *MT-ND5***,** *MT-TK*, and *MT-TW* within the mtDNA are also associated Leigh Syndrome.[34–36]

2.2 FACTORS AFFECTING THE DISEASE MANIFESTATIONS OF DNA VARAINTS

Heteroplasmy describes a cell that has a mixture of both normal and pathogenic mtDNA.[37] This effect can happen in all tissues and accounts for the complexity and variable presentation of mitochondrial diseases. As a consequence, individuals with the same pathogenic mtDNA variant can have assorted levels of heteroplasmy in different tissues.[5] Heteroplasmy magnifies the difficultly of providing accurate recurrence risk estimates to families with a maternally inherited condition.

The bottleneck effect describes the random distribution of mitochondria into egg cells during early oogenesis. This effect is responsible for heteroplasmy[21] and can produce a multitude of combinations of pathogenic and normal mtDNA in a single individual. For example, a woman with 80% heteroplasmy can have offspring with a multitude of heteroplasmic levels ranging from less than 1% up to 100%. This probability is dependent on the number of abnormal mitochondria present in each cell during embryonic cell division. An embryonic cell with high levels of abnormal mtDNA that undergoes numerous division will likely produce offspring with potentially high levels of heteroplasmy because cells will contain a high amount of abnormal mtDNA. The reverse is also possible. An embryonic cell with low levels of abnormal mtDNA that undergoes numerous divisions can produce offspring with potentially lower levels of heteroplasmy because cells will contain a low amount of abnormal mtDNA. Predicting disease prognosis and recurrence risk from the variety of combinations is often not straightforward.

Individuals with some degree of heteroplasmy may be asymptomatic depending on the amount of each mtDNA type present in each tissue. This manifestation of symptoms is attributable to the balance between mutation load and threshold effect. Mutation load refers to the amount of abnormal mtDNA present in a cell, tissue or organ.[5] Threshold refers to the degree of normal mitochondria necessary in a specific cell type, tissue, or organ produce enough energy to function.[38] Individuals can remain asymptomatic if the mutation load is low enough to preserve normal mitochondrial function within the cell, tissue, or organ. The threshold varies across different tissues and therefore mutational load present in

one tissue may have little to no phenotypic effect compared to another tissue where the same mutational load can produce the disease phenotype.[5]

Penetrance describes the proportion of individuals who inherit a pathogenic variant that will develop signs or symptoms of conditions associated with that variant. Reduced penetrance occurs when individuals carry a pathogenic variant but may not develop features of the condition associated with that variant. Variable expressivity describes those individuals affected with the same genetic condition who may exhibit different signs and symptoms within a range of clinical features.

Heteroplasmy, bottleneck, mutation load, reduced penetrance, and variable expressivity create difficulty in predicting and communicating symptom severity, prognosis, and recurrence risk to patients and their families. Genetic counselors can be instrumental to educating patients about how these factors can influence their own disease course and recurrence risk. The complexity inherent in these concepts and the lack of complete information and understanding of science also makes risk communication in the context of genetic counseling challenging.

2.3 DIAGNOSIS OF MITOCHONDRIAL DISEASES

Mitochondrial diseases are difficult to diagnose due to the high degree of heterogeneity in presentation, a variety of inheritance patterns, and other factors that can affect presentation of symptoms. Diagnostic work up can be challenging as symptoms overlap with other disorders leading to a large list of differential diagnoses.[5] Further complicating the process is the possibility that the mitochondrial dysfunction is secondary to a different primary genetic etiology.

The Mitochondrial Medicine Society (MMS) recently developed a set of consensus guidelines and recommended algorithms for the diagnosis and treatment of mitochondrial diseases.[10] The MMS recommends using a combination of clinical symptoms, biochemical studies, family history information, and genetic testing to diagnose patients with a suspected mitochondrial disease.[10] Tissue biopsies,

including muscle, skin, and liver, were once considered the gold standard for diagnosis. However, with the improvement of genetic testing, the MMS recommends tissue biopsies be performed only if genetic testing cannot be carried out or if a diagnosis cannot be confirmed with genetic testing (i.e. for functional confirmation). With the recent shift from confirming a diagnosis with a muscle biopsy towards confirmation with genetic testing, it is necessary to update patient information about such options for patients and their families.

2.3.1 Genetic Testing

The MMS recommends NGS testing for the diagnosis of suspected mitochondrial disease for its power to sequence both genomes (nDNA and mtDNA) rapidly. NGS has been used in the clinical setting for the past decade.[39] Prior to the mid-2000s, PCR based Sanger sequencing was used for nuclear mutational analysis.[8] Whole mitochondrial genome analysis became available via PCR base Sanger sequencing in the mid-2000s.[8] NGS platforms may differ in the sequencing method but all sequence multiple strands of DNA at a time unlike the traditional Sanger sequencing method which sequences one strand at a time. NGS technologies such as exome and multigene panels have more accurate detection of low level heteroplasmy (5-10%) in blood samples compared to mircoarrays.[10,40,41] Microarrays had replaced southern blot tests which were once the preferred method for testing mitochondrial deletion and duplication syndromes. This shift in testing standards is one example of how rapidly genetic technology is changing. NGS is cost effective and has a shorter turnaround time than traditional sequencing methods. As a clinical tool, NGS technologies are superior to traditional sequencing because they have higher diagnostic yields since it allows for the concurrent analysis of a large number of genes and can diagnose genetic conditions with overlapping phenotypes that mimic mitochondrial disease. [15,16]

2.3.2 Diagnostic yield

Reported diagnostic yield using exome sequencing in current literature can differ depending on cohort population characteristics, coverage depth, stringency of variant calling, and number of genes sequenced. Whole exome Sequencing (WES) has been successfully used in the clinical setting to diagnose mitochondrial disorders. One center found that of 109 patients suspected of mitochondrial disease undergoing WES, 39% received a molecular diagnosis. This is much higher compared with the diagnostic yield of 11% within the same population reported using Sanger sequencing.[39] Calvo et al. performed targeted exome sequencing, analyzing 1,034 nuclear encoded genes associated with mitochondrial function and the entire mitochondrial genome of 42 infantile onset patients with clinical and biochemical presentations suggestive of definite mitochondrial disease.[42] New molecular diagnoses were established in 31% with mutations in genes never before linked to mitochondrial disease and 24% with mutations in genes previously linked to mitochondrial disease. In total, recessive mutations in 13 novel genes never before linked to mitochondrial disease were identified in this cohort.[42] This study showcased the diagnostic utility of NGS to mitochondrial disease as 55% of individuals received a definitive diagnosis. Two novel candidate genes, AGK and NDUFB3, were identified in this study and are now considered causative of mitochondrial disease. Another study achieved a diagnostic yield of 22% performing TES for 1,598 nuclear encoded genes in 102 patients with clinical and biochemical indications of mitochondrial disease. Ages of onset ranged from infantile to adult onset with mean age of 27. Molecular diagnosis was established in 6% (5/84) of patients without a prior diagnosis and confirmed in 94% (17/18) of patients with previous molecular diagnoses. Researchers concluded that TES is an effective alternative to stepwise testing process.[15] Molecular diagnoses were also made for monogenic disorders other than mitochondrial disease

including Wolfram Syndrome, Charcot-Marie Tooth-like axonal neuropathy, and dihydropyrimidine dehydrogenase deficiency.

2.4 THE UNCERTAINTY OF RARE DISEASE: PATIENT AND FAMILY EXPERIENCE

The complexity and uncertainty associated with mitochondrial diseases plays a crucial role in shaping experiences of patients and their families.[4] Despite multiple diverse populations, two genomes, and various age of onset, studies indicate that most patients with a diagnosis of mitochondrial disease and their families share similar experiences living with a mitochondrial disease.

Parents of children with mitochondrial disease may feel responsibility and guilt that exceeds the typical role of caregiver.[43,44,45] Mothers and female relatives in a family may feel more guilt due to maternal inheritance of mtDNA. A survey of mothers with children diagnosed with a mitochondrial disease compared to mothers of children with intractable epilepsy found that the former group had significantly increased levels of caregiver burden.[43] Anxiety was the most important factor influencing caregiver burden of mothers in this cohort. Mothers in this group also experienced high levels of depression. In addition to maternal inheritance, the authors postulated that the significant increase in anxiety may be due to the lack information available about mitochondrial diseases.[43] A recent study by Senger et al. also concluded that parents of children with mitochondrial disease experience a higher degree of burden than observed in the typical caregiver role.[44] A total of 231 parents, 95% mothers, were surveyed to describe parent/caregiver experience. Participants completed the Parent Experience of Child Illness (PECI) and Pediatric Inventory for Parents (PIP) questionnaires. Parents experience high levels of stress and anxiety about what the future would hold in relation to their child's illness. Data also suggest that parents experience guilt, worry, sorrow, anger, and uncertainty associated with their child's illness.[46]

A study by Khangura et al. sought to understand the patient and family experience in inborn errors of metabolism (IEM) through semi structured interviews with IEM patient support groups from

Canada, the United States, and the United Kingdom.[3] Patient support groups can provide a unique perspective of the collective experience, challenges, and concerns of the patients they represent. In total, representatives from 18 patient organizations were interviewed. Patient groups represented a range of IEM's including mitochondrial disorders. Qualitative descriptive analysis identified three central themes, "managing the uncertainty associated with raising and caring for a child with a rare disease,", "challenges associated with the affected child's life transitions,", and "the collective struggle for improved outcomes and interventions that the rare disease community navigates."[3]

Adult patients have similar experiences to families of pediatric patients. Garrino et al. interviewed 25 adults diagnosed with mitochondrial disease caused by mtDNA pathogenic variants, in order to gain insight into their daily experiences living with the disease.[4] The topics discussed included experience of diagnosis, current and future health management, communication strategies, and role of reproductive technologies. Thematic analysis identified three central themes; personal and family experiences of illness, age and generation as factors shaping patient experience, and the importance of experiential knowledge towards reproductive choices.

Participants consistently expressed that their stress and anxiety stem from the daily uncertainty of living with mitochondrial disease and diversity of symptoms. Feeling as if mitochondrial disease is "creeping up" or slowly progressing was a common experience.[4] Patients and their families can feel as if they are playing a waiting game especially if they have yet to developed symptoms or if they experience milder symptoms than affected family members. Many responders reported that signs and symptoms developed over time and were highly variable between and within families. The experience of adult patients with mtDNA pathogenic variants was also investigated in a study by Noorda et al. in 2013.[47] One-on-one interviews were carried out with 16 patients diagnosed with MELAS, MERRF, or Leigh syndrome. Interviews were coded and analyzed for emerging themes. The central theme that was identified within this adult cohort was one of both physical and emotional loss. Subthemes revealed that many experienced loss of energy and health.[47] Loss of social interaction/support was related to patients' symptoms affecting and shaping their day to day activities.[47]

Lack of information about disease progression can produce significant stress and worry about the future. [3,4,48] These feelings can be enhanced by an individual's experience watching family members with the disease.[4] Adult patients with mitochondrial disease may rely on experiences of family members to assess their own health and disease progression as well as the health of their children. Patients have also expressed worry and uncertainty about recurrence risk in future pregnancies and the risk to other family members.[49] Seeking information via online educational resources may help patients and family members cope with worry and anxiety. Online resources can also connect patients and families seeking social support via the internet and social media.

2.4.1 Diagnostic Odyssey

A confirmatory diagnosis of mitochondrial disease is challenging due to variability in presentation and overlap of symptoms with other disorders. This contributes to a long and expensive diagnostic odyssey that is psychologically, emotionally, and physically exhausting for patients and their families. The average length of time to reach a diagnosis for patients with a rare disease is roughly 6 years.[50] Receiving a diagnosis may be the primary concern to individuals with a rare disease.[3] Interviews with IEM patient groups found that anxiety resulting from frequent misdiagnosis and/or lengthy delays is a shared experience among patients. Frustration is often expressed with the diagnostic process.[4,48] Considerable emotional stress may result from the fear of misdiagnosis.[3]

Patients often see multiple specialists and undergo a myriad of diagnostic tests in their search for a definitive diagnosis.[3,48] Uncertainty associated with prognosis and interventions of rare diseases can make patients feel anxious when interacting with healthcare professionals, particularly with primary and emergency care.[3] Khangura et al. reported patients and families experience anxiety over the thought of medical emergencies due to the perceived lack of understanding among healthcare professionals. Interviewees participating in this study acknowledged that patients cope with this strain by educating

themselves and relying on other families for information. One emerging sub theme for this study was the use of the internet to gather information linked to communication with healthcare providers.[3]

Although the informational needs of patients and their families may change over the course of their diagnostic odyssey, the desire for information remains a constant factor.[51] A pilot study performed by Noorda et al. sought to assess parent/family need for information during the diagnostic process of a suspected mitochondrial disease. This process was broken down into four phases to best identify need at different time periods of diagnosis. The phases were defined as follows: Phase 1 began at the time of referral to a metabolic specialist and continued until the initial outpatient visit or sick visits that required hospitalization after the referral. Phase 2 commenced during the medical examination and included any results disclosure or giving of information about the examination results. The examination could have occurred during an outpatient visit or hospitalization. Phase 3 was defined as the duration of time in which a muscle biopsy was taken, while Phase 4 began after a muscle biopsy procedure up until a diagnosis was known.

Two focus groups of parents whose children had undergone a muscle biopsy were interviewed. The need for information was reported as greatest during the fourth phase of diagnosis.[51] Parents believed that a combination of resources was best during this phase including internet resources, written information, and personal communication with healthcare professionals. Families in this phase of diagnosis felt that email correspondence with professionals or experts was more important compared to previous phases. This change in preference may reflect the intense desire for information and direction. Parents also stated that their desire for technical information such as treatment, risk of early death, prognosis, and inheritance increased during the fourth phase of the diagnostic process.

2.4.2 Perceived social significance of a genetic diagnosis

A genetic diagnosis may be perceived to have more social significance when compared to a clinical diagnosis in patients with mitochondrial disease.[52] A study by Krieg et al. surveyed 201 adult patients with mitochondrial disease to explore what significance and social implications were associated with a clinical vs. genetic diagnosis. Data was analyzed by descriptive statistics and thematic analysis with two independent coders. Roughly 73% of participants had a clinical diagnosis while the remaining 27% had a genetic diagnosis. Four main problems encountered by patients with mitochondrial disease emerged: barriers to medical treatment, need for disease information, lack of appropriate support resources, and no definite proof of sickness. Respondents with a clinical diagnosis but not a genetic diagnosis of mitochondrial disease perceived that they encountered more skepticism and dismissal of their disease. Without a genetic diagnosis, they perceived that there was "no proof of sickness." Participants with a clinical diagnosis believed that a genetic diagnosis would improve care by providing more targeted therapies. There was also the perception that a genetic diagnosis opens more doors such as improved insurance coverage and participation in clinical trials. Participants with a genetic diagnosis reported a sense of relief and comfort to have a known cause or reason for their symptoms.

