Assessment and Development of Online Educational Materials for Autosomal Dominant Leukodystrophy

by

Michael D. Gosky

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This thesis was presented

by

Michael D. Gosky

It was defended on

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and approved by

Committee Members:

Elizabeth M. Felter, DrPH, MCHES
Assistant Professor, Department of Behavioral and Community Health Sciences
Graduate School of Public Health
University of Pittsburgh

Thesis Co-Advisor: Robin E. Grubs, M.S., PhD,
Associate Professor, Department of Human Genetics
Graduate School of Public Health
University of Pittsburgh

Thesis Co-Advisor: Quasar S. Padiath, MBBS, PhD
Associate Professor, Department of Human Genetics
Graduate School of Public Health
University of Pittsburgh

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Abstract

Many individuals utilize online resources following a diagnosis to gain additional health information. Patients and caregivers alike in the rare disease community have shared their desire for more updated, patient-friendly online information. Autosomal Dominant Leukodystrophy (ADLD) is a rare, adult-onset demyelinating condition with symptoms typically presenting in the 4th to 6th decade of life. There is currently a limited amount of online educational resources about ADLD, and the material available varies in content and its technical nature is difficult for most readers to understand.

In this study online educational materials were assessed for readability and content. A survey was developed and shared with patients and caregivers to assess their experience in gathering information about ADLD from physicians, other healthcare professionals, and online. This survey also asked what information participants would like included in the development of educational materials. The survey was distributed through the ADLD Facebook page support group, and through an email list of individuals consented to be contacted for research purposes.

All resources evaluated were written above an 11th grade level and contained variable information on ADLD. A total of 33 participants responded to the survey. Most participants used the internet to find information about ADLD following a diagnosis. In addition to online resources, patients and caregivers utilized other resources such as physicians, and genetic counselors to learn more about ADLD, though no source was identified as being the most beneficial. Participants also

indicated that they would prefer a fact sheet to be developed by physician(s), genetic counselors, researchers, or other patients to provide information on management, risks, and current research.

Based on survey responses, a fact sheet was developed. **This study impacts public health as the development and use of updated, easily understood educational materials aids in patient and caregiver understanding, and may promote communication between patients, caregivers, and healthcare professionals.**

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Preface

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1.0 Introduction

When faced with a medical diagnosis, many people, including family members of the person with the diagnosis, turn to the internet for information. Approximately 1 out of every 3 people diagnosed with a medical condition, or who have a family member diagnosed, turn to online educational materials to better understand the diagnosis.[1] Additionally, there is an upward trend in individuals advocating for themselves to be a part of clinical trials and connecting with specialists.[2] This demonstrates that more individuals are turning to online educational materials, and desire to participate in research that may benefit themselves and others diagnosed with the same or similar conditions.

The term "rare disease" is defined differently in various parts of the world. In the United States, it is defined as a condition that affects less than 200,000 individuals, corresponding to a prevalence of fewer than 7.5 out of every 10,000 people, while in Europe its defined as a condition that affects fewer than 5 out of every 10,000 individuals.[3] There are over 6,800 different rare diseases diagnosed within the United States, and these conditions are estimated to affect between 25 to 30 million individuals. Rare diseases include conditions with a wide spectrum of phenotypic effects such as cystic fibrosis, Huntington's disease, and malignant mesothelioma.[4] While these conditions may be caused by various genetic and/or environmental factors, they fall into the same category of "rare disease" as they affect less than 200,000 people in the United States. Some of these conditions, such as Huntington's disease, have been described for decades, while others have been more recently identified. Although some conditions may have more extensive research due to earlier identification, collectively, there is a growing desire for informative, updated, accurate, and accessible information for individuals and families affected by rare diseases.[5]

Several rare diseases are considered to be neurodegenerative, or conditions characterized by the loss of neurons in the central or peripheral nervous system. This loss of neurons can lead to a variety of symptoms such as ataxia or dementia, with a wide age range of symptom onset, depending on the specific condition.[6] Additionally, some rare conditions are classified as a "leukodystrophy," which are conditions caused by the loss of myelin surrounding neuronal axons.[7] One such rare condition is Autosomal Dominant Leukodystrophy (ADLD).

ADLD is currently described in at least 24 families including over 70 individuals in the literature, though it is likely underdiagnosed.[8] It is a progressive condition characterized by autonomic symptoms such as loss of bladder control, erectile dysfunction, and autonomic cardiovascular dysfunction that can initially appear similar to the symptoms experienced by individuals diagnosed with multiple sclerosis (MS). Symptoms tend to manifest between ages 40-60, however, distinct changes on brain MRI can be identified 10 years prior to initial symptom onset.[9–15] This condition is known to be caused by pathogenic variants in the *LMNB1* gene located on chromosome 5q23.2.[16] Although the genetic etiology of ADLD may be understood, there is still a great need for ongoing research in the condition.

While the ADLD community is smaller than other rare disease communities, members still demonstrate commitment to be included in research and in the development of support groups and educational materials.[17] Even though research on ADLD diagnosis, treatment, and prognosis is currently on going, there is a limited amount of patient-friendly online educational material available for individuals and families affected by ADLD. The material that is available tends to include technical language that may be difficult for the lay public to understand. This lack of accessible and understandable information is detrimental as many individuals, including patients and caregivers alike, turn to online sources for information about their diagnosis. Many of the

online resources available provide variable information about ADLD. Some sites include basic information about how the condition is inherited while others provide more detailed and scientific information. Some sites include links to support groups that are available for related conditions while other sites do not. There is variability in what each piece of educational material includes or does not include. Although utilizing a combination of these sources and research articles may provide some clarity to patients and/or caregivers, understanding current resources requires both advanced education and a high level of health literacy.

The rationale for this study is derived from inspection of online educational materials for patients and family members affected by rare conditions. More specifically, there is a general lack of easily understandable information available online about ADLD including recurrence risk, genetic basis, features of the condition, and prognosis. This study, to our knowledge, is the first of its kind, as it assesses the current literature and available educational material, and directly surveys both patients and caregivers to assess the ease at which they can find information about ADLD online, what they would like included in online educational materials, and how they would prefer to receive this information.

1.1 Specific Aim 1

Evaluate existing patient educational resources to ascertain what information is available, determine if it is specific to ADLD, and assess the overall readability of the resource by calculating the reading level of the material.

1.2 Specific Aim 2

Design and disseminate a formative assessment to inform the development of ADLD-specific educational materials and develop culturally competent educational material for ADLD patients and their families.

2.0 Literature Review

2.1 Background

Neurodegenerative diseases are a heterogenous group of conditions that result from progressive neuronal degeneration and/or death. Currently, it is estimated that there are several hundred different neurodegenerative diseases.[18] Neurodegenerative diseases include well studied conditions such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and multiple sclerosis (MS) among others. In the case of AD, HD and PD, the primary problem is in the neuron itself, as opposed to MS which is a demyelinating disorder that eventually leads to cell death. While these conditions are clinically distinct, involving different types of neurons in different locations of the nervous system, they all share the same general feature—the condition is due to the dysfunction and ultimately death of neurons.[18]

Some neurodegenerative diseases are known to have a single genetic etiology. For example, HD is caused by extra trinucleotide repeats of cytosine, adenosine, and guanine (CAG) in the *HTT* gene encoding the huntingtin protein.[19] Other neurodegenerative conditions, such as MS, are thought to be caused by a combination of genetic and environmental factors. As conditions such as AD, HD, PD, and MS have been identified, diagnosed, and treated for decades, and as the public becomes more aware of them, numerous patient resources have become available.

While there are neurodegenerative and demyelinating conditions that have been identified, and even have their genetic etiologies well documented, there is a lack of, and clear need for accessible, updated, and understandable educational materials for individuals with these conditions and their families. One such condition is Autosomal Dominant Leukodystrophy.

2.2 Autosomal Dominant Leukodystrophy

Myelin is a lipid-rich substance synthesized and maintained in the central nervous system (CNS) by specialized cells known as oligodendrocytes. Regions that are enriched with myelinated axons are "whiter" or lighter in color than unmyelinated regions, which explains the name "white matter" (WM) as used in relation to the CNS. Myelin insulates neuronal axons and accelerate the transmission of electrical impulses.[20] Autosomal Dominant Leukodystrophy (ADLD) is one of several fatal neurodegenerative conditions characterized by loss, abnormal deposition, maintenance, or disruption of the myelin sheaths surrounding the axons of neurons in the CNS, known as leukodystrophies.[7] Some more common leukodystrophies include X-linked adrenoleukodystrophy, Canavan disease, and Krabbe disease. These conditions present with a wide variety of symptoms, from vision and hearing problems to difficulty moving and eating. [21]

In 1984, Eldridge et al. first identified and described ADLD in 10 men and 11 women which they called "hereditary adult-onset leukodystrophy simulating chronic progressive multiple sclerosis."[9] This kindred of individuals were all Irish-American, however individuals having different ethnicities, including Japanese, Irish, and Italian among many others, have been identified. [22–24] ADLD is not more common in any particular racial or ethnic group, and it is considered to be a rare condition. Currently there are at least 24 different families including over 70 individuals affected with ADLD described in the literature, although ADLD is likely underdiagnosed. [8]

2.2.1 Features of ADLD

ADLD is a progressive, adult-onset, demyelinating condition with symptoms typically starting between ages 40-60. It is characterized by radiological findings and autonomic symptoms including autonomic cardiovascular dysfunction, often followed by pyramidal and cerebellar signs, ataxia, tremor, and pseudoexacerbations.[9–13] This condition initially seems similar to multiple sclerosis, especially in relation to the combination of motor, autonomic and cerebellar problems experienced by the patient.[9] However, ADLD presents with some difficult to identify but key differences, namely the early and extensive presentation of autonomic disturbances, and specific changes seen on magnetic resonance images (MRI).[9,11,14,15]

Commonly, the first outwardly noticeable manifestations of ADLD are the autonomic symptoms, including bladder dysfunction, constipation, orthostatic hypotension, or erectile dysfunction.[8] These symptoms are often the reason why individuals initially seek medical care. However, there are indications of ADLD that can be seen by MRI a decade prior to the onset of symptoms.[10,25] These findings on T2-weighted images are typically extensive and symmetrical white matter hyperintensities seen from the frontal lobe to the cerebellum and involving the corpus collosum, posterior part of the internal capsule, and middle cerebellar peduncles. Additionally, the white matter around the ventricles seems to be less affected.[10,11,26–31] Widespread demyelination occurring throughout the CNS is also a feature of ADLD. More recent studies show that in addition to the radiological findings, there is a buildup of lactate in the cerebrospinal fluid (CSF) in the lateral ventricles of individuals diagnosed with ADLD.[26] Less common features of ADLD include a form of dementia, neurocognitive decline, REM sleep behavior disorder, and cardiovascular and skin noradrenergic failure.[7,32–36]

2.2.2 Genetic Etiology of ADLD

ADLD is caused by alterations involving the *LMNB1* gene located on chromosome 5q23.2, which encodes the lamin B1 protein.[16] The typical role of lamin B1 is to act as a component of the nuclear lamina, which is a structure that helps to support the nuclear envelope in cells.[37] The lamina plays an essential role in modulating the structure and mechanics of the nucleus, as well as aids in regulating gene expression through chromatin positioning and integrating cytoskeletal dynamics within the cell. These roles have numerous implications in cell proliferation, migration, senescence and aging.[37,38] There is also evidence to suggest that lamin proteins, such as lamin B1, are used during DNA replication, including the initiation of DNA replication.[39,40] In mouse studies, Lamin B1 is also necessary for the development of the dendrites of neurons.[41] Other studies have shown that Lamin B1 is needed for normal organogenesis, brain development, and neuronal development.[42]