2.5 PATIENT ADVOCACY AND SUPPORT GROUPS

Patient advocacy groups (PAGs) and support groups have emerged as an important resource for individuals living with a rare disease.[53] These organizations develop and maintain social networks to connect members through email, Facebook, Twitter, and Google search. PAGs can be active in creating public awareness and educational materials about the conditions they represent. PAGs play a role in shaping the research landscape of a condition in terms of medical, pharmaceutical, and patient-centered outcomes.[54] By connecting with members, PAGs can identify the community's psychosocial needs and

define patient-centered goals to improve interventions and address quality-of-life outcomes.[55] There exists a wide array of patient advocacy and support groups specific to mitochondrial diseases. The Mitochondrial Medicine Society lists a total of 19 mitochondrial disease support groups around the world.[56] The current study assessed online educational resources from seven of the most popular groups found on the list. The United Mitochondrial Disease Foundation (UMDF), MitoAction, and Genetic Alliance are based in the United States. MitoCanada provides support and resources for patients and their families living in Canada. The Lily Foundation and Children's Mitochondrial Disease Network do the same for patients and families from the United Kingdom. Patients and families living in Australia can turn to the Australian Mitochondrial Disease Foundation for resources available to them.

2.5.1 Patient Registries

Patient registries (PRs) have the power to do for rare disease research what social media has done to connect patients despite geographical barriers.[54] While PRs serve many purposes, the opportunity to gather information about diagnosis and symptoms to further knowledge about the natural history of a rare disease is arguably one of the most important. This information can help clinicians develop diagnosis/treatment guidelines, establish genotype/phenotype correlations, and determine disease prognosis. PRs play an important role in furthering clinical and pharmaceutical research whether it be through patient recruitment, providing access to data, or maximizing collaboration of researchers across the world.[57] Registry members can benefit from the partnership of PAGs and researchers. Participation in such registries can improve patient engagement, providing themselves and their families a way to give back to the rare disease community. Many believe that research and collaboration is crucial to the development of effective treatments and cures. Participants feel a sense of duty to contribute to the growing body of knowledge for their condition. Furthermore, engagement in research can give patients a voice and the opportunity to be heard.

2.5.2 Mitochondrial Disease Community Registry

The Mitochondrial Disease Community Registry (MDCR) is a patient registry sponsored and maintained by the UMDF. MDCR as a multi-condition, multi-purpose health information registry that will aid in advancing research, enable better access to support services, and more effectively serve the needs of registry members.[58] The MDCR utilizes the Platform for Engaging Everyone Responsibly (PEER) a product of Genetic Alliance, a leading nonprofit health advocacy organization. As per Genetic Alliance's website "PEER is a highly customizable registry system used to collect privacy-assured health information, which enables individuals to set their own sharing, privacy, and data access preferences in a granular and dynamic manner."[59] As a part of the PEER platform, the MDCR utilizes Privacy Layer® affording members multiple layers of consent The MDCR therefore functions differently than typical registries. Individuals enrolled in the MDCR can govern access and use of information stored in the registry. Within PEER, the participant's authorization or consent indicates his or her preference regarding the discoverability and potential accessibility for use of the information in his or her PEER account. Privacy Layer® enables members to set their privacy settings and thus determine the degree of information sharing, privacy and access preferences. Every individual decides when, what information, and with whom he or she wishes to share his or her own information, and for specifically what purpose. MDCR members have the chance to give feedback about online educational materials by completing the study survey. By engaging in this survey, patients are providing crucial insights that can help the UMDF, other PAGs, and educators develop more effective educational materials about mitochondrial disease genetics and genetic testing. Improved materials would directly benefit both the study participants and other members of the mitochondrial disease community.

2.6 ONLINE RESOURCES

Online resources are one of the more frequent outlets for patients with genetic or rare conditions to obtain information. One in three American adults report searching the web to learn about a medical condition.[60] In 2013, 70% of US adults obtained health information, care, or support from sources other than health professionals.[60] This number is greater when considering the demographic of people seeking health related information about genetic or rare conditions.[61] The lack of alternative resources for this population is a motivating force, driving this information-seeking process.[61]

Morgan et al. designed a study to characterize the type of information searched through the Genetics and Rare Disease Information Center GARD's website between 2006 and 2011.[1] GARD was created in 2002 and sponsored by the National Institutes of Health (NIH) with the goal to help people find useful information about genetic and rare diseases. A random sampling of 278 inquiries (email and web posts) was examined for content analysis. A total of 68 and 210 inquiries from 2006 and 2011, respectively were analyzed. Inquiries were made by a diverse population including patients, at risk individuals, parents/guardians, and spouses/relatives.[1] Information seekers using web-based information to learn about genetic and rare diseases frequently searched information about disease prognosis, diagnosis of symptoms, and how to find a specialist.[1] Internet resources are necessary tools for patients with rare diseases and their families to educate themselves, enabling them to be better advocate for their care. It should be noted that internet use to supplement or improve understanding of topics discussed in the doctor's office is commonplace among internet users of all demographics.[60]

2.7 HEALTH LITERACY

Health literacy is an important factor to consider when developing patient education materials. Per the Institute of Medicine, health literacy is defined as "the degree to which an individual has the capacity to

obtain, communicate, process, and understand basic health information and services to make appropriate health decisions."[62]

Health literacy is the strongest predictor of an individual's health status even when comparing age, gender, race, education level, and socio-economic status. Despite the importance of being health literate, nine out of ten American adults struggle with health literacy.[62] The average literacy level of Americans is at the 8th grade level while 21% have a literacy level on par with the 5th grade.[63]

Risk communication is one of the most challenging aspects of health literacy and in educating patients and their families affected with mitochondrial disease.[3,5] Variability in genetic testing options, inheritance patterns, ages of onset, and symptom severity make developing resources for mitochondrial disease even more challenging. Rapid advances made in genomic medicine since the completion of the Human Genome Project have led to the clinical implementation of NGS technologies. The push for clinical use of NGS technologies also raises concerns about the public's understanding of genetics or genetic literacy. Genetic literacy is defined as the "capacity to obtain, process, understand, and use genomic information for health-related decision-making."[64] Health literacy is the strongest indicator of genetic literacy.

A large, prospective study published in 2016 characterizing genetic knowledge and potential predictors of genetic knowledge determined that prior knowledge of genetics or exposure to genetic information are significant predictors of genetic literacy.[65] The Coriell Personalized Medicine Collaborative (CPMC) is conducting an ongoing study comprised of 4,062 healthcare providers, healthy individuals, and healthy individuals with chronic conditions.[65] Genetic knowledge questionnaires were completed to evaluate the participants' baseline knowledge of genetics. Questionnaires included fifteen questions about basic genetics, gene function, inheritance, complex diseases, and genetic variation. Questionnaires were developed to identify exposure to genetics by a variety of media including articles, books, previous schoolwork, websites, and genetic counseling. In general, participants displayed an understanding of concepts such as hereditary outcomes compared those discussing the structure/function or the technical aspect of genetics.[65] The multivariate linear regression analysis indicated an association

between genetic knowledge and genetic education background. Prior knowledge was found to significantly predict genetic literacy. Participants with high genetic knowledge scores reported learning about genetic from multiple sources including books, websites, medical journals/articles, and college-level courses. It is important to note that 69% of this cohort held a Bachelor's degree or higher. Exposure to genetic counseling did not correlate to high genetic knowledge scores within the 11% of participants that reported having previously received genetic counseling. However, after controlling for demographic factors, exposure to genetic counseling was a significant predictor of genetic literacy.[65] This finding suggests that the process of genetic counseling and genetic counselors are an important resource with value to patients across all demographics. However, it is important to note previous knowledge of genetics was a stronger predictor of genetic knowledge, reflected in knowledge scores, than receiving genetic counseling.

The CPMC study suggests that genomic knowledge was a predictor of genetic literacy. Therefore, a limited genetic knowledge-base is one barrier to achieving improved genomic literacy. Science standards set by the United State Department of Education can vary state to state and may inadequately cover genetic concepts necessary to individuals to be considered genetic/genomic literate.[66,67]An assessment performed by Dougherty et al. of 19 genetic concepts considered the minimum number of concepts essential for genomic literacy by the American Society of Human Genetics (ASHG) noted substantial deficiencies across the United States with 85% of states receiving a score of inadequate. Concepts of continuous variation, differential gene expression, multifactorial causation, and the connection between mutations (pathogenic variants) and inherited vs. somatic genetic disease scored the lowest. When analyzed by category, inadequate scores were found in genetic transmission/inheritance patterns, gene expression, and regulation and genetic variation.[67]

Furthermore, there is an imbalance between knowledge of scientific and medical concepts related to genetics and potential medical applications and societal consequences of testing within the general population. This suggests that besides deficiencies of knowledge of the genetic concepts noted above, there is a gap in overall understanding of the benefits, risks, and limitations of genetic testing.[68]

Altogether, this highlights the need for improved educational materials and resources about genetic inheritance, transmission, gene expression, regulation, and genetic variation. These concepts are important to understanding many of the concerns and frustrations voiced by patients such as lack of understanding risk to other family members and disease prognosis. Educational materials can be helpful to ensure families are adequately informed and prepared before undergoing genetic testing.

2.7.1 Readability: Recommendations for Patient Education Materials

The National Institutes of Health recommend that all patient education materials be written at a 6th-8th grade reading level.[63] Despite this recommendation, many online patient educational materials are written at a grade level, 10th-12th grade on average, well above the recommendation.[69–71] Other suggestions include the use of plain language, also known as living room language, that can be easily understood the first time it is heard.[72] Tone should be clear and simply written in an active voice. The simplest information should be presented first, complex information should be broken down into smaller digestible chunks, and all technical terms should be defined.[63] These things together contribute to the overall readability of patient educational materials. Readability is a characteristic of written text that is easy to read and understand.[73] It is an important factor in the development of effective patient educational material and a high degree is desired.[73] Many computerized formulas exist to assign texts a readability score that reflects the ease of reading. Each analyzes different variables of to assign an overall readability score.

2.8 SUMMARY

Mitochondrial disease, a diverse group of rare diseases, is a fitting example of the demand for improved educational resources for both patients and providers. The collective experience of those within the

mitochondrial disease community verifies the need for information and improved educational material.[3,4,47,48,51,52] While patients and their families view the internet as a primary resource for education current online educational materials are not written at level that is easy for patients to read and understand.[3,51] There is also variability in the quality and content of resources about mitochondrial disease genetics. This deficit has created a global sentiment of uncertainty that causes patients and their families significant emotional stress, worry, anxiety, and exponentially increases caregiver burden compared to other conditions.[3,4,43,46] Desired information includes information about disease severity and prognosis, inheritance and risk to other family members, recurrence risk, and the appropriate genetic testing to genetically confirm a diagnosis. The need for information exists regardless of whether or not a patient has genetic diagnosis.[52]

Within the mitochondrial disease community exists a perceived lack of provider knowledge and training as a barrier to care, regardless of a genetic diagnosis.[3,4752] Many patients, their families, and caregivers have expressed frustration at the lack of provider knowledge stating that it interfered and hindered the quality of their care.[3,4,47,48,52] One participant in a study performed by Krieg et al. remarked that one challenge was always needing to educate physicians about their diagnosis.[52] Adult patients surveyed by Noorda et al. also expressed frustration with the lack of provider knowledge and dismissal of their disease perceived as a direct consequence of this knowledge gap.[47]

Historically, diagnosing of mitochondrial diseases has been challenging due to variability in presentation, factors that affect disease manifestation, and overlap of symptoms with other disorders.[5] Patients often consult with multiple specialists and undergo a high volume of screening and diagnostic testing before a mitochondrial disease diagnosis is reached. The average length of time to reach a diagnosis for patients with a rare disease is roughly 6 years.[50] New technologies like NGS are changing the landscape of the diagnostic odyssey by allowing for the concurrent analysis of multiple genes. This has led to decreased costs, improved diagnostic yield, and a shortened turnaround time, shrinking the diagnostic odyssey. Despite the many benefits of NGS technologies, disadvantages such as ambiguous

results and incidental findings can present a challenge to patient understanding. The development of effective educational tools can lead to improved health outcomes for patients and their families.

In the context of rare disease, patients and/or their families take on the role of advocate due to the rare nature and general lack of awareness of the disease. It is important that these populations have access to resources that are accurate, concise, and written at an appropriate level for their understanding. Improved online educational materials regarding mitochondrial disease genetics and the development of disease specific-educational resources for genetic testing can led to better patient outcomes and enable patients to become informed. This information would in turn assuage some of the uncertainty associated with a diagnosis of mitochondrial disease and empower patients to better advocate for their care. In addition to improved online patient educational material, better educational interventions can be targeted to healthcare providers as an approach to ameliorate this perceived barrier to care.

3.0 MANUSCRIPT

3.1 BACKGROUND

One in three American adults report searching the internet to learn about a medical condition, with roughly 70% of US adults obtaining health information, care, or support from sources other than health professionals.[60] Members of the rare disease community use internet resources as an educational tool to improve their knowledge so they can be better advocates for themselves, their loved ones, and the people for whom they take on the role of caregiver. Often patients, parents, or caregivers report transforming into the role of disease expert because the condition is so rare that physicians may not be well informed about diagnosis and treatment.

Genetics and inheritance are among the top internet searches about genetic and rare conditions. The Genetics and Rare Disease Information Center (GARD), sponsored by the National Institutes of Health (NIH) assists people searching for information about genetic and rare diseases. Morgan et al. characterized the type of information searched through GARD's website between 2006 and 2011.[1] Inquiries were made by a diverse population including patients, at risk individuals, parents/guardians, and spouses/relatives of people with a genetic condition.[1] Information seekers using web based information to learn about genetic and rare diseases frequently searched information about disease prognosis, diagnosis of symptoms, and how to find a specialist.[1]

Patient experiences with rare conditions emphasize the importance of education to this population. A growing sentiment within the rare disease community is the collective struggle for improved outcomes, information, and interventions.[3] The complexity and uncertainty associated with

mitochondrial diseases play a crucial role in shaping experiences of patients and their families.[4] Despite different etiologies and disease manifestations studies indicate that most patients and families with a diagnosis of mitochondrial disease share similar experiences.[3] Lack of information about disease progression can produce significant stress and worry about the future. [3,4,48] Both adult patients and parents of pediatric patients report worry and uncertainty about the risk of recurrence in future pregnancies as well as the risk to other family members.[49] Adult patients often express feelings of stress and anxiety stemming from the daily uncertainty of living with mitochondrial disease. The need for readable, accurate, and informative resources have been identified by patients and their families.[3,4] Improved educational materials can clarify recurrence risk and inheritance patterns. Better educational materials can also help patients and their families feel supported when advocating for themselves. It is crucial that online educational resources be written using patient-centered language in an overall readable format targeted to the public.

Mitochondrial diseases are a group of rare disorders that illustrate the need for improved patient educational resources. Mitochondria are double membrane bound organelles that are responsible for the production of energy adenosine triphosphate (ATP) through oxidative phosphorylation. Roughly 90% of a cell's energy is produced during this process. Mitochondria are unique because they carry their own DNA (mtDNA).[19]

This diverse class of conditions is unique because they are characterized by a high degree of genetic and clinical heterogeneity.[5] As of 2017 MitoCarta, a catalogue of curated genes, lists 1,158 nDNA and mtDNA genes encoding proteins strongly implicated with mitochondrial function.[6] Although individually rare, it is estimated that collectively mitochondrial diseases occur with a prevalence of 1 in 5,000.[7] Mitochondrial diseases demonstrate a wide range of symptoms with; dysfunction typically observed in body systems requiring high amounts of energy such as the central nervous system, gastrointestinal system, musculoskeletal system, and heart. Symptoms can include low muscle tone, developmental delay, seizures, stroke, hearing loss, ophthalmologic manifestations, and gastrointestinal issues. Diagnosis typically occurs in childhood; however, onset can occur over a wide range of ages from

neonatal to adulthood. Disease and symptom severity is also variable ranging from severe to mild even in patients or within and between families with the same disease.[5] The genetics of mitochondrial disease are complex. Mitochondrial dysfunction can result from pathogenic variants within the nuclear DNA (nDNA) or within the mitochondrial DNA (mtDNA) which are necessary for energy production.[8,9] Inheritance is significantly more complex than single gene disorders given the possibility of nDNA and/or mtDNA pathogenic variants. Recurrence risk can range from 1% or less to virtually 100% depending on the disease. nDNA pathogenic variants follow Mendelian inheritance patterns. This pattern makes risk communication, which is one of the most challenging aspects of health literacy and in educating patients and their families affected with mitochondrial disease, even more difficult.[3,5] Variability in inheritance patterns, ages of onset, and symptom severity make developing resources for mitochondrial disease even more challenging.

Mitochondrial diseases are difficult to diagnose due to the high degree of heterogeneity in presentation, a variety of inheritance patterns, and other factors that can affect presentation of symptoms. Diagnostic work up can be challenging as symptoms overlap with other disorders leading to a large list of differential diagnoses.[5] The Mitochondrial Medicine Society (MMS) recommends using a combination of clinical symptoms, biochemical studies, family history information, and genetic testing to diagnose patients with a suspected mitochondrial disease.[10] Next Generation Sequencing (NGS) technologies are becoming the standard platform for genetic testing in cases of a suspected mitochondrial disease given its high diagnostic yield.[10] The MMS recommends NGS testing for the diagnosis of suspected mitochondrial disease for its power to sequence both genomes (nDNA AND mtDNA) rapidly. NGS tests allow for concurrent analysis of many genes, thus it is faster and more cost-effective than traditional sequencing methods. NGS technologies can include exome sequencing, mtDNA sequencing and multigene panels. The exome consists of all the genome's exons, which are the coding portions of genes. It makes up roughly 1% of the entire human genome (22,000 genes).[11] It has been estimated that 85% of pathogenic variants can be found in the exome.[12] Exome sequencing is typically more cost effective than testing two or more genes via Sanger sequencing.[13,14] As a clinical tool, NGS technologies are superior to traditional

sequencing because they can diagnose genetic conditions with overlapping phenotypes that mimic mitochondrial disease. [15,16] NGS tests are complex and can yield ambiguous results known as variants of uncertain significance (VUS). The probability of finding this type of result with NGS testing is high as multiple genes are simultaneously sequenced. Exome sequencing also has the potential to yield results known as incidental or secondary findings, which are unrelated to the patient's symptoms but have serious health implications for the patient and/or their family.

With the increased clinical use of exome and NGS for diagnostic confirmation, it is necessary to update patient educational information online. Online educational materials about genetic testing are limited, difficult for patients to read due to technical language, and often may be outdated due the rapid pace of developing technologies. This is particularly problematic in the context of rare conditions, like mitochondrial diseases, where the patient and/or their love ones primarily use online educational materials as a resource.[1,3] Due to the potential for ambiguous and incidental results of genetic testing, it is crucial that material about the genetics of mitochondrial disease and genetic testing be written in clear, concise, and patient-centered language. Furthermore, it is vital that patients be well informed before consenting to exome sequencing about the benefits, limitations, and types of results that NGS testing can provide before they pursue genetic testing. While patients are guided through the informed consent process by a genetic counselor or other healthcare professional, increasing baseline knowledge about genetics has been shown to increase genetic literacy.[65]

This study had two main objectives. The first was to perform an assessment of current online educational material regarding mitochondrial disease genetics for readability (reading level and ease of reading) and content. Conclusions drawn from the initial assessment were then used to guide development of an online survey to gain insight on patients' and caregivers' perceptions of current online educational material for mitochondrial genetics. Specifically, questions were targeted to readability, ease of finding resources, and perception of how helpful the online material was to learning about mitochondrial disease genetics. The survey also sought to identify information about genetic testing for mitochondrial disease including what information patients and their caregivers believe should be included in similar educational

resources. Individuals who are a part of the Mitochondrial Disease Community Registry (MDCR), a volunteer patient registry, were eligible to complete the survey.

3.2 METHODS

This study was approved by the University of Pittsburgh Institutional Review Board (PRO16070152), (Appendix C).

3.2.1 Patient Educational Material Selection

Online educational materials pertaining to mitochondrial disease genetics, inheritance, and/or genetic testing were found by performing an internet search in February 2017 using the terms “Mitochondrial Disease”. Resources evaluated for this study included those targeted to patients. Search results were categorized per the source or sponsor. The four website categories were identified as follows: mitochondrial support (MitoCanada, MitoAction, The Lily Foundation, The United Mitochondrial Disease Foundation, Australian Mitochondrial Disease Foundation, Genetic Alliance, Children's Mito Network), government sponsored websites (NIH, Genetics Home Reference), commercial health information websites (WebMD, eMedicine), and finally hospital and medical center websites (Cleveland Clinic, Mayo Clinic).

Additional mitochondrial support group websites were identified using the Mitochondrial Global Networks, a live Google map of resources for patients and clinicians maintained by the Mitochondrial Medicine Society (MMS). The MMS list includes 19 patient support/advocacy groups around the world.[56] This categorization was done to identify online resources that international patients may use, that might not have populated from the internet search results. In total, nineteen websites with educational resources were assessed.

3.2.2 Readability Analysis

Online educational materials were analyzed for readability using an online readability calculator (http://readability-score.com). Seven measures of readability can be calculated using this tool: Flesch Kincaid Reading Ease, Flesch Kincaid grade level, Gunning-Fog, Simple Measure of Gobbledygook, Coleman-Linau Index, Automated Readability Index, and an average grade level score. Each analyzes different variables to assign an overall readability score. The Flesch-Kincaid Reading Ease (FRE), Flesch-Kincaid Grade Level scores, and Automated Readability Index (ARI) were used for this study. FRE gives a readability score on a 100-point scale considering sentence length and number of syllables. Scores from FRE can be converted to an overall school grade reading level reported as the Flesch-Kincaid Grade Level scores. ARI produces a readability score based on sentence and word difficulty. Material was edited to remove tables, diagrams, subheadings, or headings that might affect the overall score.

3.2.3 Survey Development

A survey was developed to assess patient/caregiver use and perception of online educational materials regarding mitochondrial genetics. Participants' views on what educational materials for genetic testing should include were assessed via survey. The survey was comprised of seven sections and 47 questions. Each section included an introduction with instructions for completion. Demographic and disease diagnosis information was self-reported as part of the survey utilizing the same questions asked overall in the Mitochondrial Disease Community Registry (MDCR). The survey included multiple choice questions, open-ended questions, and questions based on a Likert Scale of 5. Branching logic was utilized. Participants had the option to skip questions if they did not wish to answer or if the question did not pertain to them.

The survey was built using the survey development features of the MDCR, a multi-purpose health information registry comprised of individuals affected with mitochondrial disease, caregivers, and parents

with affected children. The MDCR was created using the Platform for Engaging Everyone Responsibly (PEER) and is sponsored by the United Mitochondrial Disease Foundation (UMDF). This allows the UMDF to act as a steward of the registry by overseeing researcher access to members via the registry. The PEER system is a product of Genetic Alliance, a leading nonprofit health advocacy organization. PEER is a "highly customizable registry system used to collect privacy-assured health information, which enables individuals to set their own sharing, privacy and data access preferences in a granular and dynamic manner."[59]

The overreaching goals of the MDCR are to advance research, enable better access to support services, and more effectively serve the needs of registry members. The MDCR therefore functions differently than typical registries. Individuals enrolled in the MDCR can govern access and use of information stored in the registry. Within MDCR the participant's authorization or consent indicates his or her preference regarding the discoverability and potential accessibility for use of the information in his or her PEER account. Privacy Layer® enables members to set their privacy settings and thus determine the degree of information sharing, privacy, and access preferences. Every individual decides when, what information, and with whom he or she wishes to share his or her own information, as well as for specifically what purpose.

3.2.4 Participant Selection

All 1,900 registered members of the MDCR were eligible for participation. Members must be at least 18 years to enroll and can included patients, caregivers, and parents acting on their children's behalf. Participants were presented with a one-page introduction explaining the purpose of the study, estimated time commitment for participation, benefits and risks, and that participation was voluntary (Appendix A). The study was promoted by the UMDF via MDCR member listserv, email blasts, and social media outlets (Facebook). Notices were sent to participants one month after distribution to remind them to complete the survey. Participants had a total of two months between January/2017-March/2017 to complete the survey.

3.2.5 Analysis

Survey data was self-reported. Data from both completed and incomplete surveys were used for the reporting of descriptive statistics if the 'mitochondrial disease diagnosis' section was completed at a minimum. The data set was reviewed and then loaded into Microsoft Excel to generate descriptive statistics for multiple survey questions and included count data, percentages, mean, standard deviation, median, and range. Comparisons of patient perceptions of their knowledge on genetics and genetic testing before and after accessing online material were done using Stata/SE 14.2 statistical program. Participant data for these questions were only included for participants who answered both the before and after questions for specific comparisons.

3.3 RESULTS

3.3.1 Readability and Content Assessment

An initial assessment of patient online educational materials regarding the genetics of mitochondrial disease found that resources were well above the recommended 6-8 grade level. Flesch-Kincaid Readability Grade Level scores ranged from 7.6-15.9. Flesch-Kincaid Reading Ease scores ranged from 24.4 to 61.6. Patient resources found on commercial health information websites did not include information about genetics were not included in the readability analysis. Some resources were easy to find on websites while others were more difficult and required searching through the website.

Table 1. Readability Measures of Online Patient Educational Materials regarding Mitochondrial Disease Genetics and Inheritance

Organization	Flesch-Kincaid Readability Ease Score [a]	Flesch-Kincaid Readability Grade Level [b]	ARI [c]
Patient Support Organizations			
MitoCanada	61.6	7.6	6.7
MitoAction	57.9	9.2	10.1
The Lily Foundation	49	11.2	11.3
UMDF	36.8	12.2	11.7
Australian Mitochondrial Disease Foundation	34.4	13.4	12.2
Genetic Alliance	24.9	15.9	16.2
Children's Mito Network	24.4	14.7	14.3
Hospital/Medical Center			
Cleveland Clinic	51	9	8.4
Mayo Clinic [d]	-	-	-
Government Sponsored Organization			
Genetics Home Reference	51.4	10	9.7
NIH (Genetics and Rare Disease Center)	45.9	12.4	12.3
Commercial Health Information website			
WebMD[d]	-	-	-
EMedicine[d]	-	-	-

[a] Flesch-Kincaid Readability Ease Score is calculated on a scale from 0-100. It provides a measure of how easy content is to read. A perfect score or 100 reflects a 5th grade level. Material with this score should be easily understood by an 11-year-old. Scores of 50 and below reflects a college level of understanding

[b] Flesch-Kincaid Readability Grade Level is produced by converting the Flesch-Kincaid Readability Ease score to a grade level equivalent. An FKRE score of 70-80 will be converted to a 7th grade reading level.

[c] ARI: Automated Readability Index, produces a grade level that is representative of the reading level a person needs to understand the text. Scores of 10-6 represent 8th-5th grade comprehension. Scores above 11 represent 10th grade and above.

[d] Indicates that material regarding mitochondrial disease genetics was not present on the online resource and therefore readability analysis was not performed.

Patient support organizations were more likely to include online educational material specific to genetic testing for mitochondrial disease (Table 2). MitoAction and the United Mitochondrial Disease Foundation provided tailored resources with detailed information about genetic testing in the context of mitochondrial diseases. Both have archived presentations about genetic testing given by physicians, nurses, genetic counselors, and other medical professionals. Each provides external links for outside resources about genetic testing. Commercial health information websites, Hospital or Medical Center websites, and Government websites all mentioned genetic testing of nDNA and mtDNA as a diagnostic option. However, detailed information about genetic testing specific to mitochondrial disease was not present. The NIH had separate educational resources about genetic testing in general.

Table 2. Inventory of Online Patient Educational Material Regarding Genetic Testing of Mitochondrial Disease

Organization	Mentions genetic testing as diagnostic option	Details about genetic testing [a]	Detailed genetic testing for mitochondrial diseases[b]	External Links for additional resources
Patient Support Organizations				
MitoCanada	Yes	Yes	Yes	Yes
MitoAction	Yes	Yes	Yes	Yes
The Lily Foundation	Yes	No	Yes	Yes
UMDF	Yes	No	Yes	Yes
Mito Australia	Yes	Yes	Yes	Yes
Genetic Alliance	Yes	Yes	Yes	Yes
Children's Mito Network	Yes	No	No	Yes
Hospital/Medical Center Website				
Cleveland Clinic	Yes	No	No	Yes
Mayo Clinic	Yes	Yes	No	Yes
Government Sponsored Website				
Genetics Home Reference	Yes	Yes	No	Yes
NIH (Genetics and Rare Disease Center)	Yes	Yes	No	Yes
Commercial Health Information Website				
WebMD	No	No	No	No
eMedicine	No	No	No	No

[a] Indicates that resource provided general information about genetic testing
[b] Indicates that resource provided information about genetic testing specific to mitochondrial disease

3.3.2 Demographics

A total of 83 participants began the survey. 60 surveys were completed at the time of study closure. The response rate for this study was roughly 3%. Data from these surveys were analyzed. Participants covered a wide age range from 18-60+ with 82% (49/60) identifying as female. The highest level of education reported ranged from some high school to Master's Degree/ Professional degrees beyond a Bachelor's Degree. Over half of participants reported an education level of a Bachelor's Degree or higher. Participant demographics are reported in Table 3.