The majority of individuals with ADLD are found to have a duplication of the *LMNBI* gene.[16,43–45] However, there has been a report identifying an Italian family who have a large deletion of approximately 660 kilobases (kb) located 66kb upstream of an *LMNB1* promoter. Due to this deletion, an enhancer region was adopted, which resulted in an increase in the total amount of lamin B1 expressed in cells beyond the expected level. Interestingly, individuals with this deletion showed either no or less autonomic dysfunction than patients who have the gene duplication.[46] At least three additional families with upstream deletions have been identified. These individuals experienced earlier symptom onset, but no dysautonomia, and reduced brain stem and cerebellum involvement on MRI compared to individuals with a duplication. [47]

Exactly how these duplications, or deletion, lead to the development of ADLD is not yet entirely understood. Evidence has shown that this increased amount of lamin B1 produced in cells

can lead to different adverse effects such as nuclear rigidity, reduced axonal growth, dysregulation of genes involved in skeletal development, the immune system, and neuronal development, and the demyelination of axons.[41,48–50] Several studies have shown that in mice with *LMNB1* overexpression, the increase in lamin B1 leads to lipid dysregulation. This is specifically harmful to the ability of oligodendrocytes to create and maintain the myelin sheaths, which in turn could cause ADLD.[50–52] These mouse models provide valuable insight into the development and course of the disease, but it is important to recognize that the findings of research with animal models may not be entirely translatable to human patients. Other *in vitro* studies indicate the involvement of other cell types.[11,29,44,46]

2.2.3 ADLD Diagnosis

Commonly, people with ADLD do not show outward signs of being affected until their fourth or fifth decade of life, and in general, they live around two decades after these symptoms start to appear.[9,10] As there is no cure, the main treatment for people with ADLD is the management of symptoms through palliative care.[53] Often, one of the first challenges is to correctly diagnose ADLD since it is sometimes initially mistaken for chronic progressive multiple sclerosis.[9,11]

The diagnosis of ADLD is made through clinical evaluation, MRI analysis, and genetic testing. This genetic analysis is often done through the use of an array CGH to detect deletions and duplications, through single-gene deletion/duplication analysis of the *LMNB1* gene, or a multigene panel which includes deletion/duplication analysis of *LMNB1*.[8] While there are no established diagnostic criteria, the presence of clinical features of ADLD, including MRI findings and genetic test results indicating *LMNB1* involvement, would be consistent with a diagnosis of ADLD.

2.2.4 Psychosocial Concerns

The accurate diagnosis of ADLD comes with many implications such as altered life expectations, and family planning. These potential changes should be kept in mind by healthcare professionals including geneticists, genetic counselors, and other providers when discussing topics such as risk, and testing options.

In contrast to most other leukodystrophies which are typically inherited in an autosomal recessive or X-linked manner, ADLD is inherited in an autosomal dominant fashion.[54] Therefore, both males and females can be affected, and an individual needs only one pathogenic variant of the *LMNB1* gene to develop the condition. In addition, the children of an affected parent have a 50% chance of inheriting the pathogenic *LMNB1* variant and developing ADLD. ADLD is also an adult-onset, which is uncommon for leukodystrophies.[12]

Most women and men in the United States and elsewhere have their first child before the age of 40.[55–57] For people diagnosed with ADLD, this means that an individual with an ADLD pathogenic variant may not know they have the condition until after they have already had children. This brings up concern that an affected parent passed on the pathogenic variant of the *LMNB1* gene to their child(ren), and this parent may want to know the chances that their child did inherit the variant. Additionally, family members of individuals with ADLD may want to know their gene status for reproductive planning purposes. These are concerns that have been examined in the HD community.

A European study compared individuals who were tested for HD and found that over 50% of people who tested positive already had children prior to the positive test result As a part of this study individuals were asked what motivated them to pursue testing, and the researchers identified three major reasons: individuals wanted to know their chances of passing on the expanded gene to

their children, individuals wanted to know their status because they did not want to have a child who has a parent affected by HD, and individuals wanted to know when they should plan on having children. This study also followed individuals after their initial testing for three years and found that 69% of the non-carriers had subsequent pregnancies while only 39% of HD carriers had subsequent pregnancies.[58] While HD is more prevalent than ADLD, it is an autosomal dominant adult-onset condition similar to ADLD. Individuals with ADLD may also want to pursue testing for a number of reasons including family planning purposes.

Another concern in the HD community regarding having children is the feeling of guilt. This guilt could stem from feeling like they passed on a pathogenic copy to a child and the child would eventually develop HD, feeling like the child will have to experience challenges associated with having an affected parent, or feeling regret that he/she did not adopt a child, instead of having a biological child, or pursue prenatal testing. Two qualitative studies examine the issue of knowing or not knowing risks of having HD and reproductive decision making. In these studies one of the themes that emerges is the feeling of guilt.[59,60] Extrapolating to ADLD, it is possible that parents diagnosed with ADLD experience similar feelings of guilt because they had children without knowing that they had a pathogenic copy of a gene that their children could inherit. Genetic counselors could address this feeling of guilt to help facilitate adaptation and coping.

Similarly, since a brain MRI can identify features suggestive of ADLD years prior to a diagnosis, individuals with ADLD may wish to share this information with at-risk relatives, and genetic counselors can assist in facilitating this discussion.[8,10,25] Genetic counselors can also assist with DNA banking, or storing DNA for future use. As more research is done, it is possible that having this DNA stored could inform the individual or family members of additional risks and may promote increased screening or surveillance.

A desire to learn more information about ADLD is another concern individuals with the condition may have, but unfortunately there is a lack of educational materials available specifically about ADLD. While there is ongoing research in ADLD that is reported in peer-reviewed literature journal articles are not always easily understood by the public.

Individuals diagnosed with ADLD could have a number of concerns when meeting with a genetic counselor. They may feel guilty for having children, are in denial about the diagnosis, are worried about other family members or what the future may hold or want to gather as much information about ADLD as possible. Genetic counselors are resources for both emotional support and for providing patient education.

2.2.5 Commonalities and Differences Between ADLD and Other Diseases

The symptoms a person with ADLD may experience are similar to a number of other neurodegenerative diseases. Multiple sclerosis is often one of the initial diagnosis individuals with ADLD receive due to the commonalities between the two conditions.[9] Both ADLD and MS present in adulthood and have motor, cerebellar and autonomic disfunctions, and due to the higher incidence of MS, some with ADLD may be diagnosed with MS prior to genetic testing.[8,9,61] The similarities continue into the basis of the neurodegeneration. Both ADLD and MS are progressive demyelinating conditions, and neuronal axons lose their insulating myelin and over time the neuron itself will die. Often people with MS will have periods of relapse and remission when the neurons in the central nervous system experience inflammation which damages the neurons, then partial or complete recovery from the damage may occur.[61]

While MS and ADLD share some features, there are several notable differences between these two conditions. For example, on a brain MRI, individuals with ADLD have extensive and

symmetrical white matter hyperintensities that extends from the frontal lobe to the cerebellum and involves the corpus collosum, posterior part of the internal capsule, and middle cerebellar peduncles but the white matter around the ventricles seems to be less affected.[10,11,26–29] A person with MS will show multifocal lesions around the spinal cord, cerebellum, brain stem, and periventricular area on MRI.[8,15] These differences seen on MRI help distinguish whether an individual has MS or ADLD. Additionally, ADLD is caused by duplications or upstream deletion of the *LMNB1* gene and follows an autosomal dominant inheritance pattern while there is no precise genetic etiology identified yet for MS, and it is thought to follow a more complex inheritance pattern. There have been studies that suggest a link between MS and the major histocompatibility complex located on chromosome 6p21.3, although pathogenic variants in one specific gene has not been found to be associated with MS[15]

X-linked adrenoleukodystrophy (X-ALD) is another disorder similar to ADLD. X-ALD is caused by pathogenic variants in the *ABCD1* gene located on the X chromosome.[62] Around 95% of men with X-ALD inherited a pathogenic variant from their mother, while at least 4.1% of cases are *de novo*.[63] X-ALD affects both the white matter in the nervous system and the adrenal cortex. There are three major phenotypes of X-ALD: childhood cerebral, adrenomyeloneuropathy (AMN), and Addison disease. Around 35% of individuals with X-ALD have the childhood cerebral phenotype, characterized by what initially looks like attention-deficit disorder, but progresses into impaired cognition, and behavioral, vision, hearing, and motor dysfunction. Typically, boys are diagnosed between four to eight years old and become totally disabled between 6 months to 2 years after initial diagnosis. AMN affects about 40-45% of men with X-ALD. This typically presents between age twenty to fifty and is characterized by the progressive loss of muscle control including stiffness and weakness in the legs as well as loss of sphincter control. Between 40-45%

of men with AMN show signs of brain involvement on MRI, and in 10-20% of these men, the brain involvement is severe and leads to cognitive and behavioral disturbances.[62] About 10% of men have Addison disease only which is characterized by adrenal insufficiency by age seven and a half, and commonly presents with unexplained vomiting and weakness. In about 70% of men with AMN and 90% of neurologically symptomatic boys, adrenal function is abnormal.[62] The AMN phenotype closely resembles that of ADLD due to the age of onset, gait disturbances, loss of sphincter control, and sexual dysfunction that can be seen in both conditions.[8,62]

While there are some similar features shared by ADLD and X-ALD, these two conditions result in distinct changes seen on MRI and have different genetic etiologies. X-ALD is inherited in an X-linked manner and in the majority of cases a male inherited a pathogenic variant from his mother. This also means that an affected male will have all carrier daughters but no affected sons unless his female partner is a carrier for the condition. It is also important to note that although X-ALD is more often thought of as a condition only men are diagnosed with, there are cases where a female has inherited a maternal pathogenic *ABCD1* variant and inherited a paternal Xq27-Ter deletion leading to a diagnosis of cerebral X-ALD.[64] Additionally, over 20% of female carriers will develop spastic paraparesis and appear like they have AMN when they are middle-aged.[62] Lastly, only 40-45% of affected individuals with X-ALD will have clinical or radiologic brain involvement whereas in ADLD the symmetric white matter hyperintensities are a key feature in an individual with the condition.[62]

Huntington's disease (HD), another adult-onset neurodegenerative condition, shares some similar features to those of ADLD. HD is caused by having a trinucleotide repeat expansion of cytosine, adenine, and guanine (CAG) in the *HTT* gene.[65,66] This repeat expansion eventually causes the loss of neurons in the putamen, caudate, cerebrum, substantia nigra and several other

brain regions..[66,67] Due to this loss of neurons, individuals progressively start to lose motor control, and experience cognitive decline and personality changes.[66] Similar to ADLD, HD is an adult onset condition with the average age of diagnosis being 45 years with an average age of death between 54 to 55 years, and it is inherited in an autosomal dominant fashion.[66,68,69]

However, in contrast to ADLD there is anticipation that occurs with the size of the CAG repeats in the *HTT* gene.[66] Therefore, from one generation to the next the size of the repeat can expand, and this is correlated with an earlier age of symptom onset.[70] Studies have shown that anticipation in HD is largely due to instability of the CAG repeat during spermatogenesis, so nearly all large expansions are inherited from an affected individual's father.[71] However, there have been reported cases of juvenile onset HD that have been found to be due to maternally inheriting an expansion.[72] Another difference is that there have been reports of Alzheimer's disease co-occurring in patients with HD.[73] This difference, while not insignificant, may simply be due to the fact that HD has been studied much longer than ADLD.