Table 3. Participant Demographics

		n (n=60)	%
Age	18-30	12	20%
	31-40	11	18%
	41-50	11	18%
	51-60	17	28%
	>60	9	15%
Sex	Female	49	82%
	Male	11	18%
Race	Caucasian	57	95%
	African American	2	3%
	Other	1	2%
Marital Status	Single	20	33%
	Married	33	55%
	Divorced	7	12%
Education	Some primary or high school	1	2%
	High School	6	10%
	Vocational/Trade school	1	2%
	Associates Degree	6	10%
	Some College but more than 1 year	11	18%
	Bachelor's Degree	19	32%
	Master's Degree	11	18%
	Professional Degree beyond a bachelor's degree	4	7%
	Other	1	2%
Income (USD)	Less than 20,000	16	27%
	20,000-24,999	4	7%
	25,000-29,999	2	3%
	30,000-34,999	1	2%
	35,000-39,999	4	7%
	40,000-44,999	1	2%
	45,000-49,999	1	2%
	50,000-54,999	5	8%
	55,000-59,999	2	3%
	60,000-64,999	4	7%
	65,000-69,999	2	3%
	70,000-74,999	1	2%
	75,000-79,999	0	0
	80,000-84,999	0	0
	85,000-89,999	0	0
	90,000-94,000	0	0
	95,000-99,999	1	2%
	100,000-149,000	4	7%
	150,000-199,999	5	8%
	250,000 +	2	3%
	Decline to Provide	5	8%

3.3.3 Mitochondrial Disease Diagnosis

For most participants, a diagnosis was made between 41-50 years of age (Figure 1). Half of survey participants reported having a diagnosis of mitochondrial disease but did not act as caregivers to an affected individual (50%, 30/60) (Table 4). Caregivers made up 27% (16/60) of participants. Five of 16 caregivers reported that they themselves were also affected, making up 8% of all participants. Nine of 60 participants did not know if they had a diagnosis. In total, 59 respondents reported the disease classification they or the person they cared for had received. Fifty-eight percent (34/59) reported receiving a definite diagnosis.

There were three categories of mitochondrial disease provided based on the suspect etiology which included mtDNA mutation syndrome, nDNA mutation syndrome, and depletion syndromes. Participants had the option to choose multiple categories. Fifty-two of 56 participants reported a diagnosis of an mtDNA mutation syndrome, 37 of 56 participants reported a diagnosis of an nDNA mutation syndrome, and 35 of 56 participants reported a diagnosis of a depletion syndrome.

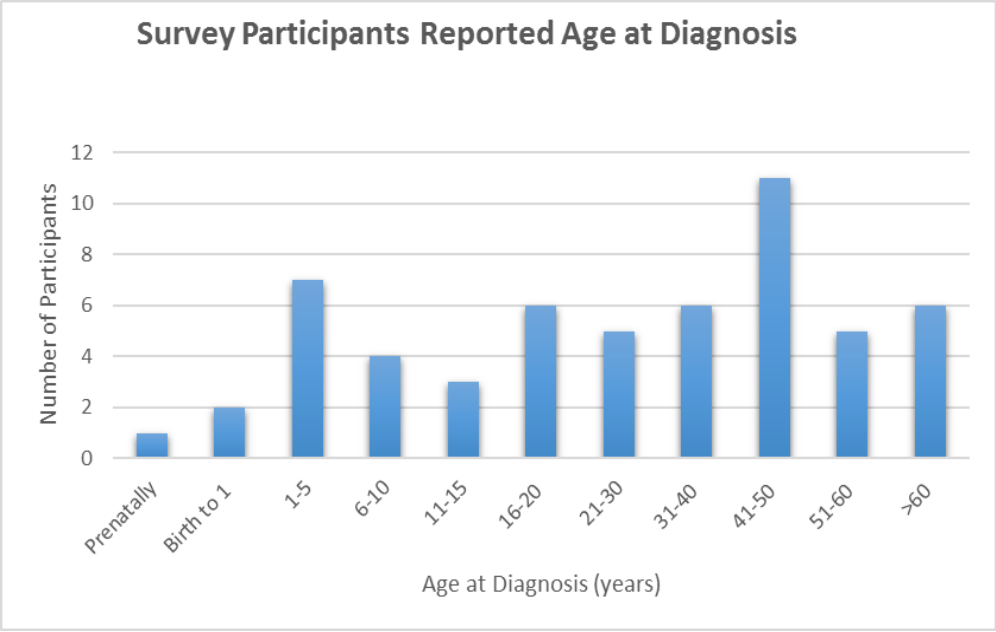

Figure 1. Age of Diagnosis

Table 4. Reported Mitochondrial Disease Diagnosis

I have been diagnosed with a mitochondrial disease (n=60)	**n**	**%**
Yes		
Caregiver	30	50%
Not a caregiver	5	8%
No		
Caregiver	5	8%
Not a caregiver	11	18%
I don't know		
Not a caregiver	9	15%
How has a medical doctor classified your mitochondrial disease or that of the person you provide care? (n=59)	n	%
Definite	34	58%
Probable	17	29%
Possible	2	3%
Unlikely	1	2%
Not yet classified	5	8%
Suspected or confirmed mitochondrial DNA mutation syndrome(s) (n=52)	n	%
Mitochondrial encephalomyopathy with lactic acidosis and stroke like episodes (MELAS)	6	12%
Myoclonic epilepsy and ragged red fibers (MERRF)	4	8%
Maternally Induced Diabetes and Deafness (MIDD)	1	2%
Leber hereditary optic neuropathy (LHON)	1	2%
Other mtDNA	39	75%
Suspected or confirmed nuclear gene disorder(s) (n=37)	n	%
Alpers-Huttenlocher syndrome or other POLG disorder	5	14%
Mitochondrial neurogastrointestinal encephalopathy (MNGIE)	2	5%
Mitochondrial DNA Depletion Syndrome	6	16%
Sensory Ataxia Neuropathy	2	5%
Sensory Ataxia Neuropathy Dysarthria Ophthalmoplegia (SANDO)	2	5%
Other nDNA	20	54%
Suspected or confirmed mitochondrial depletion syndromes (n=35)	n	%
Chronic Progressive External Ophthalmoplegia (CPEO)	5	14%
Kearn-Sayre Syndrome (KSS)	5	14%
Other	25	71%

3.3.4 Consultation with Genetic Professional

Seventy-five percent (44/59) of participants reported that they and/or the person they care for have consulted with a professional trained in genetics. Twenty-five percent (15/59) reported they had not

consulted with a genetic professional (geneticist and/or genetic counselor). Participants could select more than one answer. Participants were characterized per their responses. Fifty-four participants identified what type of genetics professional they or the person they provide care had seen for a consultation regarding their diagnosis or suspected diagnosis. Fifty-seven percent (31/54) reported consulting with at least a genetic counselor. Four participants reported seeing a genetics professional other than a geneticist or a genetic counselor.

3.3.5 Genetic Testing

Seventy-two percent (42/58) of survey participants reported that they and/or the person they care for have undergone genetic testing (Table 5). Twenty-one percent (9/42) of participants reported having more than one type of genetic test preformed. Fifty-two percent (22/42) of participants reported having genetic testing that included a multi gene panel, and 36% (15/42) reported having had genetic testing that included exome sequencing. Single site and single gene testing were also among the tests performed in this population. Seventeen percent (7/42) of participants completing this question did not know what type of genetic testing was performed. Table 5 summarizes the combination of genetic tests being reported in this population.

Table 5. Combinations of Genetic Tests Performed on Participants

Single Site	Single Gene	Multigene Panel	Exome	Other	n (n=42)	%
		X			15	36
			X		6	14
		X	X		5	12
				X	2	5
	X				2	5
	X	X	X		2	5
X			X		1	2
	X		X		1	2
X					1	2

3.3.6 Resources

A focus of this study was to assess the types of resources accessed by participants to gain information about mitochondrial disease. A total of 57 participants (95%) responded about the type of resources they used to learn more about mitochondrial disease genetics. Participants were characterized per their responses. The internet was the most frequently utilized resource (84%, 48/57). Forty-two percent of participants (24/57) considered a genetic counselor as a resource, and 65% (37/57) reported relying on information from a physician to learn more about mitochondrial disease genetics. Additionally, survey responses indicated that many participants used a combination of resources to learn about mitochondrial disease genetics with 77% (44/57), reporting using two or more resources. Additional information about the types of educational resources utilized by survey participants is summarized in Table 6.

Table 6. Resource Type and Combination Utilized in Participant Self Education about Mitochondrial Disease Genetics

Internet Resources	Genetic Counselor	Physician	Written Material	Other Resources	n (n=57)	%
X					10	18
X	X	X	X		8	14
X	X	X			7	12
X		X			7	12
X		X	X		6	11
X			X		3	5
X	X				2	4
	X	X			2	4
X	X	X	X	X	2	4
		X			2	4
				X	1	2
X		X	X	X	1	2
X	X		X		1	2
X			X	X	1	2
X	X			X	1	2
		X	X		1	2
	X		X		1	2
		X		X	1	2

3.3.7 Website Categories

Participants who indicated that they used online educational resources were further questioned about the type of websites they visited for this purpose, and 56 participants completed this question. Participants could select multiple websites. Fifty-three out of 56 participants (95%) reported visiting mitochondrial disease support/specific websites. Commercial health information websites were the second most common type of website with 66% of participants' (37/56) visiting them. Roughly half visited government website (52%, 29/56) and 42% (24/56) reported visiting a hospital or medical center website. Participants used a combination of websites to learn about mitochondrial disease. Eighty percent (45/56) reported using two or more of the specified website categories, 43% (24/56) of participants visited three or more website categories and 25% (14/56) reported using four or more.

Table 7 provides a detailed breakdown of individual websites within each category. Nearly all participants who accessed mitochondrial support/disease specific websites used the UMDF website (98%, 52/53). MitoAction was the second most visited mitochondrial disease/support website visited by 74% of participants (39/53) using websites within this category. The NIH had the most visited of government sponsored websites being visited by 97% (28/29) of responders using this type of website to learn about mitochondrial disease genetics. WebMD was the most common commercial health information website among participants using resources from this category (76%, 28/37).

Table 7. Websites Accessed by Participants for Online Educational Materials about Mitochondrial Disease Genetics

	n	%
Mitochondrial Support/Disease specific websites n=53		
MitoCanada	11	21%
MitoAction	39	74%
The Lily Foundation	4	8%
The United Mitochondrial Disease Foundation (UMDF)	52	98%
Australian Mitochondrial Disease Foundation	2	4%
Genetic Alliance	4	8%
Children's Mitochondrial Disease Network	5	9%
Other	5	17%
Commercial Health Information Websites n=37		
WebMD	28	76%
Genetics Home Reference	7	19%
GeneReviews	9	24%
eMedicine	10	27%
Raredisease.com	20	54%
Government Sponsored Websites n=29		
CDC	13	45%
NIH	28	97%
OMIM	6	21%
Other	1	3%
Hospital and/or Medical Center Websites n=24		
Mayo Clinic	17	71%
Cleveland Clinic	12	50%
Other	10	42%

3.3.8 Best methods

Participants were asked to select from a total of 10 educational modalities which ones they believed would be the most helpful to their learning about mitochondrial disease. Participants could choose multiple options and had the chance to write in modalities that were not listed. The following educational tools were provided:

- Websites
- Online literature
- Webinars
- Online videos

- In person discussion with my mitochondrial specialist, a genetic counselor, or physician
- In person seminar, symposium, or educational session
- In person support group meetings
- Brochures and pamphlets
- Newspaper
- Connecting with other people affected with mitochondrial disease or caregivers online or through social media
- Other_____

A total of 56 participants answered this multiple-choice question for a total of 197 responses. The top three methods were websites (23%,45/197), In-person discussion with mitochondrial disease specialist, genetic counselor, or physician (21%, 41/197), and online literature (19%, 37/197). Participants reported that multiple educational modalities were the best way to learn with 96% (54 out of 56) selecting two or more methods. Seventy-five percent (42 out of 56) selected three or more and 50% (28 out of 56) selected four or more methods.

3.3.9 Perceived knowledge before and after reading online educational material

To determine the perceived effect of online information on patient knowledge, participants who indicated that they accessed online educational materials were asked to rate their knowledge of the genetics of mitochondrial disease, genetic testing for mitochondrial diseases, and understanding of the risk to other family members to have the disease before and after reading online educational material. Responses were rated on a Likert like scale with 1 being “very poor” and 4 being “very good”. Before and after responses were paired and compared using a Wilcoxon Signed Rank Test. Results show a statistically significant change in perceived participant knowledge from before to after accessing the websites in all areas questioned. These results are summarized in Table 8.

Table 8. Means and Wilcoxon Signed Rank Scores of Participants' Perceived Learning Before Reading Online Educational Material Compared to Afterwards

	Mean Before (± SD)	Mean After (± SD)	Z Score	Prob > |z|
Knowledge about mitochondrial disease genetics	2 (±1.06)	2.71 (±.55)	-2.578	0.0099
Understanding of mitochondrial disease inheritance	2 (±1.1)	2.92 (±.65)	-3.277	0.0010
Understanding of the risk to other family members	2.08 (±1.14)	2.71 (±.69)	-2.138	0.0335
Knowledge about genetic testing options available to diagnose mitochondrial diseases	1.75 (±0.90)	2.63 (±.58)	-3.252	0.0011
Understanding of genetic testing advantages and disadvantages	1.83 (±0.92)	2.71 (±.75)	-2.969	0.0030

3.3.10 Ranking

Participants were asked to rate on a scale of 1-5 (Strongly Disagree, Disagree, Neutral, Agree, Strongly Agree) in response to questions about online materials' readability and accessibility. Table 9 shows the means and standard deviation. An ANOVA analysis indicated that there was not a significant difference between the means across website category. (p=0.418)

Table 9. Mean Rating of Participants' Consensus with Statements about Online Educational Material Categorized by Website

	Mitochondrial Support Websites	Government Sponsored Websites	Medical Search Websites	Hospital/Medical Center Website
	Mean (±SD)	Mean (±SD)	Mean (±SD)	Mean (±SD)
Inheritance and genetic testing resources I found on the websites were easy to read	3.49 (±1.25)	3 (±1.26)	2.92 (±1.29)	3.17 (±1.41)
Graphics provided were helpful to learning about inheritance and genetic testing	3.39 (±1.25)	2.83 (±1.30)	3.04 (±1.33)	3.18 (±1.36)
Resources were easy to find on the websites.	3.07 (±1.21)	2.66 (±1.21)	2.73 (±1.20)	2.90 (±1.27)

3.3.11 Where participants heard about genetic testing

Eighty-five percent (45/53) of the participants had discussed the possibility of genetic testing with their primary physician, mitochondrial disease specialist, or genetic counselor. The remaining 15% (8/53) responded that they had not discussed testing. Participants were asked if they first heard about genetic testing from genetic counselors, physicians, support groups, friends/family, or mitochondrial research organizations. This was a multiple-choice question. A total of 54 participants were characterized by their responses to this multiple-choice question. Almost half (44%, 24/54) claimed to have exclusively heard about genetic testing from their physician while 7% (4/54) heard about genetic testing from only a genetic counselor. Twenty-two percent (12/54) of participants heard about genetic testing from sources other than a physician or genetic counselor such as support groups, friends and family, or mitochondrial research organizations.

3.3.12 Top reason for genetic testing

Of 54 total participants, 48% (26/54) stated that their top reason for pursuing genetic testing was to confirm a diagnosis of mitochondrial diseases (Figure 2). This was a single choice question. Nineteen percent (10/54) stated the chance "To learn more about the severity and outcome of the disease" was their top reason for genetic testing. Eleven percent of participants stated their top reason for learning about genetic testing was to provide information about the risk to pass the disease to future generations. An additional 11% stated their top reason was to gain information about the risk for other family members to have the same disease.

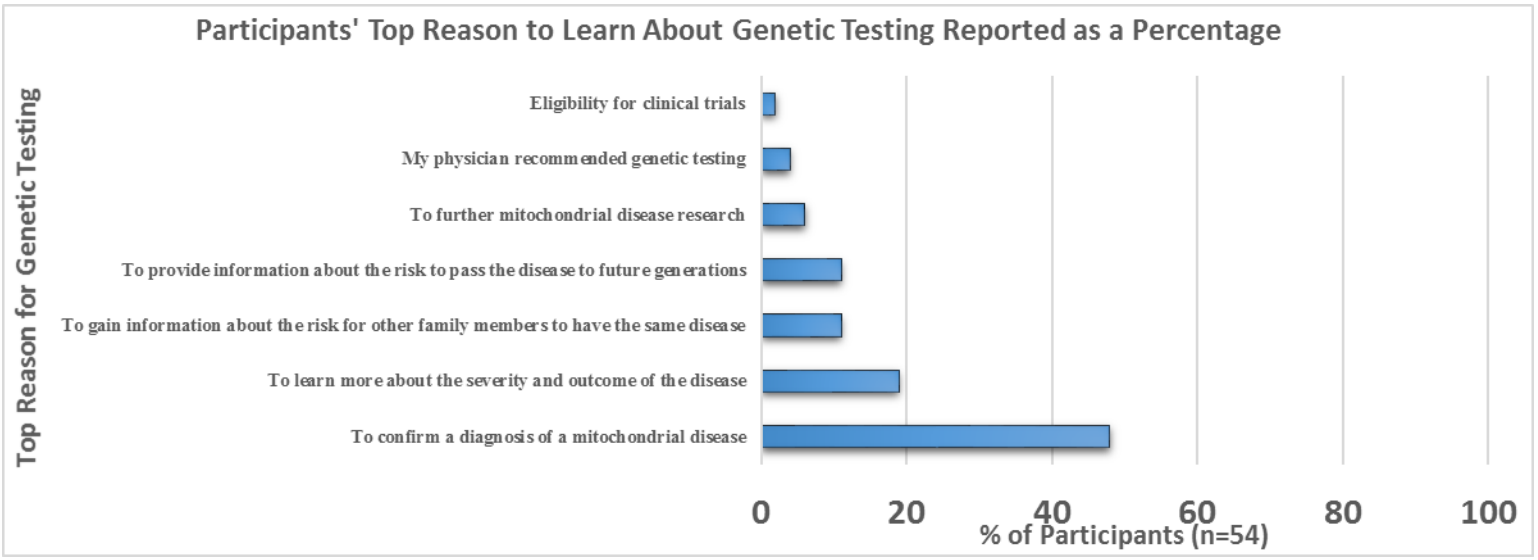

Figure 2. Participants' Top Reason to Learn about Genetic Testing

3.3.13 Genetic Testing Topics for Educational Resources

The top five topics participants reported wanting to be included in an educational resource for genetic testing were in order as follows:

- The type of genetic testing is recommended for my and/or my loved one's suspected mitochondrial disease
- Limitations of genetic testing to confirm a diagnosis of a mitochondrial disease
- How effective genetic testing can be to diagnose mitochondrial diseases
- Genetic test results could mean about my family members' risk for inheriting the same mutation
- Uncertain results and what that might mean

Please see Appendix B for a complete list of possible choices provided to participants. Participants were also able to write in an answer other than the ones provided for this question.

3.4 DISCUSSION

Mitochondrial disease, a diverse group of rare disorders, is a fitting example of the demand for improved education and awareness among patients and providers. The collective experience of those within the mitochondrial disease community verifies the need for information and improved educational material.[2,3,8,9,49,52] This deficit has created a global sentiment of uncertainty that causes patients and their families significant emotional stress, worry, anxiety, and exponentially increases caregiver burden compared to other conditions.[2,3,45,48] This study set out to assess patient/caregiver use and perception of online educational materials regarding mitochondrial genetics readability as well as the topics they believe should be included in educational materials for genetic testing of mitochondrial diseases.

In the current study, readability scores provided a measure of reading comprehension and reflect the grade level necessary for a person to understand the mitochondrial disease educational material assessed by investigators. The readability of such material is important as the average

American adult reads at the 8th grade level while 21% have a literacy level on par with the 5th grade.[63] National Institutes of Health recommend that all patient education materials be written at a 6th-8th grade reading level.[63] Despite this recommendation, many online patient educational materials are written at or above the 8th grade level, 10th-12th grade on average.[69–71,74,75,76] Online patient educational material regarding mitochondrial disease genetics assessed in this study received Flesch-Kincaid and Automated Reading Index grade level scores above the 8th grade suggesting that the average adult would likely have trouble comprehending the material. Twelve out of thirteen resources tested were written at or above a 9th grade level. Most educational materials assessed included information about genes and chromosomes, the difference between Ndna and mtDNA, autosomal dominant/recessive inheritance, X-linked inheritance, and maternal inheritance. However, a number were lacking in concepts that can complicate mitochondrial disease inheritance and predicting severity. This dearth includes heteroplasmy, bottleneck, threshold, and mutational load. Investigators noted that patient resources found on commercial health information websites did not include information about genetics. The online educational materials were produced by a variety of organizations all of which targeted at the general population. There is a global need for the improvement of the readability of patient materials.

Of the resources assessed, MitoCanada, a patient support organization, had the best readability scores in both reading ease (FKRE of 61.6) and reading grade level (FKRGL of 7.6 and ARI of 6.7). This ARI score represents a 5th grade reading level. It should be noted that although readability measures rely on different formulas, they all provide a similar picture of a text's overall readability. Readability assessments provide scores based on reading difficulty but do not assess content. Study investigators noted that resources with better readability scores were

not reflective of content. For example, MitoCanada provided basic online resources about genes, chromosomes, and inheritance patterns including maternal, autosomal recessive, and autosomal dominant inheritance. Information about X-linked inheritance, threshold, mutation load, bottleneck, reduced penetrance, and variable expressivity were not included. An informational table about heteroplasmy was provided.

Online educational material assessed from MitoAction and the United Mitochondrial Disease Foundation provide examples of resources that did not score within a 5th-8th grade level but included most of the concepts discussed above. Both non-profit patient support organizations provide tailored resources about genetic testing for mitochondrial disease and discussed topics like insurance billing, test results, and the type of tests available. Each provides external links for outside resources about genetic testing. Both utilize webinars, seminars/symposiums, graphics, and presentations to reach a broad audience. This multimedia approach is important to this population as affected individuals have varied learning needs depending on their symptoms, which can affect vision, hearing, and neurocognitive function. The investigators noted that information about genetic testing varied depending on the category of website.

The development of effective genetics educational material is especially challenging considering that the general population has low health literacy and low genomic literacy or baseline knowledge about genetics. However, this problem is compounded by the reality that a 5th-8th grade reading level may be too simplistic to convey the necessary information about genetics and genetic testing to patients. This issue has been encountered by organizations developing educational material targeted to cancer patients as such material generally cannot be written at the recommended grade level due to the necessary technical terms.[70] To minimize this disparity, one should consider which topics can be written at a 5th-8th grade level and which ones

require a more advanced level. Although a good compromise, this solution would introduce other concern such as developing methods to teach patients the technical language associated with genetics and genetic testing so that they can understand and master material written at a higher level. A multimedia approach could be effective to educating about more complex concepts.

Organizations such as the Genetics and Rare Disease Information Center (GARD) sponsored by the NIH have separate educational resources about genetic testing for the public. Medical search websites, Hospital or Medical Center websites, and Government websites generally include genetic testing of nuclear and mitochondrial DNA as a diagnostic option. However, resources may not include detailed information about the utility of genetic testing, insurance, and possible results that patients and their families feel are important. Additionally, the material may not be specific to mitochondrial diseases. Several topics survey participants believed would be useful were not included in the resources assessed. The top five topics desired for inclusion listed from most reported to least reported were:

- The type of genetic testing is recommended for my and/or my loved one's suspected mitochondrial disease.
- The limitations of genetic testing to confirm a diagnosis of a mitochondrial disease
- The effectiveness of genetic testing to diagnosing a suspected mitochondrial disease.
- The possible genetic test results and their implications of risk for family members to inherit the same mutation.
- An explanation of uncertain results and what this results may mean for patients and their families.

These topics are a part of standard genetic counseling appointment. This highlights the value of genetic counseling to informing patients about genetic testing. It is important to note that these question options (a full list is included in Appendix B) were written by a research team

that included genetic counselors and a genetic counseling student. These results may indicate the topics participants considered most important of those provided on the survey.

However, the survey may have failed to capture the elements truly thought to be important to participants. Even though there was an “other” category people often do not fill these out.

Participants did not seem to understand their specific genetic diagnosis. While this certainty is an informative observation as this survey used the same demographic and diagnosis questions asked by the initial survey that participants complete when they enroll in the MDCR. For diagnosis questions, participants had the option to select “mitochondrial disease caused by nDNA pathogenic variant(s)” and/or “mitochondrial disease caused by mtDNA pathogenic variant(s).” Depending on their answer, a list of disorders caused by either class of variant was displayed. Participants had the option to write in their specific diagnosis or pathogenic variant if it was not provided in the list. Multiple participants answered as having both classes of pathogenic variants. The probability of this duality occurring is unlikely. Furthermore, participants wrote information that indicated they either did not understand the question or did not understand their diagnosis. For example, a participant selecting that they had a mitochondrial disease caused by an mtNDA pathogenic variant and wrote in that they had a pathogenic variant in *POLG*. This demonstrates the participant my not understand the difference between nDNA and mtDNA as *POLG* is a nuclear gene that encodes the mitochondrial protein polymerase gamma. Misreported information such as diagnosis within the main MDCR database could have significant implications for research studies recruiting MDCR members or using MDCR data.

The internet was the most frequently reported resource utilized to learn about mitochondrial disease genetics (84%). A survey of 3,014 adults in the United States conducted by the Pew Internet Research and American Life Project initiative found the 72% of adults

reported using the internet to find health information while 35% reported using the internet to specifically determine what medical condition they or someone else might have.[60] The percentage of internet use observed in this study supports the claim that there is a general lack of resources available to the rare disease community resulting in a greater number of individuals seeking information online.[61] Participants tended to visit two or more website categories (80%) in their search for information. This may reflect the need for resources that are readable and accurate. Despite being a primary educational resource for the rare disease community, patients and their families have noted that the internet can be a source of misinformation.[2] Patients and their families should be judicious in using the internet for education.[77,78] Nicholl et al. found that parents of children with rare diseases visited multiple websites but were selective in the content used to learn about their children's conditions. When viewing online resources, parents considered how up to date, accurate, and relevant the information appeared as well as the reliability of the source or organization sponsoring the resource.[77] Although the current study did not identify if or how participants judged the validity of online material, the use of multiple websites may be one method that patients employ to verify information found on the internet.[78]

Study participants also reported using a variety of resources to learn about mitochondrial disease genetics with 77% using two or more resources. The survey asked participants to select the combination of resources used from a provided list. The most frequent combination was the internet, speaking with a genetic counselor, a physician, and written material (8/57). The second most reported combination included the internet, speaking with a genetic counselor, and speaking with a physician (7/57). One explanation may be that patients and their families use online resources to supplement information acquired from in person interactions with a physician or genetic counselor. Alternatively, patients may consult with physicians and genetic counselors

to clarify and/or verify information from patient support groups, online educational resources, or written material.[77] Information seeking may also serve as a coping mechanism for patients and their families.[79]

The current study also found that participants believed websites, in person discussions with mitochondrial disease specialists including genetic counselors or physicians, and online literature were the most effective educational tools for learning about mitochondrial disease genetics. Noorda et al. reported similar findings based on interviews of parents whose children underwent a diagnostic workup for a mitochondrial disease. Parents believed a combination of internet resources, written material, and personal communication with healthcare professionals was most informative.[8]

The top three website categories visited were mitochondrial support (disease specific) (95%), commercial health information websites (66%), and government sponsored (52%). It is not surprising that mitochondrial support (disease specific) websites were reported as the most frequented category because educational support is one of the key functions of such groups, which included patient support and advocacy groups.[53,54] Information found on these websites is often targeted towards patients and therefore educational resources are expected to be written at the recommended reading level for patients. The United Mitochondrial Disease Foundation was the most frequented website in this category. In total, 98% of participants (52/53) reported visiting the UMDFs website. This result is not unexpected given that the UMDF is one of the top mitochondrial disease advocacy groups in the United States. Furthermore, the registry used to distribute the survey is sponsored by the UMDF, so it is likely that MDCR members also used educational resources provided by this organization. MitoAction is another major patient

advocacy group in the United States and was the second most frequented website in this category (74%, 39/53).

WebMD was the most used commercial health information website, likely because it is one of the first medical search websites to populate when searching for “mitochondrial disease”. Hospital and medical center websites were the least visited website category of those provided. The Mayo Clinic and Cleveland Clinic were the most frequented websites in this category. Others reported included Penn Health, Kennedy Krieger Institute, CHOP, Seattle Children’s, and Stollery Children’s Hospital.

The percentage of participants visiting government websites for information may reflect the trust participants have in the information found on these websites. Previous studies have found that in general people trust that health information and online resources provided by government agencies is accurate given the established credibility and reputation of such agencies.[80,81] However, the current study suggests that the resources found on government websites are not written at the recommended level and are likely difficult for patients to read. Another important reason why government resources should be improved is that government sponsors such as the NIH or the CDC are neutral sources of information in comparison to information produced by hospitals and patient-run organizations. Parent focus groups have suggested organizations be clear in their motives and information sources in order to increase information seekers’ trust.[78]

Frustration with a perceived lack of knowledge among healthcare providers has been expressed by members of the rare disease community. Members of this population have reported feelings of stress and anxiety particularly when encountering primary and emergency care because of this uncertainty.[2,52] Lack of provider knowledge has even been identified as a barrier

to improved care.[52] Despite this finding, study participants viewed healthcare providers and physicians as important resource to their learning about mitochondrial disease genetics and testing options. Sixty-five percent of respondents reported using physicians as a resource to learn about mitochondrial disease genetics. According to participants, in-person discussions with mitochondrial disease specialists, genetic counselors, or physicians were the best way to learn about this disorder. In addition to improving online educational resources, this study indicates that there may be a benefit to designing better educational interventions targeted to healthcare providers. Improvement in this area can lead to better outcomes for patients and their families while decreasing potential anxiety over medical encounters. It should be noted that almost half of participants (44%, 24/54) first heard about genetic testing from a physician. Therefore, targeted interventions to healthcare providers should include the necessary information about NGS technologies to ensure maximum benefit to patients and their families.