There are a number of conditions that share features with ADLD. Although these conditions may clinically overlap with each other, it is clear that ADLD is a unique diagnosis. MS, X-ALD, and HD have been studied for decades and more research has been done on these conditions when compared to ADLD, and ADLD is a more recent discovery. There have been specific online sites created for MS, X-ALD, and HD that have created and maintained educational materials about these conditions. Additionally, there are a number of support groups available for individuals and families dealing with a diagnosis. Individuals affected by HD also have a number of national organizations such as the Huntington's Disease Society of America and the European Huntington Disease Network that engage in research, educational, and advocacy efforts.[74,75] These online sites and support groups can be a valuable resource for families. An online search for ADLD-specific

educational materials yields few results. Much of the available online information comes from the National Center for Biotechnology Information's GeneReviews, the National Institutes of Health's Genetic and Rare Diseases Information Center, and the Online Mendelian Inheritance in Man. There is a clear need for the creation of educational materials for individuals and families dealing with a diagnosis of ADLD.

2.3 Current Resources

At present, searching online for support groups or educational materials for individuals affected by neurodegenerative diseases yields over one billion of hits depending on which specific condition is being searched. However, in comparison, searching specifically for "ADLD support groups" yields just 16,400 hits, dramatically fewer when compared to other conditions such as HD, X-ALD, or MS.

Similarly, there are significantly more websites created that contain educational material for these other conditions. ADLD is a rare condition, affecting far fewer individuals than MS, X-ALD, or HD, yet there is a need for support groups and understandable educational materials. Often, one of the first things individuals with a new diagnosis do is to search for information about the diagnosis. While this can include speaking with healthcare professionals, people frequently turn to searching online and try to identify information from websites. Over 80% of Americans turn to the internet to find health information, including information about a specific disease, specific treatments, or alternate treatment options. Additionally, 20% of people look online to find out more about ongoing research and experimental treatments.[76] Globally, this correlates to over 70,000 health-related searches on Google each minute, or over 1 billion searches a day according

to Google's Health Vice President Dr. David Feinberg.[77] Therefore, it is crucial for websites aimed at patients and their families to use language that most people can understand.

In the case of ADLD, much of the available information comes from scientific journal articles. These articles are intended for researchers, healthcare professionals, or generally use technical language, and the overall readability of these has gone down over time.[78]

Understanding the literacy level of a target audience is a key component in the creation of educational materials. This is especially true when it comes to medical information. Currently, the average American reads at the 7th to 8th grade level.[79–81] Both the American Medical Association (AMA) and National Institutes of Health (NIH) recommend that medical information intended for the public should be written at or below a 6th grade reading level.[80,82,83] Additionally, the government in the United Kingdom suggests that authors should aim for a reading level of age 9.[80,84] Additionally, when it comes to online reading, people tend to only read about 18% of what is written on a page.[85] Therefore it is also important that information be conveyed in a concise manner.

2.3.1 Patient support/advocacy resources

Having a diagnosis of ADLD is considerably more rare than having a diagnosis of MS, which affects 3.6:100,000 women and 2:100,000 men.[86] Individuals with MS can be referred to several different support groups, including to online sites such as the National Multiple Sclerosis Society, MS World, and Patients Like Me, among many others.[87–89] In comparison, while the exact incidence of ADLD is not yet known, the number of online support groups is limited. Presently, the only online site is a Facebook group available specifically for individuals or families affected by ADLD.[90]

While support groups specifically intended for those affected by ADLD are limited, other support groups are available. Some of these support groups include Hunter's Hope, Leukodystrophy Australia, and the United Leukodystrophy Foundation.[91–93] While these groups do provide information and support for individuals with leukodystrophies, they are not specifically geared toward ADLD. ADLD does share many commonalities with other leukodystrophies, however, individuals with ADLD face challenges that those with more common leukodystrophies do not.

In general, support groups offer individuals and families affected by a condition many benefits such as reducing feelings of isolation or stigmitization. They can also help alleviate stress, provide a sense of empowerment, and can act as a resource to provide more information about treatments, or how a condition progresses over time.[94] While studies have shown that in-person support groups lead individuals to be more open and honest, online support groups also offer opportunities for individuals to share their experiences. Additionally, online support groups have the benefit of providing more flexible schedules and can connect people who do not live near enough to attend in-person sessions.[94,95] Online groups are particularly useful for individuals with a rare disorder as they can provide support in creating a "new normal" for patients and their families, act as a place where individuals can freely share their experiences, act as a source for crowdfunding new treatments, and provide information for new members, or those more recently diagnosed.[96,97]

Additional support group opportunities could connect individuals affected by ADLD, care takers, healthcare providers, and researchers to provide information on the condition and provide a stronger sense of community. As demonstrated in an online webinar hosted by the United Leukodystrophy Foundation, this community is committed to finding out more information about

ADLD.[17] While the development and implementation of an ADLD-specific support group may take months or longer to fully form, this community possesses a strong desire to learn as much as they can about ADLD, and one way to provide them with this information is by creating educational materials.[17]

2.3.2 Educational Resources

Since the identification of ADLD as a unique disease, there has been a significant amount of research that has been done to accurately define the condition. While this research provides clarity on manifestations and disease progression, these studies are published in scientific journals which tend to be written at a level most readers cannot understand.[78] Often, after a new diagnosis, individuals will search for the condition online in order to further their understanding of what the diagnosis means for themselves, relatives, and friends.

Much of the online information available to ADLD patients comes from the National Center for Biotechnology Information's GeneReviews, the National Institutes of Health's Genetic and Rare Diseases Information Center (GARD), the National Institutes of Health's MedlinePlus and the Online Mendelian Inheritance in Man (OMIM).[8,98–100] Additionally, searching for "Autosomal Dominant Leukodystrophy," "ADLD symptoms," or "Adult Onset Autosomal Dominant Leukodystrophy," on the YouTube platform yields no results, limiting the amount of available information further. While GeneReviews, GARD, MedlinePlus and OMIM are reputable for providing accurate information, there is a clear need for additional online educational materials.

All three of these resources offer a detailed overview of the condition. The GARD site is intended for people who have rare or genetic diseases as well as healthcare providers, researchers, advocacy groups, and members of the general public.[101] This site utilizes Orphanet, a European

reference portal to create the disease summary, and the Human Phenotype Ontology database to create a summary of the condition and describe possible symptoms.[102,103] While this site does provide a concise overview of ADLD, it does lack in areas such as providing additional resources or support groups. The support group noted on the GARD site is Alex the Leukodystrophy Charity, which provides support and information for genetic leukodystrophies, but is not focused solely on ADLD.[99,104]

GeneReviews acts as a resource for clinicians, and provides comprehensive information for inherited conditions including diagnosis, management, and genetic counseling considerations.[105] Thus, the target audience for this source is not individuals affected by a condition, rather for healthcare providers. While this site is more comprehensive than other sites, it is written in a journal format, which is not ideal for most readers.[78]

The MedlinePlus site provides a thorough description of ADLD including many possible symptoms and the genetic basis for the condition. The goal of the site is to provide free, reliable, easy to understand, and advertisement-free information about many different conditions.[100,106] While this site may accomplish those goals, it does not provide any links to support groups, nor does it thoroughly describe how ADLD is inherited.

The OMIM site provides detailed information about ADLD, including a description, clinical features, inheritance, diagnosis, gene mapping, molecular genetics, and cytogenetics. This site does not provide links to any support or advocacy groups. Additionally, it was last updated in 2016.[98] Since 2016, research has advanced understanding of ADLD, and therefore, this site is not the most up-to-date of the sources where individuals can find information about ADLD. Of note, the site directly states that while this information is available to the public, it is intended for physicians, researchers, and advanced students of science and medicine.[107]

Utilizing these sources along with other research articles may help provide an understanding of what to expect after a diagnosis of ADLD, however, the available sites could possibly be missing relevant information for individuals affected by ADLD and/or present information in a scientific manner that would not be understood by the lay public. Prior to the creation of educational materials it would be important to elicit the information needs of individuals affected by ADLD.[17]

2.4 Creating Educational Materials

The creation of well-designed and easily understandable educational materials can be a challenging task. There are a number of important factors to consider in the development of educational resources such as the type of information to include, the organization and format of the information, as well as the target audience.

When developing medical-based educational materials, a key consideration is general literacy and health literacy. Studies have shown that the average American reads at the 7th to 8th grade level.[79–81] Both the American Medical Association (AMA) and National Institutes of Health (NIH) recommend that medical information intended for public use should be written at or below a 6th grade reading level.[80,82,83] While this is the current recommendation, not all authors follow this suggestion. This can lead to misunderstanding as readers may not completely comprehend what is written, and/or fail to make appropriate health decisions.

Health literacy is tied to general literacy but is more specific to the ability of a person to comprehend basic medical information needed to make informed healthcare decisions.[108] Over one-third of the population in the United States has “below basic” or “basic” health literacy skills,

meaning that they have “no more than the most simple literacy skills” or they have “the skills needed to perform simple literacy tasks.” These individuals do not show the ability to summarize information, make inferences from material, recognize relationships within text, or understand the purpose of less common tests.[109,110] These are vital skills when attempting to comprehend medical information.

One of the major initiatives by Healthy People 2030, a group organized by the U.S. Department of Health and Human Services in order to create and promote public health initiatives, is to increase the health literacy level in the United States.[111] About half of the U.S. population has an “intermediate” literacy level, meaning that they have the ability to summarize information, make inferences from material, recognize relationships within text, or understand the purpose of less common tests, but do not have the skills necessary to read or understand lengthy texts, make complex inferences, or summarize information from complex works.[109,110] Therefore, most individuals struggle with comprehending complex medical information including understanding a diagnosis, treatment options, or a provider’s medical plan. This, in turn, could mean that many individuals are not making informed medical decisions for themselves, rather relying on their provider to make choices for them. For example, one study on this topic found that over half of the individuals in the study preferred to let their physician have the final say in decisions related to their medical care.[112] This indicates that some people would rather trust their physician to make their healthcare decisions, rather than relying on their own understanding, and this could lead to a physician making a decision for a patient that the patient would not have made for her/himself, which is not always negative, but is incompatible with the ethical concept of autonomy.

An additional consideration when creating educational material is the importance of ascertaining the informational needs of the audience. There are numerous ways to come to

understand of the needs of the target audience. One could conduct a survey, review what has previously been done, and/or create a focus group, among other choices. When choosing how to gather information, the author has a several factors to consider such as ease, cost, and efficiency. In the case of creating educational materials for a rare disease community, it may be appropriate to directly survey the members, or create a focus group. Through these platforms, one could identify the current understanding of the condition, and ascertain the educational needs of the community. This direct understanding may lead to the development of more specific and applicable material and benefit the community more than generalized information.

Lastly, the format of the material is another factor to consider when developing educational resources. Some individuals may prefer to receive this information in the form of a fact sheet, while others may prefer a video with a comment section. In general, individuals tend to understand written medical information better when clear and concise language is used, preferably alongside pictures or illustrations.[113] While the overall goal of providing information is the same, not all individuals prefer the same type or style of material distribution.