Mitochondrial disease inheritance is significantly more complex than single gene disorders given the possibility of nDNA and/or mtDNA pathogenic variants and other factors that influence disease manifestations.[4] Given these challenges, the current study aimed to gain insight into the perceived effectiveness of online patient educational materials in meeting the educational needs of participants. In general, respondents perceived an increase in knowledge or understanding of mitochondrial disease genetics, inheritance, and recurrence risk and risk to family members before and after reading online educational material. There was also a perceived increase in knowledge of the genetic testing options available to diagnose mitochondrial disease and the understanding of advantages and disadvantages of genetic testing. This evidence suggests that participants believed online educational materials were somewhat effective and contributed their learning. While this study showed that participants' perceived knowledge about

mitochondrial disease and genetic testing increased after accessing information on websites, ($p=0.009$), the mean scores on a Likert like scale indicated by participants were still between 2.63 and 2.92 or a rating of understanding between poor and good. Mean scores on a Likert scale before accessing educational material were 1.75-2.08, or a rating of understanding between very poor and poor. This calls into question participant perception and the true contribution of online educational material to patient learning.

The perceived difference in knowledge before and after reading online educational material may be due to study design and not reflective of increased learning. A Likert like scale of 1-4 (very poor, poor, good, and very good) was provided to gauge perception of knowledge, however a five point Likert like scale might have been a better choice as a neutral option could be included. One could argue that there is a significant difference between possessing "Poor" and "Good" knowledge. A response in between such as "Neutral" would bridge this gap and perhaps provide a more complete representation of participants' perceived knowledge. Participants might have chosen different before and after ratings because a neutral option was not available. Even if they felt they had minimal increase in knowledge, participants may have felt dishonest choosing the same ratings as this would signify that their knowledge did not change with use of resources. It is important to note that learning was self-reported and this study did not measure actual knowledge.

While online educational material may have an impact on learning, the authors conclude that these results indicate there is room for improvement. It is disturbing that despite 58% of the study population having a Bachelor's Degree or higher, participant knowledge after online resources were rated as less than good. This lack of knowledge is even more alarming as the study population was not representative of the average adult in regards to education level.

A comparison of educational resources grouped by website category determined that there was not a significant difference between participant experience regarding the ease of reading and ease of locating educational resources across various categories of websites. ($p=0.418$) Mean scores on a Likert like scale ranged from 2.66-3.49 or a rating of agreement between disagree and neutral. Standard deviations occurred over a broad range indicating that participant responses varied and covered a wide spectrum (Table 9). The variety in responses suggest that online educational material regarding mitochondrial disease genetics, regardless of source, is not effective as an educational tool for much of this patient population. This may also be reflective of the different types of learning that are best for people. Participant recall may have also played a role as participants were asked to rate online materials based on their initial experiences learning about mitochondrial diseases.

Roughly half (48%) of survey participants stated their top reason for learning more about genetic testing was to confirm a diagnosis, thus supporting previous findings that receiving a genetic diagnosis may be the primary concern to patients with rare diseases.[2] [52] These findings indicate the importance of a diagnosis to members of the rare disease community and hints at the value placed on genetic testing. When surveying adult patients, Krieg et al. found that participants perceived that a genetic diagnosis had increased social significance, would improve care by providing more targeted therapies, and would open doors such as improved insurance coverage and participation in clinical trials.[52] Adult patients with a clinical diagnosis but not a genetic diagnosis of mitochondrial disease perceived that they encountered more skepticism and dismissal of their disease.[49,52] Patients may also desire to genetically confirm a diagnosis because having a reason for why they developed the disease may provide a sense of relief and comfort.[52] Other top reasons reported by study participants included “To learn about severity and outcome

of the disease", "To gain information about the risk for other family members to have the same disease," and "To provide information about risk to pass on the disease to future generations." These topics are major sources of stress and anxiety for patients and their families due in particular, to the perceived lack of information available about these topics.[2,3,45,48,52] These results indicate that participants believe genetic testing is an essential tool to their care that has potential to answer important questions.

3.4.1 Limitations

There are several limitations associated with this study. It is important to note that readability measures do not assess content. Data collected from this survey was self-reported and relied on participants' ability to recall their initial use of internet resources when they first heard about mitochondrial disease as a potential diagnosis. This reliance on memory could have introduced recall bias into the study sample as participants may over or underestimate to degree to which online educational material contributed to their learning. Survey participation was voluntary and therefore volunteer bias is one limitation of this study. The results may reflect the views of those who were motivated to complete the survey. For example, people who encountered difficulty when using online educational material might have been more motivated to participant than those who did not encounter the same level of difficulty. Selection bias was introduced into this study by surveying members of a registry sponsored by the UMDF. This bias is evident considering that 98% of participants accessing mitochondrial disease support group organizations reported using the UMDF website. Participants might be biased in favor of the UMDF and/or did not want to give feedback that would reflect poorly on this organization. The results might have been different if a different population was surveyed, such as members of MitoAction or another patient organization.

The response rate was just above 3%. This is concerning given that there are currently 1,900 members enrolled in the MDCR. Though it is likely that many factors contributed to this low response rate, one reason may be that individuals with ophthalmological manifestations would have had trouble completing the survey in the format that it was presented to participants. It is important for researchers to consider their audience to develop materials and research tools that are most effective and inclusive of their target population. Furthermore, it will be important for stewards of this database to gather further information about why the response rate was low so that this can be improved for future research studies that utilize the MDCR database.

3.4.2 Future Research

Focus groups and qualitative interviews could better characterize participants use and opinions about current online educational resources. By participating in focus groups, patients could provide feedback about the topics that resources should contain and evaluate whether material is understandable if it is written above a 5^{th}-8^{th} grade level. Participant input would also inform investigators about the use of multimedia tools, such as webinars, lectures/symposiums, graphics, and/or interactive learning, to develop effective educational material for the necessary technical information. Focus groups could also help identify whether the online information is easy for patients to access. Additionally, future studies could measure participant knowledge about mitochondrial disease genetics and genetic testing. This expansion would provide a frame of reference for organizations developing educational material. Finally, future research can include developing and piloting online educational resources to a small group of participants prior to distribution.

3.5 CONCLUSION

The investigators hypothesized that online patient educational materials for mitochondrial diseases were low in readability, difficult to locate, variable in content, and difficult for patients to understand. This study provides support for this hypothesis through the evaluation of websites and patient and/ or their caregivers' opinions gathered via a survey.

Readability assessments provided evidence that current online resources available to patients and their families are written at a grade level and reading ease that is above the recommended 6th-8th grade level. Despite a perceived a difference in knowledge of genetic concepts after reading online material, mean response indicated ratings between poor and good understanding with broad standard deviations. Participants' reporting of their diagnosis also called into question what they truly understood about mitochondrial disease genetics as many seemed unsure of their diagnosis.

In addition to the internet, survey participants reported accessing a variety of resources to learn about mitochondrial disease genetics. Participants visited multiple websites but heavily relied on resources from mitochondrial disease support organizations such as the UMDF and MitoAction. Additionally, participants expressed the desire to obtain information from their physician or other healthcare professional. Participants place immense value on the ability of genetic tests to confirm a diagnosis and provide them with information about inheritance, recurrence risk, prognosis, and treatment.

The following steps are recommended:

- Online patient educational material can be written at a 6th-8th grade reading level. Resources such as http://www.plainlanguage.gov exist to help develop materials written in language that is easily understood by the average American.
- Use clear and concise language and define terminology when composing materials which cannot be written at the 6th-8th grade level.
- Develop educational resources for genetic testing of mitochondrial diseases that include the type of genetic testing recommended for mitochondrial diseases, the limitations of genetic testing to

confirm a diagnosis, how effective genetic testing can be for diagnosis, genetic test results and the implications for family members, and uncertain results and what they mean for affected individuals.

- Pilot educational materials with patients and families prior to distribution to ensure readability and confirm that such resources meet their needs
- Target education towards physicians and other healthcare professionals.

4.0 RESEARCH SIGNIFICANCE TO GENETIC COUNSELING AND PUBLIC HEALTH

4.1 GENETIC COUNSELING

Genetic counselors have a unique combination of skills to develop patient materials and educate the public about genetic disorders.[75] They often serve as a resource for patients, families, and caregivers to learn about the genetics and inheritance of a condition and may provide additional support or educational resources found online. There is an abundance of information on the internet about genetics, but not all resources are targeted to patients.[74] Genetics educational materials targeted to the public are not necessarily written at a reading level that is easily understood by the average individual. Genetic counselors should remain well informed about which online patient educational resources are the best for their patients' educational endeavors based on readability and ease of understanding. Also, given that the study showed that patients often utilize several methods for obtaining information, it is important for genetic counselors to continue to provide their patients with helpful online resources, and to continually evaluate resources to determine their appropriateness for patients. Additionally, genetic counselors should be aware of the accuracy of information found online, even resources produced by trusted organizations. Rapid advancements to genetics and medicine occur frequently, and it can be difficult for organizations producing educational material to remain up-to-date. Therefore, genetic counselors should know which resources may have information gaps, be outdated, or not applicable to provide patients with anticipatory guidance.

Genetic counselors are often involved in the development of patient educational materials produced by patient support or advocacy groups, government organizations such as the NIH, and/or

hospital/medical centers.[75] They may be involved in planning or presenting at patient and family education days sponsored by a medical institution or a patient advocacy group.[75] Thus, it is important for genetic counselors to have knowledge about health and genetic literacy in order to provide useful and understandable educational materials for their targeted audience.

Next Generation Sequencing (NGS) technologies are becoming the standard platform for genetic testing when a rare disease is suspected given its high diagnostic yield.[10] Many insurance companies require patients to have a consultation with a genetic counselor before they will cover genetic testing. This prerequisite ensures that genetic counselors educate and counsel patients about the advantages, disadvantages, and potential results of exome sequencing. The components of a standard genetic counseling session were the most frequently reported topics desired for inclusion in genetic testing educational resources. These results imply that people could benefit from a genetic counseling session, however, also raises questions of access. Currently, barriers to care such as limitations of the genetic counseling workforce, insurance coverage, and accessibility may prevent individuals from undergoing a genetic counseling session. One solution may be to develop alternative means to deliver the information discussed in a session in an understandable format to the public.

Online educational materials about genetic testing are limited, may be difficult for patients to read due to technical language, and often may be outdated due the rapid pace of developing technologies. This rapid turnover is particularly problematic in the context of rare conditions, such as mitochondrial diseases, where the patient and/or their love ones primarily use online educational materials as a resource. Thus, it is crucial that material about the genetics of mitochondrial disease and genetic testing be written in clear, concise, and patient-centered language. It is vital that patients be well-informed before consenting to exome sequencing about the benefits, limitations, and types of results that NGS testing can provide. Patients are requesting information about genetic testing and genetic counselors can help provide this information.

This study found that participants seemed unsure of their diagnosis. Participants wrote information that indicated they either did not understand the question or did not understand their

diagnosis. For example, a participant selecting that they had a mitochondrial disease caused by an mtNDA pathogenic variant did not see their diagnosis in the list and wrote a pathogenic variant in *POLG*. This demonstrates the participant my not understand the difference between nDNA and mtDNA as POLG is a nuclear gene that encodes the mitochondrial protein polymerase gamma. Genetic counselors can be instrumental in helping patients understand their diagnosis and other areas of concern where online educational materials are lacking information or not adequately fulfilling patient need. This lack of information can include inheritance, recurrence risk, reduced penetrance, and the factors affecting disease manifestation that complicate predicting severity/prognosis.

4.2 PUBLIC HEALTH

The public health implications for the role of patient advocacy/support groups and the use of patient registries within rare disease communities are numerous. Traditionally, rare diseases were not considered a public health issue given their low prevalence compared to common diseases such as diabetes or heart disease.[76] However, combined, individuals with rare diseases make up a substantial section of the population as roughly 25 million individuals in the United States, 30 million individuals in Europe, and 400 million worldwide are affected by a rare disease.[2]

The combination of a small population and large geographic distribution have proven a unique barrier to the forward progress of rare diseases,[76] which has caused a general lack of disease information and rare disease research. Downstream consequences have included difficulty in receiving a diagnosis, unknown etiologies or disease mechanism, and a lack of standards of care for surveillance and management. In general, there is limited disease natural history or longitudinal data for rare diseases.[76] Registries can help ameliorate several of these challenges by comprising impressive cohorts and generating large amounts of data. This information can help researchers better characterize a condition, develop standards of practice, diagnostic and screening guidelines, develop new or improve existing

drugs/treatments and identify underlying etiologies, disease mechanisms, and genotype/phenotype correlations. Registries have been crucial to furthering clinical and pharmaceutical research whether it be through patient recruitment, providing access to data, or maximizing collaboration of researchers across the world.[57,77,78] Information gathered from registries can provide data to support the development of a variety of public health policies. This has the power to improve outcomes and develop necessary interventions for the rare disease community.

The Mitochondrial Disease Community Registry (MDCR) was an effective means of distributing the study survey. Although the survey could have been developed and distributed using other methods, email and postal mail, the MDCR was efficient because it was easy to send to the target population. Unlike other online survey platforms and postal mail, the registry allowed the United Mitochondrial Disease Foundation to send members study reminders and updates about the survey. Additionally, MDCR enrollees understand that research participation is an opportunity provided with their membership. Thus, the survey sample is a group that is aware and motivated to participate in research. However, the quality of data collected can be one challenge investigators and the patient-centered registry face in that information captured within the registry is self-reported by members. Self-report surveys inherently introduce concerns such as introspective ability of participants, recall bias, and response bias into the data generated.[82] Interpretation of questions may vary between participants. In the case of the MDCR questions may challenge the participants understanding of mitochondrial diseases.

The challenge of self-reported data was evident in the current study survey when considering participant reporting of diagnosis. The current study found that multiple participants answered as having both classes of mtDNA and nDNA pathogenic variants and/or writing in a diagnosis in the wrong category. This is concerning for the MDCR as well since the same diagnostic questions are used in the initial survey MDCR members complete upon enrollment. The goal of patient registries is to compile large cohorts of data that outside researchers can access for future studies. The quality of data residing in patient registries could adversely affect such research.

This example highlights the importance to creating simple, yet concise questionnaires with the target population in mind. Piloting surveys before distribution is one way to avoid this problem. Another solution may be to include an educational primer for individuals enrolling in registries that rely on self-report before they can enter information. This informational inclusion may be especially helpful as previous studies suggest that previous knowledge of genetic concepts is a strong predictor of genomic literacy.[65] Additionally, science standards set by the United State Department of Education can vary state to state and may inadequately cover genetic concepts necessary to individuals to be considered genetic/genomic literate.[66,67] The addition of a primer will provide a review of genetics and perhaps improve participant understanding of questions, which may also serve to decrease recall bias.

Alerting participants that it would be helpful to review their medical records before answering questions is another method to ensure that correct diagnostic information is reported. It could also be informative to include patients in the planning and development process of surveys and other patient-centered research to be carried up using the MDCR.

Patient registries are helping to solve barriers to improved patient outcomes within the rare disease community such as lack of disease information and research by collecting large amounts of patient data. The Mitochondrial Disease Community Registry was a useful tool for developing and distributing the study survey. The challenge of patient registries in the way of self-reported diagnosis information was identified in this study. Researchers and organizations sponsoring patient registries should be aware of the pitfalls and limitations associated with this tool as well as the impact it can have on the outcomes and development of necessary interventions for the rare disease community.

APPENDIX A: SURVEY INTRODUCTION

Research Study on Online Educational Materials for Mitochondrial Disease Genetics

Thank you for your interest in participating in this research study. This is a voluntary research study aiming to assess online resources for mitochondrial genetics and to identify information about genetic testing for mitochondrial disease which patients and their loved ones would like to see included in similar educational resources.

Mitochondrial disease can affect multiple systems of the body. It is estimated that collectively; mitochondrial diseases occur for every 1 in 5,000 births in the US. Mitochondrial disease can be caused by mutations in the nuclear or mitochondrial genome. They can be passed down through a family in a variety of inheritance patterns or be a new change to a person's DNA code. While many resources about mitochondrial disease genetics exist online, these materials are not always written on a level that is readable yet informative to the public.

Diagnosing mitochondrial disease can be challenging even for experienced specialists. Advancements in technology are making genetic tests a useful tool for clinicians to reach a correct diagnosis faster, shortening a potentially long diagnostic odyssey.

This survey will take approximately 20 minutes to complete. You must be enrolled in the Mitochondrial Disease Community Registry (MDCR) to complete the survey. You can take this survey from any profile in your MDCR account, whether it is a caregiver profile or one for someone affected with a mitochondrial disease. However, you only need to take the survey once per account. Questions will ask information about diagnosis and an assessment of online education information. Identifying information such as names will not be asked. Your completion of this survey serves as your consent in this study. Participation is voluntary. You can end the survey at any time however if you have begun the survey, that portion of the survey will remain part of the research study. Your survey responses will remain in the MDCR for the duration of the study and viewed by the United Mitochondrial Disease Foundation only if your profile's privacy settings allow for it. Survey data will not be linked to any identifying information when shared with the study researchers. Survey data will be stored separately from any contact information provided during account creation.

Anticipated risks to participants include potential emotional discomfort when discussing a diagnosis of mitochondrial disease. As with any online activity, there is the potential for breach of confidentiality of the data. To minimize this risk, the survey does not collect identifying information. Per the security procedures of the MDCR, members will immediately receive an email should a suspected breach of privacy occur. The MDCR adheres to strict data security and monitoring plan to keep all data safe. *Authorized representatives from the University of Pittsburgh Research Conduct and Compliance Office may review your data solely for the purpose of monitoring the conduct of this study.*

There are no costs to participate in this research study. You will not receive payment or direct benefit from your participation in this study. However, your participation may aid in the improvement and development of educational resources.

Please feel free to contact the study investigator Sara Blankenship (slb147@pitt.edu) with any questions or concerns regarding this study. *If you have any questions about your rights as a research*

subject please contact the Human Subjects Protection Advocate at the University of Pittsburgh IRB Office, 1.866.212.2668.
Thank you for your participation. Please click continue to begin the survey.

Sara Blankenship
Genetic Counseling Student
Pittsburgh University, School of Public Health
Genetic Counseling Program

APPENDIX B: SURVEY TOOL

ASSESSMENT OF EDUCATIONAL MATERIALS REGARDING THE GENETICS OF MITOCHONDRIAL DISEASE

Section I Demographics

This survey will begin by gathering demographic data such as gender, age, income, etc. Questions may be repeats of those asked during the creation of your MDCR account but are necessary for this study.

1. What is your age?
   - ☐ 18-30 years old
   - ☐ 31-40 years old
   - ☐ 41-50 years old
   - ☐ 51-60 years old
   - ☐ > 60 years old

2. What is your gender?
   - ☐ Male
   - ☐ Female
   - ☐ Prefer not to answer

3. What race do you identify with?
   - ☐ African American
   - ☐ Caucasian
   - ☐ Asian/Pacific Islander
   - ☐ Native American
   - ☐ Other

4. What is your marital status?
   - ☐ Married
   - ☐ Divorced
   - ☐ Single

5. What is your highest level of education?
   - ☐ No schooling completed

- ☐ Some primary or high school
- ☐ High School
- ☐ GED or equivalent
- ☐ Vocational/Trade school
- ☐ Associates Degree
- ☐ Some College but more than 1 year
- ☐ Bachelor's Degree
- ☐ Master's Degree
- ☐ Professional Degree beyond a bachelor's degree
- ☐ Doctorate Degree
- ☐ Other_____

6. What is your income (USD)?
   - ☐ Less than 20,000
   - ☐ 20,000-24,999
   - ☐ 25,000-29,999
   - ☐ 30,000-34,999
   - ☐ 35,000-39,999
   - ☐ 40,000-44,999
   - ☐ 45,000-49,999
   - ☐ 50,000-54,999
   - ☐ 55,000-59,999
   - ☐ 60,000-64,999
   - ☐ 65,000-69,999
   - ☐ 70,000-74,999
   - ☐ 75,000-79,999
   - ☐ 80,000-84,999
   - ☐ 85,000-89,999
   - ☐ 90,000-94,999
   - ☐ 95,000-99,999
   - ☐ 100,000-149,000
   - ☐ 150,000-199,999
   - ☐ 200,000-249,999
   - ☐ 250,000 and above
   - ☐ Decline to provide

Section II Mitochondrial Disease Diagnosis

Section Instructions: This section will ask questions about mitochondrial disease diagnosis. Mitochondrial disease will be categorized as follows: Mitochondrial DNA mutations, nuclear DNA mutations, Mitochondria Depletion syndromes, and Biochemical Disorders. Questions can be skipped if they do not apply to you and/or the person for which you provide care.

1. Have you been diagnosed with a mitochondrial disease?
   - ☐ Yes
   - ☐ No
2. How has your medical doctor classified your mitochondrial disease?
   - ☐ Definite
   - ☐ Probable
   - ☐ Possible
   - ☐ Unlikely

- ☐ Not yet classified

3. Are you a caregiver for person(s), other than yourself, with a diagnosis of a mitochondrial disease?
   - ☐ Yes
   - ☐ No
4. How has the medical doctor of the person you care for classified their mitochondrial disease?
   - ☐ Definite
   - ☐ Probable
   - ☐ Possible
   - ☐ Unlikely
   - ☐ Not yet classified
5. What mitochondrial disease diagnosis have you received from a physician? Please check all that apply

I have a diagnosis of or a suspected diagnosis of the following mitochondrial DNA mutation syndrome(s)

- ☐ Amnioglycoside-Induced Deafness (AID)
- ☐ Leber hereditary optic neuropathy (LHON)
- ☐ Mitochondrial encephalomyopathy with lactic acidosis and stroke like episodes (MELAS)
- ☐ Myoclonic epilepsy and ragged red fibers (MERRF)
- ☐ Neurogenic weakness with ataxia and retinitis pigmentosa (NARP)
- ☐ Maternally Induced Diabetes and Deafness (MIDD)
- ☐ Maternally Inherited Leigh Syndrome (MILS)
- ☐ Other

You selected "Other". Please specify the mitochondrial mutation syndrome(s) for which you have a diagnosis or suspected diagnosis. Please type your response in the text box provided. _____

I have a diagnosis or a suspected diagnosis of the following mitochondrial deletion syndromes

- ☐ Chronic Progressive External Ophthalmoplegia (CPEO)
- ☐ Kearne-Sayre Syndrome (KSS)
- ☐ Pearson syndrome
- ☐ Other

You selected "Other". Please specify the mitochondrial depletion syndrome(s) for which you have a diagnosis or suspected diagnosis. Please type your response in the text box provided. _____

I have a diagnosis or a suspected diagnosis of the following nuclear gene disorder(s)

- ☐ Alpers-Huttenlocher syndrome or other POLG disorder
- ☐ Mitochondrial neurogastrointestinal encephalopathy (MNGIE)
- ☐ Barth syndrome
- ☐ Mitochondrial DNA Depletion Syndrome
- ☐ Sensory Ataxia Neuropathy
- ☐ Sensory Ataxia Neuropathy Dyssarthria Ophthalmoplegia (SANDO)
- ☐ Other

You selected “Other”. Please specify the nuclear gene disorder(s) for which you have a diagnosis or suspected diagnosis. Please type your response in the text box provided.____

I have a diagnosis of or a suspected diagnosis of the following Biochemical Disorders.

- ☐ Complex I Deficiency
- ☐ Complex II (SDH) Deficiency
- ☐ Complex III Deficiency
- ☐ Complex IV Deficiency
- ☐ Complex V Deficiency
- ☐ CoQ Deficiency
- ☐ Multiple Respiratory Chain Enzyme Deficiencies
- ☐ Other

You selected “Other”. Please specify the biochemical disorder(s) for which you have a diagnosis or suspected diagnosis. Please type your response in the text box provided.

6. What mitochondrial disease diagnosis has the person you care for received from a physician? Please check all that apply

The person I care for has a diagnosis of or a suspected diagnosis of the following mitochondrial DNA mutation syndrome(s)

- ☐ Amnioglycoside-Induced Deafness (AID)
- ☐ Leber hereditary optic neuropathy (LHON)
- ☐ Mitochondrial encephalomyopathy with lactic acidosis and stroke like episodes (MELAS)
- ☐ Myoclonic epilepsy and ragged red fibers (MERRF)
- ☐ Neurogenic weakness with ataxia and retinitis pigmentosa (NARP)
- ☐ Maternally Induced Diabetes and Deafness (MIDD)
- ☐ Maternally Inherited Leigh Syndrome (MILS)
- ☐ Other

You selected “Other”. You selected “Other”. Please specify the mitochondrial DNA mutation syndrome(s) for which the person you care for has a diagnosis or suspected diagnosis. Please type your response in the text box provided. _____

The person I care for has a diagnosis or a suspected diagnosis of the following mitochondrial deletion syndromes

- ☐ Chronic Progressive External Ophthalmoplegia (CPEO)
- ☐ Kearne-Sayre Syndrome (KSS)
- ☐ Pearson syndrome
- ☐ Other

You selected “Other”. Please specify the mitochondrial depletion syndrome(s) for which the person you care for has a diagnosis or suspected diagnosis. Please type your response in the text box provided. _____

The person I care for has a diagnosis or a suspected diagnosis of the following nuclear gene disorder(s)

- ☐ Alper-Huntten Locher syndrome or other POLG disorder
- ☐ Mitochondrial neurogastrointestinal encephalopathy (MNGIE)
- ☐ Barth syndrome
- ☐ Mitochondrial DNA Depletion Syndrome
- ☐ Sensory Ataxia Neuropathy

- ☐ Sensory Ataxia Neuropathy Dyssarthria Ophthalmoplegia (SANDO)
- ☐ Other

You selected "Other". Please specify the nuclear gene disorder(s) for which the person you care for has a diagnosis or suspected diagnosis. Please type your response in the text box provided. _____

The person I care for has a diagnosis of or a suspected diagnosis of the following Biochemical Disorders

- ☐ Complex I Deficiency
- ☐ Complex II (SDH) Deficiency
- ☐ Complex III Deficiency
- ☐ Complex IV Deficiency
- ☐ Complex V Deficiency
- ☐ CoQ Deficiency
- ☐ Multiple Respiratory Chain Enzyme Deficiencies
- ☐ Other

You selected "Other". Please specify the biochemical disorder(s) for which the person you care for has a diagnosis or suspected diagnosis. Please type your response in the text box provided. _____

7. Age of diagnosis

   What age were you when you were diagnosed with a mitochondrial disease?

- ☐ Prenatally
- ☐ Birth to 1 year old
- ☐ 1-5 years old
- ☐ 6-10 years old
- ☐ 11-15 years old
- ☐ 16-20 years old
- ☐ 21-30 years old
- ☐ 31-40 years old
- ☐ 41-50 years old
- ☐ 51-60 years old
- ☐ > 60 years old

What age was the person(s) you care for when they were diagnosed with a mitochondrial disease?

- ☐ Prenatally
- ☐ Birth to 1 year old
- ☐ 1-5 years old
- ☐ 6-10 years old
- ☐ 11-15 years old
- ☐ 16-20 years old
- ☐ 21-30 years old
- ☐ 31-40 years old
- ☐ 41-50 years old
- ☐ 51-60 years old
- ☐ > 60 years old

8. Have you or the people you care for seen a genetics professional?

- ☐ Yes, both myself and the person I care for have seen a genetics professional
- ☐ Yes, I have seen a genetics professional
- ☐ Yes, the person I care for has seen a genetics professional

- ☐ No, I have not seen a genetics professional
- ☐ No, neither myself nor the person I care for seen a genetics professional

9. What kind of genetics professional did you see? Please check all that apply
   - ☐ Geneticist (Physician specializing in genetic medicine)
   - ☐ Genetic Counselor
   - ☐ Other medical professionals

10. Have you or the person you care for undergone genetic testing?
    - ☐ Yes, both myself and the person have undergone genetic testing
    - ☐ Yes, I have undergone genetic testing
    - ☐ Yes, the person I care for has undergone genetic testing
    - ☐ No, I have not undergone genetic testing
    - ☐ No, neither myself nor the person I care have undergone genetic testing

11. What type of genetic testing was done?
    - ☐ Single site testing
      - o With this test, one location of a gene is sequenced or read for spelling errors. This test may be recommended for people with a family with a known mutation.
    - ☐ Single gene testing
      - o With this test, an entire gene is sequenced or read for spelling errors, rearrangements, or missing or extra pieces of DNA
    - ☐ Multi gene panel
      - o With this test, more than one gene is read for spelling errors, rearrangements or extra or missing pieces of DNA.
    - ☐ Exome
      - o Test that sequences or reads for spelling errors or extra or missing pieces of DNA at the portion of gene that tells the body how to grow and develop. Changes to DNA in this portion have been most related to diseases.
    - ☐ Other_____

Part III. Mitochondrial Genetics and Inheritance Educational Resources

1. What resources did you use to learn more about mitochondrial disease genetics? Check all that apply
   - ☐ Internet resources
   - ☐ Genetic counselor
   - ☐ Physician
   - ☐ Written material
   - ☐ Other_____

2. What internet websites did you visit? Check all that apply
   Mitochondrial Support/Disease specific websites

- ☐ The United Mitochondrial Disease Foundation (UMDF)
- ☐ MitoAction
- ☐ The Lily Foundation
- ☐ Genetic Alliance
- ☐ MitoCanada
- ☐ Australian Mitochondrial Disease Foundation
- ☐ Children's Mitochondrial Disease Network
- ☐ Other_____

Government websites

- ☐ CDC
- ☐ NIH
- ☐ OMIM
- ☐ Other_____

Medical Search websites

- ☐ WedMD
- ☐ Genetics Home Reference
- ☐ GeneReviews
- ☐ eMedicine
- ☐ Raredisease.com
- ☐ Other_____

Hospital and medical center websites

- ☐ Mayo Clinic
- ☐ Cleveland Clinic
- ☐ Other_____

Other

- ☐ Mitochondrial Medicine Society
- ☐ North American Mitochondrial Disease Consortium

Section IV. Prior knowledge of mitochondrial disease inheritance and genetic testing

The purpose of this section is to gain insight into your knowledge about mitochondrial disease inheritance and testing prior to reading online education resources. Please think back to when you were first informed about mitochondrial disease as a possible diagnosis for you or the people you provide care.