2.5 Summary

Although ADLD is a rare disorder, it serves as an example for the increasing demand for updated, easily understandable, and accessible educational information for patients and caregivers in the rare disease community. As more people are diagnosed with rare conditions, and as more people turn to the internet for health information, it is important that these individuals have the resources necessary to understand a diagnosis and make informed medical decisions.

Currently, there is limited information available online for individuals and family members affected by ADLD, and the information that is available is not written at an easily understood level.[78] This lack of ADLD-specific information is striking when compared to other similar conditions including other neurodegenerative disorders and leukodystrophies.

While exact information needs of the ADLD community have yet to be determined, comparisons between other rare disease communities and the ADLD community can be drawn for the purpose of creating educational material including anticipated concerns or topics to be addressed in the resource such as psychosocial concerns, features of the condition, and ongoing research.

In general and within the rare disease community, there is a growing number of people advocating for their inclusion in ongoing research including clinical trials and longitudinal studies to benefit individuals diagnosed with the same or a similar condition in the future, and this trend is demonstrated within the ADLD community.[2,17] The lack of updated, easily understandable, online information available to the ADLD community, combined with the increased patient desire to participate in research allows for a unique opportunity to address the concerns of the community.

3.0 Manuscript

3.1 Background

In the United States, there are over 6,500 conditions classified as a "rare disease" meaning that the condition affects less than 200,000 individuals.[3,4] These conditions are caused by a variety of genetic and/or environmental factors, and express a variety of phenotypic characteristics. Some rare diseases are considered to be "neurodegenerative" and ultimately leads to the death of neurons in the central and/or peripheral nervous system.[18] Some neurodegenerative conditions are adult-onset such as Huntington's disease (HD), or Parkinson's disease (PD). Whereas HD and PD are primarily due to problems that arise from within the neuron leading to cell death, other neurodegenerative diseases are leukodystrophies, or conditions caused by loss, abnormal deposition, maintenance, or disruption of the myelin sheaths surrounding the axons of neurons in the CNS.[7,21] One adult onset leukodystrophy is Autosomal Dominant Leukodystrophy (ADLD).

ADLD is an adult-onset, progressive neurodegenerative condition, with symptoms typically beginning in the 4th to 6th decade of life. It is currently described in 24 families, including over 70 individuals, but is likely underdiagnosed. Accurate diagnosis of ADLD is often difficult as the symptom presentation initially appears similar to that of multiple sclerosis (MS), however, through clinical evaluation and genetic testing, an individual experiencing symptoms may be identified as having a pathogenic variant involving the *LMNB1* gene located on 5q23.2, and thus diagnosed with ADLD.[8] Although it is a unique diagnosis, ADLD, like many other rare diseases, shares similarities with other conditions including MS, HD, and other leukodystrophies such as X-linked adrenoleukodystrophy (X-ALD).

Some of the first symptoms an individual with ADLD may experience are autonomic dysfunction including neurogenic bladder, constipation, orthostatic hypotension, erectile dysfunction and feeding difficulties. Additionally, individuals with ADLD often experience subsequent coinciding onset of pyramidal and cerebellar impairment leading to ataxia, spasticity, and/or tremor that is often more prominent in the lower extremidies.[8] Additionally, there are reports indicating initial preservation or mild impairment of cognitive ability early on in the course of the disease, but as it progresses psychiatric conditions and dementia can occur as late manifestations.[10,32] Additionally, individuals with ADLD may experience pseudoexacerbations, where symptoms of the condition are exacerbated by fever or infection, but return to baseline after recovery.[10]

Aside from the outwardly visible manifestations of ADLD, identifiable features of the condition can be seen on brain and spine MRI years prior to diagnosis. These characteristic findings include symmetric T2-weighted hyperintensities starting at the motor cortex, down to the medulla oblongata through the posterior limb of the internal capsule. Eventually, these changes extend to the frontoparietal and occipital lobes, and lastly the temporal lobe. Optic radiations and U-fibers are not involved, and the periventricular white matter is mildly affected or spared entirely. Atrophy of the brain stem and spinal cord are noted and often show homogenous T2-weighted hyperintensity, and cerebrum, cerebellum and corpus callosum atrophy occur over time.[8,10,29–31] These findings are important to note as many individuals undergo MRI for a variety of reasons and such findings may lead to a diagnosis.

Although the manifestations of ADLD are diverse, ADLD shares similarities with a number of conditions including MS, HD, and other leukodystrophies. For example, some of the symptoms experienced by individuals with MS are similar to what may be experienced by an

individual with ADLD, such as the combination of autonomic, motor, and cerebellar dysfunction.[9] Additionally, as HD is another adult-onset neurodegenerative condition, individuals in the ADLD community may experience similar features, or psychosocial challenges as those in the HD community. Individuals with X-ALD, particularly those with the adrenomyeloneuropathy (AMN) phenotype of X-ALD, and individuals with ADLD share many similar symptoms including erectile dysfunction and sphincter control abnormalities.[8,62] However, as these conditions are more common and have been studied for a longer period of time than ADLD, patients, family members of an affected individual, and caregivers have more resources to turn to. These resources include national organizations, online patient-friendly material, and disease-specific support groups. Some of these sources help provide an understanding of a diagnosis, information on symptom management, and connections to other specialists or other support groups and organizations.

Individuals diagnosed with ADLD do not have the benefit of numerous resources. Online support groups are nearly nonexistent, with the exception of one Facebook group. Many of the available online educational materials provide links to general leukodystrophy support groups, or none at all. Additionally, should a patient or caregiver desire more information about ADLD, they have limited sources available to them outside of academic or research articles which may be difficult to understand.

This study had two main aims. The first was to ascertain the readability and content of currently available online educational material for ADLD. This initial review and assessment prompted the second aim of the study, which was to design and disseminate a formative assessment through a survey to individuals in the ADLD community to assess their experience with finding information about ADLD from physicians, other healthcare workers, and online, and assess the

educational needs of the community. Ultimately, this study was developed in part to help provide culturally competent educational resources to this community.

3.2 Methods

This study was approved by the University of Pittsburgh Institutional Review Board (CR19100151-001) (Appendix D). The survey utilized in the study was approved as an exempt addition to the study (STUDY21020157) (Appendix D.1).

3.2.1 ADLD Educational Material Selection

To identify and assess publicly available educational materials for ADLD an online search for "Autosomal Dominant Leukodystrophy" was done in February of 2021. Websites identified in this study are largely intended for medical professionals but are also available to patients and caregivers. This search identified four major sources of available educational materials.

This study assessed the National Center for Biotechnology Information's MedlinePlus and GeneReviews, the National Institutes of Health Genetic and Rare Disease (GARD), the Orpha.net, and the Online Mendelian Inheritance in Man (OMIM) pages for Autosomal Dominant Leukodystrophy. Additionally, one support group was identified on Facebook, although assessment of this source was not performed.

3.2.2 Readability

To assess the readability of these sources, an online readability calculator was used (https://readabilityformulas.com/free-readability-formula-tests.php). This site processes text through 7 different readability formulas and provides results including the Flesch Reading Ease score, Gunning Fog, Flesch-Kincaid Grade Level, The Coleman-Liau Index, The SMOG index, Automated Readability Index, and the Linsear Write Formula. Each of these formulas analyze different variables to determine the readability score. In this study, the Flesch Reading Ease score, the Flesch-Kincaid Grade Level, and Automated Readability Index were used. The Flesch Reading Ease score provides a score from 0-100 based on average sentence length and average number of syllables per word, and this score can be converted into a school grade reading level as reported by the Flesch-Kincaid Grade Level score. The Automated Readability Index provides a score based on the average number of letters per word and average number of words per sentence. As a part of this study, some material including tables, diagrams, headings and subheadings were removed, and this may affect the overall scores generated.

3.2.3 Formative Assessment

A formative assessment was conducted through use of a survey, which was constructed using the University of Pittsburgh licensed Qualtrics (Appendix C). Prior to and during survey construction, input was sought from a geneticist with expertise in ADLD, a genetic counselor, and a health communication expert. Prior to distribution, the survey was piloted by 7 genetic counseling students, two genetic counselors, and a geneticist with expertise in ADLD and modifications to the survey were made based on feedback. This survey was designed to assess

patient and caregivers' experience with obtaining educational material from physicians, other healthcare providers, and online. It also asked participants what they would like to know about ADLD, and how they would prefer to receive this information. This survey was composed of a total of 25 questions consisting of multiple-choice questions, open-ended questions, a Likert Scale, and ranking. Skip logic was utilized so that individuals only answered questions relevant to their situation. Additionally, participants could freely skip questions.

3.2.4 Participant Selection

Individuals diagnosed with ADLD, as well as related and unrelated caregivers for those diagnosed with ADLD 18 years of age and older were eligible to take the survey. Individuals younger than 18, or not affected with ADLD nor a caregiver for someone with ADLD were excluded from the study. A link to this survey was posted on the ADLD support group Facebook group (Appendix B.2). Additionally, ADLD patients who had consented to being contacted for research purposes as a part of Dr. Quasar Padiath's ongoing research were sent an email (Appendix B) with the survey introduction (Appendix A) and link to complete the survey. Participants had 1 month to complete the survey between February 25th, 2021 and March 21st, 2021. A reminder email was sent out on March 11th, 2021 (Appendix B.1).

3.2.5 Analysis

All of the survey responses were self-reported and anonymous. Data from all surveys were analyzed including both partial and complete responses. Data were analyzed using Qualtrics and Microsoft Excel to generate tables and descriptive statistics such as count, mean, median, standard

deviation, range, and percentages. In order to perform a Kruskal-Wallis test, the perceived ability of each resource to provide ADLD information was separated by resource and entered into R, which then performed the statistical test.

3.2.6 Material Creation

Creation of educational material was based on survey responses. Ultimately, as a part of this project a factsheet was created (Appendix E) and will be distributed through the ADLD support group Facebook page. The creation of this fact sheet included information derived from survey responses, as well as general information such as features, management, and genetic basis of ADLD.

3.3 Results

3.3.1 Readability and Content Analysis

Initial inspection of available online educational material for individuals diagnosed with ADLD revealed that the material is written at a level well above the recommended 6th grade level. Flesch Reading Ease scores ranged from 13-34.2, and Flesch-Kincaid Grade Levels ranged from 12.6-16.4. Additionally, the Automated Readability Index of these sites ranged from 11.2 to 16 (Table 1).

Table 1. Readability Measures of Online Educational Material for ADLD

Online Site	Flesch Reading Ease score[A]	Flesch-Kincaid Grade Level[B]	Automated Readability Index[C]
GeneReviews	13.0	16.4	16.0
OMIM	31.2	12.6	11.2
Orpha.net	18.2	14.6	14.6
MedlinePlus	33.8	13.6	14.1
GARD	34.2	12.6	12.7

[A]Flesch Reading Ease score is given as a number between 0-100. Scores ranging from 0-29 indicate that the material is very confusing, 30-49 is considered difficult to read, 50-59 is fairly difficult, 60-69 is standard, 70-79 is fairly easy, 80-89 is easy, and 90-100 is very easy to read.

[B]Flesch-Kincaid Grade Level is the conversion of the Flesch Reading Ease score into the grade level equivalent. The number in front of the decimal indicates the grade level, for example, a score of 12.5 indicates that the average U.S. student in 12th grade or 1st year in college can read and understand the material.