For the following questions, please rate your understanding of mitochondrial disease inheritance and genetic testing **prior to reading online material.**

1. Prior to reading online educational materials, I would rate my knowledge of the genetics of mitochondrial disease as_____
    - ☐ Very poor
    - ☐ Poor
    - ☐ Good
    - ☐ Very good
2. Prior to reading online educational materials, I would rate my understanding of how mitochondrial diseases can be passed down through families as_____
    - ☐ Very poor
    - ☐ Poor
    - ☐ Good
    - ☐ Very good
3. Prior to reading online educational materials, I would rate my understanding the risk to other family members to have the disease.
    - ☐ Very poor
    - ☐ Poor
    - ☐ Good

- ☐ Very good

4. Prior to reading online education materials, I would rate my knowledge about the genetic testing options available to diagnose mitochondrial diseases as _____
    - ☐ Very poor
    - ☐ Poor
    - ☐ Good
    - ☐ Very good
5. Prior to reading online education materials, I would rate my understanding of the advantages and disadvantages of genetic testing as_____
    - ☐ Very poor
    - ☐ Poor
    - ☐ Good
    - ☐ Very good

Section V: Knowledge of mitochondrial disease inheritance and genetic testing gained after reading online material.

The purpose of this section is to assess how the educational resources you used affected your knowledge about mitochondrial disease inheritance and genetic testing

1. After reading online educational material, I would rate my knowledge of the genetics of mitochondrial disease as_____
    - ☐ Very poor
    - ☐ Poor
    - ☐ Good
    - ☐ Very good
    - ☐
2. After reading online educational material, I would rate my understanding the risk to other family members to have the disease.
    - ☐ Very poor
    - ☐ Poor
    - ☐ Good
    - ☐ Very good

3. After reading online educational material, I would rate my understanding of how mitochondrial diseases can be passed down through families as_____
    - ☐ Very poor
    - ☐ Poor
    - ☐ Good
    - ☐ Very good
4. After reading online education material, I would rate my knowledge about the genetic testing options available to diagnose mitochondrial diseases as _____
    - ☐ Very poor
    - ☐ Poor
    - ☐ Good
    - ☐ Very good
5. After reading online education material, I would rate my understanding of the advantages and disadvantages of genetic testing as_____

- ☐ Very poor
- ☐ Poor
- ☐ Good
- ☐ Very good

Section VI. Assessment of Educational Resources

For this section, please refer to the website categories presented above. On a scale of 1-5 with 1 being strongly disagree and 5 being strongly agree please indicate your thoughts regarding the educational material found on the websites.

Mitochondrial Disease Support Group websites:

1. In general, mitochondrial disease inheritance and genetic testing resources I found on these websites were easy to read
   N/A 1 2 3 4 5

2. In general, graphics provided were helpful to my learning about mitochondrial disease inheritance and genetic testing
   N/A 1 2 3 4 5

3. In general, mitochondrial disease inheritance and genetic testing resources were easy to find on the websites.
   N/A 1 2 3 4 5

Government Websites

1. In general, mitochondrial disease inheritance and genetic testing resources I found on these websites were easy to read
   N/A 1 2 3 4 5

2. In general, graphics provided were helpful to my learning about mitochondrial disease inheritance and genetic testing
   N/A 1 2 3 4 5

3. In general, mitochondrial disease inheritance and genetic testing resources were easy to find on the websites.
   N/A 1 2 3 4 5

Medical Search websites

1. In general, mitochondrial disease inheritance and genetic testing resources I found on these websites were easy to read
   N/A 1 2 3 4 5

2. In general, graphics provided were helpful to my learning about mitochondrial disease inheritance and genetic testing
   N/A 1 2 3 4 5

3. In general, mitochondrial disease inheritance and genetic testing resources were easy to find on the websites.
   N/A 1 2 3 4 5

Hospital and Medical Center Websites

1. In general, mitochondrial disease inheritance and genetic testing resources I found on these websites were easy to read
   N/A 1 2 3 4 5

2. In general, graphics provided were helpful to my learning about mitochondrial disease inheritance and genetic testing
   N/A 1 2 3 4 5

3. In general, mitochondrial disease inheritance and genetic testing resources were easy to find on the websites.
   N/A 1 2 3 4 5

4. The following methods were the best way for me to learn about mitochondrial disease:
   - ☐ Websites
   - ☐ Online literature
   - ☐ Webinars
   - ☐ Online videos
   - ☐ In person discussion with my mitochondrial specialist, a genetic counselor, or physician
   - ☐ In person seminar, symposium, or educational session
   - ☐ In person support group meetings
   - ☐ Brochures and pamphlets
   - ☐ Newspaper
   - ☐ Connecting with other people affected with mitochondrial disease or caregivers online or through social media
   - ☐ Other_____

Section VII Genetic Testing Educational Resources
The goal of this section is to identify information relating to genetic testing and mitochondrial diseases that patients and their loved ones believe is necessary to have in online education material.

1. I first heard about genetic testing from
   - ☐ Physician
   - ☐ Genetic Counselor
   - ☐ Support Group
   - ☐ Friends/Family
   - ☐ Mitochondrial research organization
     - o Mitochondrial Medicine Society (MMS)
     - o North Atlantic Mitochondrial Disease Research Consortium (NAMDC)

2. I have discussed the possibility of genetic testing with my primary physician, mitochondrial disease specialist, or genetic counselor.

- ☐ Yes
- ☐ No

3. If you had to choose your **top** reason for learning more about genetic testing it would be:
   - ☐ To confirm a diagnosis of mitochondrial disease
   - ☐ To learn more about the severity and outcome of the disease
   - ☐ To gain information about the risk for other family members to have the same disease
   - ☐ To provide information about the risk to pass the disease future generations
   - ☐ To gain access to improved insurance coverage and eligibility for clinical trials
   - ☐ To further mitochondrial disease research
   - ☐ To find support groups
   - ☐ My physician recommended genetic testing
   - ☐ Other_____

4. Which other reasons are important to you?
   - ☐ To confirm a diagnosis of mitochondrial disease
   - ☐ To learn more about the severity and outcome of the disease
   - ☐ To gain information about the risk for other family members to have the same disease
   - ☐ To provide information about the risk to pass the disease future generations
   - ☐ To gain access to improved insurance coverage
   - ☐ Eligibility for clinical trials
   - ☐ To further mitochondrial disease research
   - ☐ To find support groups
   - ☐ My physician recommended genetic testing
   - ☐ Other_____

5. Please indicate what information about genetic testing you feel would be helpful to include on an educational resource to aid in your learning about genetic testing. Check all that apply

- ☐ Information about which type of genetic testing is recommended for my and/or my loved ones' suspected mitochondrial disease
- ☐ Information about potential risks and benefits of genetic testing to myself and my family
- ☐ Information about the limitations of genetic testing to confirm a diagnosis of a mitochondrial disease
- ☐ Information about how effective genetic testing can be to diagnose mitochondrial diseases
- ☐ Information about how the test is performed
- ☐ Information about how genetic test result may affect my insurance coverage
- ☐ Information about how my genetic information will be stored in my medical records and by the lab performing the test
- ☐ Information about privacy laws in relation to genetic test information
- ☐ Information about how my family members can pursue genetic testing
- ☐ Information about how to talk to my family about my test results
- ☐ Information about what my genetic test results could mean about my family members' risk for inheriting the same mutation
- ☐ Information about how test results can affect my care
- ☐ Information about uncertain results and what that means
- ☐ Can genetic testing provide me with information other genes?

- ☐ Other_____
- ☐ All of the above

6. Please select any of the following barriers that you believe are barriers to receiving genetic testing.

- ☐ Insurance coverage
- ☐ Lack of information about genetic testing
- ☐ Distance to a medical center to have the test performed
- ☐ Access to genetics professional
- ☐ Other

7. In 2-3 sentences, please describe what information you believe would be helpful and should be included on educational material about genetic testing
8. What advice would you give to anyone creating educational material about mitochondrial disease?

APPENDIX C: UMDF: SURVEY PROMOTIONAL EMAIL FOR MDCR MEMBERS

Research Opportunity Alert

An exciting research opportunity is available to members enrolled in the Mitochondrial Disease Community Registry (MDCR). This is a chance to give your input about online resources for genetic inheritance (or how a condition is passed through families) and genetic testing of mitochondrial disease.

Many of us use the Internet to learn about mitochondrial diseases. For many patients and their families, the internet is the one of the first places they turned when they heard about the possibility of a mitochondrial disease. Online resources made for the mitochondrial disease community are not always easy to read and understand. They may lack information that matters to patients and their families. This is especially true of materials about genetic inheritance and genetic testing.

The goal of this study is to assess online resources for patients and their families about how mitochondrial diseases are passed through families and the options for genetic testing. Researchers are interested to learn from members and their experiences using online resources. A survey will be used to achieve this goal. Your participation may help improve current resources and/or add new education tools. Please consider participating. Your input is important for increasing awareness and improving care for mitochondrial disease.

Participation in this study is voluntary and the survey should take less than 20 minutes to complete.

How can I participate?

You must be enrolled in the MDCR. For more details about the study, log into your MDCDR account and clink on the “Dashboard” button to the left of the page.

C.1 UMDF: SURVEY PROMOTIONAL SOCIAL MEDIA POST

Social Media Post

Are you interested in contributing to the improvement of online resources for mitochondrial disease? A new research study is available to members enrolled in the MDCR. The study will ask about your experience with educational resources about mitochondrial disease genetics and genetic testing found online. Participation is voluntary and will take less than 20 minutes of your time. Your input is important for increasing awareness and improving care for mitochondrial disease.

Members enrolled in the MDCR can access more details about the study by logging into their account. Information can be found by clicking on the Dashboard button.

Not a member of the MDCR? There's still time to enroll. Follow this link http://www.umdf.org/registry/ for more information about the registry. Once enrolled, you will be eligible to participate in the study.

C.2 UMDF: SURVEY PROMOTIONAL EMAIL TO UMDF MEMBERS

Research Opportunity Alert

An exciting research opportunity is available to members enrolled in the Mitochondrial Disease Community Registry (MDCR). This is a chance to give your input about online resources for genetic inheritance (or how a condition is passed through families) and genetic testing of mitochondrial disease.

Many of us use the Internet to learn about mitochondrial diseases. For many patients and their families, the internet is the one of the first places they turned when they heard about the possibility of a mitochondrial disease. Online resources made for the mitochondrial disease community are not always easy to read and understand. They may lack information that matters to patients and their families. This is especially true of materials about genetic inheritance and genetic testing.

The goal of this study is to assess online resources for patients and their families about how mitochondrial diseases are passed through families and the options for genetic testing. Researchers are interested to learn from members and their experiences using online resources. A survey will be used to achieve this goal. Your participation may help improve current resources and/or add new education tools. Please consider participating. Your input is important for increasing awareness and improving care for mitochondrial disease.

Participation in this study is voluntary and the survey should take less than 20 minutes to complete.

How can I participate?

You must be enrolled in the Mitochondrial Disease Community Registry (MDCR) to participate. The study survey will be distributed to member through the registry. To learn more about the MDCR or to enroll, please click the following link. http://www.umdf.org/registry/ Once enrolled, you will be asked to complete an initial survey that captures diagnostic and demographic information as well as opinions on the MDCR and how it should be used in the future. After completing this survey, you can view details about the study survey.

What is the MDCR?

The MDCR is a patient centered registry. The purpose of this registry is to collect patient-centric health data that will be utilized to develop treatments, identify new symptoms, and provide information to researchers that seek to study mitochondrial disease. Caregivers and family members of those affected, whether they themselves are affected or not, are also encouraged to register and contribute to the community. Please also consider registering even if you are already part of another database. Each registry has its own unique utility, and MDCR has been built in a flexible way to assure appropriate sharing of data with other registry efforts.

The MDCR is different from other registries because members have total control of their information. Based on your privacy settings, you can decide who can see your information in an anonymous way (no means of identifying who you are), 2) who can analyze your anonymous data and lastly, 3) who can reach out to you via the registry if you are interested in participating in a relevant

research study or clinical trial. Every registrant is in full control of their privacy settings, and can change them at any time. There are also videos of mito community-active guides available to help you select privacy settings with which you can be comfortable.

Once your privacy settings are established, you will be presented an initial survey that captures diagnostic and demographic information as well as opinions on the MDCR and how it should be used in the future. The MDCR is not simply a contact database, rather it is a tool meant to continually engage the community.

To learn more about the MDCR or to enroll please click the following link. http://www.umdf.org/registry/ Your participation is helping us lay the foundation that will enable research necessary to find treatments and cures for mitochondrial disease.

Thank you in advance for your important participation!

APPENDIX D: IRB APPROVAL LETTER

University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

Memorandum

To: Sara Blankenship ,
From: IRB Office
Date: 1/10/2017
IRB#: PRO16070152
Subject: Assessment of Educational Materials Regarding the Genetics of Mitochondrial Disease

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The University of Pittsburgh Institutional Review Board reviewed and approved the above referenced study by the expedited review procedure authorized under 45 CFR 46.110 and 21 CFR 56.110. Your research study was approved under:

45 CFR 46.110.(7)

The IRB has approved the waiver for the requirement to obtain a written informed consent for all study procedures.

The IRB has approved the advertisement that was submitted for review as written. As a reminder, any changes to the advertisement other than to edit contact information requires IRB approval prior to distribution.

The risk level designation is Minimal Risk.

Approval Date: 1/10/2017
Expiration Date: 1/9/2018

For studies being conducted in UPMC facilities, no clinical activities can be undertaken by investigators until they have received approval from the UPMC Fiscal Review Office.

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

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