[C]Automated Readability Index produces an approximate U.S. grade level needed to understand the material. Grade 1 corresponds to the reading level of an individual who is around 6 years old, while grade 12 corresponds to a reading level of an individual who is 17 years old.

In addition to readability, these sources were evaluated for the information included on the webpage (Table 2). This includes accurate description of symptoms an individual with ADLD may experience, as well as information on the genetic basis of ADLD that mentions both duplications of *LMNB1* and upstream deletions. These pieces of content were identified on all five webpages with the exception of the MedlinePlus site which did not specifically mention the upstream deletions that may cause ADLD. Whether or not the source provided detailed information on the inheritance pattern of ADLD including risk to children and siblings of a proband was assessed, with only the GeneReviews page including that information. Lastly, only the GeneReviews and

GARD pages provide links to possible support resources, though neither specifically included the ADLD Facebook page.

Table 2. Content Assessment of Online Educational Material for ADLD

Online Site	Description of Symptoms	Information on Genetic Basis	Detailed Information on Inheritance[A]	Links to Support Resources
GeneReviews	Yes	Yes	Yes	Yes
OMIM	Yes	Yes	No	No
Orpha.net	Yes	Yes	No	No
MedlinePlus	Yes	No[B]	No	No
GARD[C]	Yes	Yes	No	Yes

[A]In order to receive a 'Yes' in this column, the source had to mention autosomal dominant as the inheritance pattern and include risk to offspring and/or siblings of a proband.

[B]While the MedlinePlus site does identify that duplications of *LMNB1* can cause ADLD, it failed to mention possible upstream deletions leading to the development of the condition.

[C]The GARD site utilizes information from Orpha.net to provide information such as the description of symptoms.

3.3.2 Demographics

A total of 33 participants started the survey. A response rate for this survey was not able to be calculated due to the fact that the total number of people who could access the survey is unknown. Calculating how many people saw the survey is not possible as people may have seen the Facebook post or email and shared it with family members not in the email list, nor in the Facebook group. Data from the 33 responses were analyzed. Approximately half of all respondents (16/33) were individuals diagnosed with ADLD, and nearly half were family members of an individual diagnosed with ADLD (16/33). One individual marked that they were not diagnosed

with ADLD but did not provide additional information. A majority of participants (12/23) were between ages 41-65, and 57% (13/23) of respondents were female. Additionally, most reported an Asian or Pacific Islander ethnic background (15/23). The highest level of education reported was a graduate or professional degree beyond an undergraduate degree, with 78% (18/23) reporting that they had an undergraduate degree or graduate or professional degree. Additionally, 78% (18/23) were married and 59% of respondents (13/22) had at least 1 biological child. Demographic information is reported in Table 3.

Table 3. Participant Demographics

		n	%
Diagnosed with ADLD (n=33)	Yes	16	48.48%
	No	17	51.52%
Age (n=23)	18-40	10	43.48%
	41-65	12	53.17%
	66 or older	1	4.35%
Gender (n=23)	Male	10	43.48%
	Female	13	56.52%
Race (n=23)	Asian or Pacific Islander	15	65.22%
	White/Caucasian	4	17.39%
	Hispanic/Latino/Spanish origin	1	4.35%
	Other	3	13.04%
Education (n=23)	Some High School	2	8.70%
	High School/GED	2	8.70%
	Some College	1	4.35%
	Undergraduate Degree	6	26.09%
	Graduate or Professional Degree	12	52.17%

Table 3 (continued)

Marital Status (n=23)	**Single**	**5**	**21.74%**
	Married	18	78.26%
Biological Children (n=22)	Yes	13	59.09%
	No	9	40.91%
Number of Biological Children (n=13)	1	5	38.46%
	2	3	23.08%
	3	3	23.08%
	4	2	15.38%

3.3.3 Age of Diagnosis

Participants who indicated that they were diagnosed with ADLD were asked at what age they were diagnosed. A majority of respondents (13/16) indicated that they were diagnosed between ages 41-65. The range of age at diagnosis for ADLD patients is provided in Table 4.

Table 4. Age of ADLD Diagnosis - Patients

	n (n=16)	**%**
Younger than age 40	2	12.50%
Age 41-65	13	81.25%
Age 66 or older	1	6.25%

Similarly, participants who indicated that they were family members of an individual diagnosed with ADLD were asked the age at which their family member was diagnosed. A

majority of responses (15/16) indicated that their family member was diagnosed between ages 41-65 (Table 5).

Table 5. Age of ADLD Diagnosis - Family Member

	n (n=16)	**%**
Younger than age 40	1	6.25%
Age 41-65	15	93.75%
Age 66 or older	0	0%

3.3.4 Genetic Services

Participants were asked if they or their family member had been seen by a geneticist. Just over half of respondents (16/30) indicated that they had, while the remainder did not. Additionally, when asked more specifically which healthcare professional they or their family member has seen, 47% (9/19) of respondents indicated they had met with a geneticist, while only 16% (3/19) respondents indicated that they, or their family member, had met with a genetic counselor. Nearly two-thirds of respondents (18/29) indicated that they had not received any genetic testing. Table 6 summarizes data regarding genetic professionals and genetic testing.

Table 6. Specialists Seen and Genetic Testing

		n	%
Has Seen Geneticist (n=30)	Yes	16	53.33%
	No	14	46.67%
Specific Specialist Seen (n=19)	Geneticist	9	47.37%
	Genetic counselor	3	15.79%
	Other medical professional	4	21.05%
	Don't know / Unsure	3	15.79%
Received Genetic Testing (n=29)	Yes	10	34.48%
	No	18	62.07%
	Don't know / Unsure	1	3.45%

3.3.5 Educational Material Sources and Timing

Participants were asked what resources they used to find out about ADLD and were able to select multiple provided answers. The most popular source for information about ADLD were online resources (10/40). Additionally, 37.5% of respondents (15/40) indicated that they reached out to a geneticist or other physician for information. All participants who selected the "other" option included family members as their source of information. Table 7 describes the sources participants used to find out information about ADLD.

Table 7. Source for Information on ADLD

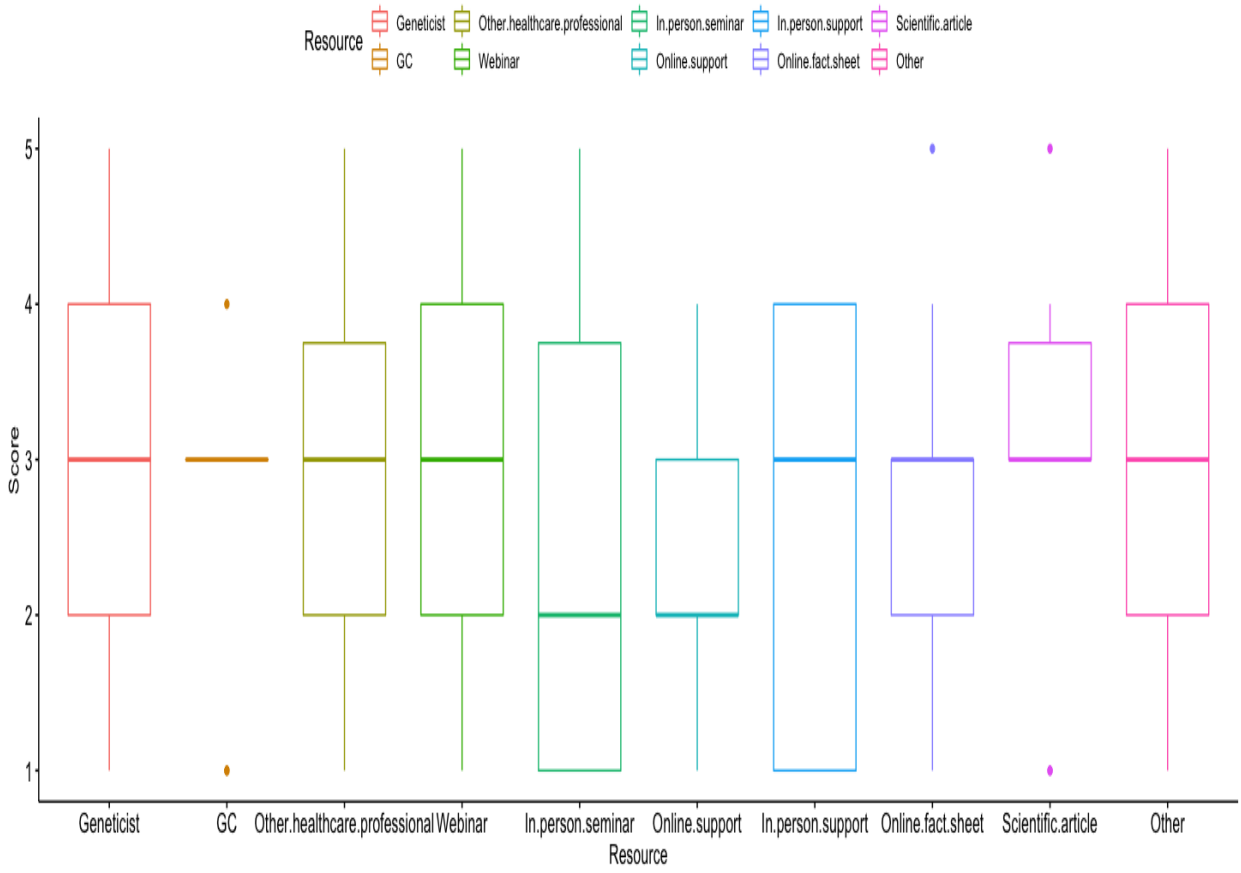
Source	n (n=40)	%
Geneticist	7	17.5%
Other physician	8	20.0%
Genetic counselor	3	7.5%
Other healthcare professional	3	7.5%
Support group	4	10.0%
Online resources	10	25.0%
Other	5	12.5%

Additionally, participants were asked to rank sources on a Likert scale from 1-5 (1=Not helpful at all, 2=Slightly helpful, 3=Somewhat helpful, 4=Very helpful, 5=Extremely helpful) regarding how helpful each source was in providing understandable information about ADLD. Table 8 shows the count, mean, standard deviation, and median scores. Figure 1 shows a box and whisker plot comparing the median scores of resources on their ability to provide information about ADLD. A Kruskal-Wallis test did not identify a significant difference in median across the source type (p=0.98).

Table 8. Rating of Participants' Perceptions of Sources Helpfulness in Providing Information on ADLD

Source	Count (n)	Mean	Sample Standard Deviation	Median
Geneticist	14	2.86	1.29	3
Genetic counselor	9	2.67	1.00	3
Other healthcare professional	14	2.86	1.17	3
Webinar	11	3.00	1.48	3
In-person seminar	6	2.50	1.76	2
Online support group	9	2.44	0.88	2
In-person support group	7	2.57	1.51	3
Online fact sheet	9	2.78	1.30	3
Scientific articles	14	3.07	1.07	3
Other	3	3.00	2.00	3

Figure 1. Box and Whisker Plot Comparing Median Scores of Resources



3.3.6 Online Educational Sources

Nearly 90% of respondents (23/26) indicated that they have looked for information about ADLD online. Nearly half of participants (12/26) indicated that they check online once or a few times a year for information about ADLD, while 38% of respondents (10/26) indicating that they check at least once a month. Nearly one-third (9/26) of respondents indicated that when they or their family member was first diagnosed with ADLD it took them over two hours to find an answer

to their question, or they have yet to find an answer. Table 9 describes participants' experience with finding online information about ADLD.

Table 9. Respondents' Ability to Locate Information About ADLD Online

		n (n=26)	%
Looked for info online	Yes	23	88.46%
	No	3	11.54%
Frequency	Once or a few times a day	0	0%
	Once or a few times a week	1	3.85%
	Once or a few times a month	9	34.62%
	Once or a few times a year	12	46.15%
	Never	4	15.38%
Length of time to find answer	< 30 minutes	3	11.54%
	30 minutes to 1 hour	2	7.69%
	1 to 2 hours	2	7.69%
	2+ hours, or have yet to find answer	9	34.62%
	N/A	10	38.46%

Additionally, participants were asked which online source, if any, was most beneficial in providing information about ADLD. A majority of participants (12/22) indicated that none of the online resources included in the survey question were most beneficial. Participants could optionally write-in a resource, though none did. Table 10 shows which source was found to be most beneficial.

Table 10. Online Source Participants Identified as Most Beneficial

Source	n (n=22)	%
GeneReviews	1	4.55%
OMIM	1	4.55%
NIH's Genetic Home Reference[A]	5	22.73%
Orpha.net	3	13.64%
None	12	54.55%
[A]As of October 2020 The Genetic Home Reference has become MedlinePlus		

3.3.7 Material Development and Distribution

Participants were asked to indicate what information they would most like included in a developed educational material. Approximately half of the respondents (42/82) indicated that they wanted to see information on management of ADLD, and current research on the condition in a newly developed educational material. Additionally, participants were able to specify anything else they wanted to be included in the created material, and answers noted timeline to therapies, stage of research for therapies, how to maintain quality of life, and availability of treatments or preventative measures for family members. Table 11 shows what respondents want to see in an online educational material.

Table 11. Information to Include in a Developed Educational Material

Item/Concern	n (n=82)	%
Risk to family members	13	15.85%
Risk to future pregnancies	7	8.54%
Features of the condition	15	18.29%
Management of the condition	23	28.05%
Current research	19	23.17%
Other	5	6.10%

Participants were asked to rank formats of educational material on a 1-5 scale (1 being the best, 5 being the worst). As shown in Table 12, the majority of respondents ranked a fact sheet as the best way to receive information about ADLD.

Table 12. Most Beneficial Format of Educational Material

Source	Mean (±SD)	Rank 1 n (%) n=21	Rank 2 n (%) n=21	Rank 3 n (%) n=21	Rank 4 n (%) n=21	Rank 5 n (%) n=21
Fact sheet	2.10 (±1.06)	8 (38.10%)	6 (28.57%)	4 (19.05%)	3 (14.29%)	0 (0%)
Infographic	2.43 (±0.85)	3 (14.29%)	8 (38.10%)	8 (38.10%)	2 (9.52%)	0 (0%)
Video	2.33 (±1.08)	7 (33.33%)	3 (14.29%)	8 (38.10%)	3 (14.29%	0 (0%)
Comment Section	3.24 (±1.27)	3 (14.29%)	4 (19.05%)	1 (4.76%)	11 (52.38%)	2 (9.52%)
Other	4.9 (±0.29)	0 (0%)	0 (0%)	0 (0%)	2 (9.52%)	19 (90.48%)

Participants were asked to designate their preferred source to create, develop, and share educational material with them. Most respondents (7/9) indicated that they would prefer a

physician to be involved. Additionally, responses included other patients, researchers, and genetic counselors as potential sources of this material.

The readability of the developed fact sheet was calculated using an online readability calculator (https://readabilityformulas.com/free-readability-formula-tests.php). Table 13 shows the Flesch Reading Ease, Flesch-Kincaid Grade Level, and Automated Readability Index of the developed material (Appendix E).

Table 13. Readability of the Developed Fact Sheet

Source	Flesch Reading Ease score	Flesch-Kincaid Grade Level	Automated Readability Index
ADLD fact sheet	62.5	8.3	8.2

3.4 Discussion

ADLD is a leukodystrophy that exemplifies the need for updated patient-friendly resources for providers, patients, and caregivers within the rare disease community. Although the ADLD community is smaller than other rare disease communities, patients and caregivers have expressed a desire for updated and easily understandable educational material.[17] This study was developed to ascertain currently available online educational material for ADLD, and to determine ADLD patient and caregiver experience with gathering information from physicians, other healthcare providers, and online. It also elicited participants' educational needs, preferred source of information, and desired format of educational resource.

3.4.1 Assessment of ADLD Online Educational Resources

In this study, online educational materials for ADLD were evaluated for readability and content. Readability scores were based on three measures, Flesch Reading Ease, Flesch-Kincaid Grade Leve, and Automated Readability Index. The Flesch Reading Ease score is the result of a formula that considers sentence length and syllable number of the material assessed, and indicates the ease at which an individual could read said material. Flesch-Kincaid grade level, and Automated Readability Index scores represent the grade level necessary to understand the material. The readability of educational material is an important factor to consider as the average American reads at the 7th-8th grade reading level.[79–81] The American Medical Association and the National Institutes of Health both recommend that medical information intended for public use should be written at or below a 6th grade reading level.[80,82,83] Although this recommendation has been made, many online sources are written well above an 8th grade reading level, and there has been a general decrease in readability of scientific articles.[78] Online educational material for ADLD assessed in this study were given Flesch Reading Level, Flesch-Kincaid Grade Level, and Automated Readability Index scores. Flesch-Kincaid Grade Level and Automated Readability Index scores were above the 8th grade reading level indicating that the average American would have difficulty understanding the material. All of the sources evaluated in this study scored above a 12 for the Flesch-Kincaid Grade Level, and above an 11 for the Automated Readability Index indicating that an individual would need to have beyond an 11th grade reading level to understand the material. Of note, the GARD site utilizes information provided by Orpha.net which may have impacted the overall readability scores for the site. Readability scores are based on formulas that assess both sentence length, and number of syllables present, though the type of content included in the resources is not evaluated by these programs.

The content included in these sources was examined by reviewing each resource. All of the sources provided information about ADLD including an overview of possible symptoms, and genetic basis of the condition, though of note, only the MedlinePlus site did not specifically include that upstream deletions may cause ADLD. Additionally, only the GeneReviews page included detailed information about inheritance including possible risks to children and siblings of an affected individual. Also, only the GeneReviews and GARD pages provided links to support groups, though neither specifically included the ADLD Facebook page. A newly diagnosed individual or caregiver may have to go to several different resources to understand the diagnosis, but even then, each source included in this study requires a reading level beyond that of the average American.

3.4.2 Survey Demographics

About half of the respondents of this survey were individuals diagnosed with ADLD while the rest were family members of an individual diagnosed with ADLD. Most patients (81.25%) indicated that they were diagnosed between age 41-65, and most family members (93.75%) also indicated that their affected relative was diagnosed between ages 41-65. This is consistent with previous findings indicating that the average age of diagnosis ranges from age 40-60.[8–10]

Interestingly, over half of respondents (52.17%) indicated that they have a graduate or professional degree, suggesting that they likely could read and understand the currently available online resources. Though over 20% (5/23) indicated that they had some college education or less, indicating that they may encounter difficulty with understanding the available educational materials. Although many respondents indicated that they have an undergraduate degree or higher,

it is not a guarantee that they can understand medical information even if it is written at a level that they "should" be able to because they may not have the numeracy or scientific literacy needed.

Additionally, a majority of participants (78.26%) are married, and nearly 60% had at least 1 biological child. The finding that many participants have a child is consistent with the fact that over 40% of participants (10/23) were between the ages of 18-40, and the average American has their first child before age 40.[55–57]

3.4.3 Perceived Ability of Sources to Provide Information

Over 80% of participants indicated that they or their family member has met with a geneticist, genetic counselor, or other healthcare professional. These specialists would likely be able to provide information about genetic conditions including ADLD. In addition to these resources, both patients and caregivers often use the internet to look for more information following a diagnosis.[76] This is consistent with the current study as over 88% of participants indicated that they used online resources to learn more about ADLD. Participants were asked how frequently they searched for information about ADLD online, and how long it took them to find an answer to their question. Nearly 40% of participants indicated that when they or their family member was first diagnosed, they searched for information at least once a month, and over one-third of participants indicated that it took them 2 or more hours, or they have yet to find an answer to their question. This finding may indicate that meeting in-person with a specialist or meeting with a support group could be more beneficial in individuals' quest to gather relevant information about ADLD than using online resources. However, when asked to rank various in-person and online sources on their ability to provide information about ADLD, scores averaged between "slightly helpful" and just above "somewhat helpful" with scientific articles averaging the highest

score. A box and whisker plot demonstrates the spread of scores, and median score for each resource evaluated. A Kruskal-Wallis test was performed to compare the medians of each group and it was found that not one source had a statistically significant higher or lower median score ($p=0.98$). This may further indicate that participants did not significantly favor or disfavor one source. This test may be the most appropriate statistical test as it compares the median scores of resources from within the same population.

Currently, there is limited online educational material for ADLD. As demonstrated in this study, patients and caregivers regularly check online resources for information about ADLD. Available information is primarily found in scientific journal articles which often contain technical information that can be difficult for a person to understand.[78] Participants were asked which online resource, if any, was the most beneficial in terms of helping them answer their questions about ADLD. Options provided to participants included the GeneReviews page, the OMIM page, the Orpha.net page, the NIH's Genetic's Home Reference page, and an option to write in a response. A majority of responses (54.55%) indicated that none of the provided resources were most beneficial. The second most popular response was the NIH's Genetic Home Reference page. Of note, since the development of the study survey, the NIH's Genetic Home Reference page has been converted into the MedlinePlus page for ADLD. This survey question included the option to include a specific resource through a text entry box, though no participant selected that option. It is possible that participants felt like one source not included in the survey question was the best, but due to the fact that they would have to type it in, chose to not include it.

3.4.4 Informational Needs

When developing educational materials, assessing the informational needs of the target audience is a crucial step. Assessing these needs provides guidance in what information should or should not be included in the educational material. It is also a way to help promote patient-centered care. Patient-centered care involves care that is respectful of and responsive to patient preferences, needs, and values.[114,115] This includes active communication between patients and physicians, but also applies to the development of educational materials as educational material may promote the communication between patients and their providers. Studies have shown that patient-centered care improves health outcomes for patients and increases the efficiency of care.[116] Therefore, promotion of communication between patients and their doctors and developing tools such as educational material to aid this communication is likely beneficial. In the current study, participants were asked to indicate what information they would most like included in a developed educational material. 28.05% (23/82) of respondents wanted information about management of the condition and 23.17% (19/82) wanted current research to be included. Nearly one-fourth (20/82) of participants indicated that they want risk to family members and future pregnancies included in a developed educational resource. This may indicate that participants are unclear about the inheritance pattern or the risks for relatives. It is also possible that participants want this information for family planning purposes. Nearly 60% of participants had at least 1 biological child, which may indicate additional psychosocial concerns such as fear of passing on the genetic variant, or fear of having a child that may witness a parent experience the symptoms of ADLD, that could be addressed in an educational material. Additional responses included that participants want to know if there are specific therapies currently available, what the timeline until a therapy is available may look like, and if there are preventative measures family members may take in

order to reduce the risk of having ADLD or symptom severity. Currently, there are no management guidelines available for individuals diagnosed with ADLD, nor are there any available clinical trials for therapy. Current treatment involves evaluation by numerous specialized physicians, and is based on presenting symptoms.[8] Additionally, much of the ongoing research is attempting to further identify and classify possible disease manifestations, and the underlying basis for genetic alterations involving the *LMNB1* gene. As genetic alterations involving the *LMNB1* gene are inherited in an autosomal dominant manner, the risk to a future pregnancy of a proband is 50% regardless of gender, and the risk to siblings is dependent on the genetic status of the proband's parents. If one of the proband's parents is found to have ADLD, then the risk to the proband's sibling is 50%. Once a familial variant is identified, preimplantation genetic diagnosis (PGD) or preimplantation genetic testing for familial mutations (PGT-M) may be considered for couples considering using *in-vitro* fertilization (IVF) to conceive a pregnancy.[8] Including this information in a developed educational material may help to provide clarity for patients about genetic risk factors, and aid in family planning. It may also help foster communication between ADLD patients and their physicians regarding possible reproductive options.

It is possible that participants want risk to future pregnancies or family members included in a developed educational material due to concerns of possibly passing on a pathogenic variant to a child. As seen in this study, many participants already had children, and may fear that their child inherited the ADLD pathogenic variant. This issue has been well studied in other adult-onset disease communities, including the Huntington's disease community. These studies found that individuals in the Huntington's disease community felt a sense of guilt after having a biological child even if they did not know their genetic status prior to conception of the child.[59,60]

Extrapolating to ADLD, it is possible that individuals feel a similar sense of guilt, and wish to know risks for their current and possible future children.

3.4.5 Preferred Format of Educational Material

Participants were asked to rank formats of educational material on a 1-5 scale, with 1 being the best format, and 5 being the worst format in terms of conveying information about ADLD. Based on the responses, a video was ranked as the second-best format, while an infographic was third. Interestingly, participants ranked a fact sheet as their preferred format for a developed educational material. This may, in part, be due to the fact that 78% of participants (18/23) hold an undergraduate degree or higher, and have higher literacy skills, promoting a desire for written text rather than visual material. Studies have shown that the use of illustrations tend to allow for better understanding of material when coupled with clear and concise language.[113] Therefore, an infographic, or video may have been considered to be the best format, had this survey not assessed the preference of participants.

Fact sheets tend to be clear and concise, highlighting important information in an understandable manner, while infographics use pictures with minimal text providing an overview of a topic. Infographics are a beneficial way to communicate ideas particularly to individuals with lower health literacy, since they use visuals rather than extensive text. However, they may not provide as much detailed information as a fact sheet.[113,117,118] Additionally, videos are also a format that may aid in patient understanding. The Patient Education Video Program found that 86% of individuals surveyed after watching a video about their care felt that the video helped them understand their treatment plan, medical condition, and overall health.[119] Therefore, a multimedia approach may also be beneficial to aid in ADLD patient and caregiver understanding. An

additional consideration may be in the development of additional online, and/or in-person support groups for individuals and families affected by ADLD. Studies have found that support groups are beneficial for individuals in the rare disease community.[96,97] Individuals in the ADLD community have one online disease-specific support group available to them. Therefore, the creation of additional support groups may benefit the community as support groups often decrease the feelings of isolation and stigmatization. They may also provide a sense of empowerment and provide additional resources among other benefits.[94–97]

3.4.6 Preferred Source of Information

Participants were asked to designate their preferred source of information in the development of an educational material. Nine participants wrote in responses. A majority of responses indicated that participants desire a geneticist or physician to be the primary source of information. Additionally, responses included other patients, researchers, and genetic counselors as possible sources of this material.

Physicians have extensive training in diagnosing and treating medical conditions. Similarly, geneticists diagnose and treat medical conditions related to an underlying genetic cause.[120,121] Therefore, both of these sources offer a unique perspective in the development of educational material as they are well-versed in possible symptoms an individual may experience, current treatments available, and are often up-to-date on the research into many different conditions. Researchers often have diverse educational backgrounds, and should they focus on a particular disease such as ADLD, may provide specific information on the basis of that disease, symptoms a person may experience, and efficacy of treatments. These experiences also give them a unique perspective in the development of educational materials. Genetic counselors have

advanced training in both genetics and counseling, and often provide information and support to individuals diagnosed with genetic conditions.[122] Genetic counselors regularly have to identify, and evaluate educational material prior to providing it as a resource to patients or caregivers, and often have experience in creating educational materials.[123] Therefore, a combined approach by a team of physicians, researchers, and genetic counselors may be an ideal source for the development of educational materials.

3.4.7 Considerations for Development of Educational Material

The development of accessible, patient-friendly material is often a difficult task considering the low general literacy and health literacy of the lay public. The difficulty of conveying important ideas while writing below a 6th grade reading level may be exacerbated because key concepts related to diagnosis, genetics, inheritance, treatments, and surveillance may require terms that are considered to be above an 8th grade reading level. A number of studies have found that often online educational material is identified to be written above the NIH and AMA's recommendation, though this may be due to the polysyllabic nature of necessary medical information.[124,125] In order to convey information in an understandable manner, one should consider which topics require more advanced education and which can be written at or below a 6th grade reading level. Additional consideration might be given to developing additional educational material that can explain advanced or complex topics in an understandable manner. Studies have found that the inclusion of figures or visual aids tend to assist in patient understanding, especially when conveying risk information and would likely be beneficial in developed resources intended for the ADLD community, or other rare disease community.[126]

The fact sheet developed as a part of this study was found to have a Flesch Reading Ease score of 62.5 which is considered to be a "standard" or "average" score. It was also found to have a Flesch-Kincaid Grade level of 8.3 and an Automated Readability Index of 8.2 indicating that the developed material is written at the NIH and AMA's recommended reading level as individuals with an 8th grade reading level could likely read and understand the fact sheet.

3.4.8 Limitations

There are several limitations that can be identified for this study. Data collected from the readability calculator is the result of a calculation based on sentence length and number of syllables within the source and does not assess content of the inputted material. The polysyllabic nature of the technical language necessary to convey ideas in the evaluated educational resources may have caused the readability scores to be elevated.

All survey responses were self-reported. Participants' had to recall how long they spent searching for online information, and how frequently they did this search, after they were first diagnosed, which may have been several years from the time they completed the survey. This could lead to inaccurate data if the participant could not precisely recall how frequently they searched for information or how long the searches took them. Additionally, years ago information was more limited in its availability which could have caused participants to spend longer times searching than they currently do.

A further limitation of this study is that the ADLD Facebook page was not analyzed for readability or content. While this source is not directly intended to act as a primary source for information on ADLD, it does act as a place where patients, caregivers, and researchers interact.

Evaluation of this source would be difficult to do as individuals regularly post about experiences, and not all posts are directly providing educational information about ADLD.

Selection bias is also a possible limitation of this study as the survey was posted online to the ADLD Facebook group but was not posted on all sites that individuals affected by ADLD visit. Individuals may have been motivated or deterred from participating based on the source they used to come across this survey, whether through email or online. The results may have been different if other sites were utilized for participant recruitment.

Another limitation is volunteer bias as the survey was voluntary and only individuals motivated to participate did so. It is possible that individuals who initially took longer to locate educational materials online were more motivated to participate in this study than individuals who did not have this experience.

A Kruskal-Wallis test was performed in this study to compare the median scores of resources' perceived abilities in providing information on ADLD. This test is non-parametric and does not require that data follow a normal distribution. This test is often used to compare groups from within the same population as the observations within a group are not independent. This test also had a p-value of 0.98. This is likely due to the low count observed in the study as median values may change with additional observations. It is possible that combining groups into different categories and then comparing medians may yield different results, though this was not performed. It is also possible that performing a more limited assessment of only 4 resources may provide more responses and participant engagement. Additionally, a more expanded assessment, such as having 7 possible Likert scale values may identify significant differences between resources, though participants may be overwhelmed with options if there are too many resources to evaluate. Alternatively, a different statistical test may yield different results.

While the exact response rate could not be determined, it is possible that individuals did not participate due to a number of factors including having difficulty accessing the survey, personal feelings toward providing information, lack of time to participate, or challenges in reading the survey. It is critical for researchers to recognize barriers that may prevent individuals from participating in research and to develop strategies to enhance recruitment.

3.4.9 Future Research

In the future, focus groups or qualitative interviews could be pursued to better determine participants' use, opinions, and understanding of available online educational materials. In these settings, participants could more thoroughly describe the information they would like included in the development of educational materials, and they could evaluate the readability of available online educational materials. This input could inform investigators about the use of other tools or platforms where they could present information, such as through webinars, lectures, or interactive learning. Qualitative interviews and focus groups could also assess the ease at which a participant can locate online educational material.

The analysis did not examine patients and family members separately when assessing the preferred format of educational material, preferred information to be included in a developed material, or preferred source of information on the developed material. This type of analysis may be considered in future research as it is possible that patients and family members have different preferences and therefore, educational material could be tailored to meet the preferences of these two groups.

Future research could include the development and piloting of additional educational materials, as well as having various stakeholders such as physicians, patients, caregivers, and

researchers evaluate the material for accuracy, readability, and ease of access. An additional resource that could be considered is the creation of an educational video as it was ranked as the second-best format for providing ADLD information in this study. Additionally, this study may serve as an example for assessing the educational needs of individuals in other rare disease communities and developing material for these communities.

3.5 Conclusion

This study found that online educational material for ADLD was limited in availability, difficult to read and understand, and includes variable content.

The assessment of readability found that all of the studied online educational materials were written at a grade level well above the current recommendation of below a 6^{th} to 8^{th} grade level. Additionally, the evaluated resources provided different content about ADLD with some providing information about the genetic basis of the disease, inheritance and/or risks to pregnancies or siblings, while others did not.

Participants indicated that they had tried to utilize resources outside of the internet for more information about ADLD, though no resource was identified as being the most helpful in finding information about ADLD.

Additionally, this study found that participants desire a fact sheet to be developed that would provide information about management, risks, and current research. Participants also indicated that they would prefer this information to come from physician(s), researchers, genetic counselors, or other patients.

In the development of patient-friendly educational resources, the following steps are recommended:

- Material should be written at or below a 6^{th}-8^{th} grade level.
- Clear and concise language throughout the material should be used, and the inclusion of pictures and visuals to aid explanations is encouraged.
- The material should meet the educational needs of the target population.
- The material should be piloted with various stakeholders including patients, family members, caregivers, and physicians.
- Stakeholders should evaluate developed material.
- The material should be shared on an accessible platform.

4.0 Significance to Genetic Counseling and Public Health

4.1 Genetic Counseling

Genetic counselors are heath care professionals with specialized training in genetics and counseling and act as a resource for individuals with a suspected or confirmed genetic diagnosis. Provision of genetic information is part of the genetic counselor's role and this may include offering additional online educational materials to patients. This often puts genetic counselors in a unique position as they review the material for accuracy, readability, and relevance. Moreover, genetic counselors often have experience developing patient-facing educational materials.[123] Genetic counselors may interact with individuals in various rare-disease communities, and encounter situations where they are unable to provide educational materials or information on specific support groups, which are highly beneficial.[96,97] Therefore, they may have first-hand experience in recognizing a lack of available resources for an individual or community, and be able to assist in the development of additional resources.

Numerous online resources provide information about genetic conditions, though not every resource uses understandable language. Genetic counselors should be aware of the current NIH and AMA reading level recommendations when assessing what resource might be best to share with their patients. Additionally, research into genetic conditions is growing, and as our understanding of genetics evolves, it is crucial to evaluate information, even from reputable sources, that may be provided to a patient for readability, accuracy, and relevance.

This study demonstrates that individuals in the ADLD community often search for information about ADLD online, with varying levels of success in getting answers to their

questions. Genetic counselors are uniquely positioned to help address the concerns of individuals diagnosed with, or are suspected of having, a genetic condition and are often involved in the creation of educational materials to benefit these individuals. It is important that genetic counselors are aware of literacy, and health literacy concerns of the lay public during the development of educational material.

Participants of this study also indicated that they want current research included in a developed educational resource. This demonstrates the desire for updated information. As the field of genetics rapidly evolves, and our understanding of rare diseases progresses, genetic counselors should be aware that many sources may be considered out-of-date by the time they are reviewing them.

This study also found that many participants have biological children. Since ADLD is a genetic condition, parents may be concerned regarding the risk for their child(ren) to be affected. Developed educational material should address the risk for family members and possible future pregnancies. Additionally, when relevant, educational material should include information on preimplantation genetic diagnosis, and prenatal testing. This information may help foster communication between patients, family members and healthcare providers, including genetic counselors, which in turn may enhance patient understanding.

4.2 Public Health

Public health efforts often address challenges that may affect many people in a given population, and public health initiatives are typically developed to try to prevent people from

experiencing these challenges.[127] Therefore, issues pertaining to rare diseases are not often thought about as traditional public health concerns.[128] That said, there are over 6,800 rare diseases that affect an estimated 25 to 30 million people in the United States alone, and there is compelling evidence to suggest that public health initiatives addressing concerns of individuals in the rare disease community may be beneficial.[4,128]

One of the essential core functions of public health is to inform, educate, and empower.[127] This means that individuals working to improve public health should help inform and educate others. This is particularly important when addressing rare diseases as the knowledge and understanding of the condition can change rapidly.

One challenge to providing education is the low level of literacy and health literacy in the general public. The average American reads at or below a 7th-8th grade level, and over one-third of the lay public has below basic, or basic health literacy skills, meaning that they do not have the skills to interpret complex information, or make inferences about material that could pertain to their health.[109,110] These skills are crucial to understanding educational material, especially when the material is addressing a medical condition. To address this public health issue, Healthy People 2030 promotes a public health initiative attempting to raise the health literacy of the public.[111] When developing educational material, it is important to recognize that the material may be accessed by individuals with low general and health literacy skills.

This study found that many participants held an undergraduate degree or higher, indicating that they may have higher general literacy and health literacy skills. However, writing educational material about ADLD at or above the collegiate level would be a disservice as many people who may come across the information would not be able to read or understand it. Additionally, this study demonstrates the need for educational materials to be clear and concise as many individuals

indicated that none of the available online resources were most beneficial in aiding their understanding of ADLD. This may be due to the fact that the answer to their question was not included in any of the resources, or potentially it was, but the material was too dense or confusing for the reader to find the answer. As most individuals only read about 18% of what is written on a page, developed educational materials should be concise in order to facilitate understanding.[85]

Other public health initiatives, such as the creation of disease-specific support groups, may benefit individuals in the rare disease community. This may help promote aspects of public health, though both the "inform, educate and empower" and "mobilize community/partnerships" core functions. Support groups are often beneficial for individuals facing a diagnosis of any medical condition, but are particularly beneficial for members of the rare disease community.[96,97] Support groups allow for connections to be made between patients, family members, and providers, and often lessen the feeling of isolation and stigmatization, and encourage open communication and may provide a sense of empowerment.[94–97] This is true for both in-person and online support groups.[95,96] Online support groups offer the benefit of connecting people who do not live nearby each other, and allow for more flexible schedules, which may be seen as a benefit over in-person support groups. As individuals in the ADLD community currently do not have access to any ADLD-specific online support groups outside of the ADLD Facebook group, they would likely benefit from an additional opportunities to share their experiences and connect with other individuals/families and providers/researchers.

Appendix A Survey Introduction

ADLD educational materials survey - Introduction

We are inviting you to take part in a survey that is trying to determine the need for educational materials for individuals and families affected by Autosomal Dominant Leukodystrophy (ADLD). Ultimately, this research will help in the creation of educational resources for individuals and families affected by ADLD caused by alterations to Lamin B1 (*LMNB1*).

We are surveying individuals diagnosed with ADLD, their family members, and unrelated caregivers and asking them to complete a brief (10 to 15 minute) survey. If you are willing to participate, this survey will ask about your experience with getting information about ADLD from doctors, other healthcare workers, and online. It will also ask about what you would like to learn about ADLD, and how you would prefer to receive this information.

There are minimal risks associated with completing this survey including, but not limited to the infrequent breach of confidentiality. You will not receive any form of compensation for completing this survey.

This survey is anonymous, so your responses will not be identifiable. All responses are confidential and electronically secured. Your participation is voluntary. You may skip questions, or stop the survey at any time, though any responses up to the point of exiting will be kept. If you choose to withdraw from this study, all data collected prior to withdrawal will be used.

This survey can be accessed through clicking on this link, or copying and pasting it into your browser:

https://pitt.co1.qualtrics.com/jfe/form/SV_9mGpJ4kp0wDYyTb

You can reach out to the study Principal Investigator, Dr. Quasar Padiath (qpadiath@pitt.edu) if you have any questions. Thank you for considering participating and we appreciate your help in providing information that will be important in the creation of educational materials for individual and families affected by ADLD.

Appendix B ADLD Survey Email

Dear Friends

We are carrying out a survey to assess the need for educational materials for individuals and families affected by ADLD (details attached).

The survey is anonymous, very brief (~ 10 minutes) and is for ADLD patients, caregivers and family members. It is one survey per person.

The same information has also been posted to the ADLD Facebook page.

Please fill out the survey using the link below or in the attached file. Ultimately, this research will help in the creation of educational resources critical for the ADLD community.

So, I encourage you to participate and also let others know about the survey. Do not hesitate to contact me for any further information.

Best

Dr. Quasar Padiath

Link to survey

https://pitt.co1.qualtrics.com/jfe/form/SV_9mGpJ4kp0wDYyTb

Appendix B.1 ADLD Survey Reminder Email

Dear Friends

I am following up on my previous email (below) to remind everyone about the Survey on Educational materials for ADLD (details attached).

I wanted to thank everyone who has filled out the survey so far. Sixteen participants have filled out the survey and we would really like to have between 25-30 responses to be able to draw any meaningful conclusions.

I would encourage any of you who have not filled it to do so and also encourage other ADLD family members/caregivers and patients to fill out survey . Please also forward the link to anyone who think might be interested. The survey will be closed for response submission after March 19th, 2021 so that we can start analyzing the data.

The link to the survey is below.

Link to survey

https://pitt.co1.qualtrics.com/jfe/form/SV_9mGpJ4kp0wDYyTb

I hope that everyone is keeping safe.

Thank you and Best Regards

Quasar

Appendix B.2 ADLD Facebook Group Post

"Patients, family members and caregivers: Please take 10-15 minutes to read about and complete the following *anonymous* survey for Dr. Padiath's ADLD research team at UPITT. Direct link to the survey: https://pitt.co1.qualtrics.com/jfe/form/SV_9mGpJ4kp0wDYyTb"

Appendix C ADLD Survey

ADLD Survey 1

Q1 Have you been diagnosed with Autosomal Dominant Leukodystrophy (ADLD) due to mutations or alterations involving Lamin B1 (LMNB1)?

- Yes
- No

Q2 Are you a family member of someone diagnosed with ADLD due to mutations or alterations involving Lamin B1 (LMNB1)?

- Yes
- No

Q3 Are you a caregiver (related or unrelated) for someone diagnosed with ADLD due to mutations or alterations involving Lamin B1 (LMNB1)?

- Yes
- No

Q4 At what age were you diagnosed with ADLD?

- Younger than age 40
- Age 40-65
- Age 66 or older

Q5 At what age was the person you care for, or family member, diagnosed with ADLD?

- Younger than age 40
- Age 40-65
- Age 66 or older

Q6 Have you or your family member seen a doctor who specializes in genetic medicine?

- o Yes
- o No

Q7 What kind of genetics professional have you or your family member seen? Please check all that apply.

- □ Geneticist (doctor who specializes in genetic medicine)
- □ Genetic counselor
- □ Other medical professional
- □ Don't know / Not sure

Q8 Have you gotten genetic testing?

- o Yes, I have gotten genetic testing
- o No, I have not gotten genetic testing
- o I don't know, or am unsure if I have gotten genetic testing

Q9 People get information about ADLD from many different sources. Where did you go to get answers for your questions and to look for information about ADLD? Please check all that apply.

- □ Geneticist
- □ Other physician
- □ Genetic counselor
- □ Other healthcare professional
- □ Patient navigator
- □ Support group
- □ Online resources
- □ Other (please specify)
  - _____

Q10 Have you looked for information about ADLD online?

- o Yes
- o No

Q11 How often do you look for information about ADLD online?

- Once or a few times a day
- Once or a few times a week
- Once or a few times a month
- Once or a few times a year
- Never

Q12 Thinking back to when you, or your family member, were first diagnosed with ADLD, how long did it take you to find an answer to your question about ADLD online?

- Less than 30 minutes
- 30 minutes to 1 hour
- 1 to 2 hours
- 2+ hours, or I have yet to find an answer to my question
- N/A

Q13 For the following items, please indicate how helpful they were in providing understandable information about ADLD (including possible symptoms, inheritance, finding additional resources, etc…).

	Not helpful at all	Slightly helpful	Somewhat helpful	Very helpful	Extremely helpful	N/A
Geneticist	○	○	○	○	○	○
Genetic counselor	○	○	○	○	○	○
Other healthcare professional	○	○	○	○	○	○
Webinar	○	○	○	○	○	○
In-person seminar	○	○	○	○	○	○
Online support group	○	○	○	○	○	○

In-person support group	○	○	○	○	○	○
Online fact sheet	○	○	○	○	○	○
Scientific Articles	○	○	○	○	○	○
Other (please specify)	○	○	○	○	○	○

Q14 What online resource, if any, did you find most beneficial to answering your questions about ADLD?

- ○ GeneReviews
- ○ Online Mendelian Inheritance in Man (OMIM)
- ○ National Institutes of Health (NIH)'s Genetic Home Reference
- ○ Orpha.net
- ○ Other (please specify)
  - _____
- ○ None

Q15 Please tell us what specific information you would like to find in an online educational resource with regard to ADLD. Please check all that apply.

- □ Risk to family members
- □ Risk to future pregnancies
- □ Features of the condition
- □ Management of the condition
- □ Current research
- □ Other (please specify)
  - _____

Q16 What would be the most helpful ways to deliver information about ADLD to you? Please check all that apply.

- □ Fact sheet (a 1 to 2 page document that describes ADLD)

- Infographic (a 1 page document that is made up of pictures with some text that explains ADLD)
- Video from a genetics specialist
- Comment section (Area where people could ask questions and a specialist could respond)
- Other (please specify)
    - _____

Q17 Please rank the following formats in terms of most helpful to least helpful in conveying information about ADLD to you. A 1 would be most helpful and a 5 would be least helpful. These are the same items from the previous question. (Click and drag your selection up or down to place in your specified order).

_____Fact sheet

_____Infographic

_____Video from a genetics specialist

_____Comment section

_____Other (specified in previous question)

Q18 If you could choose where you want this information to come from, what source would that be? This could be doctors/genetic counselors, other patients, other caregivers, etc…

- Please select this option and specify below

_____

Q19 What is your age?

- 18-40 years old
- 41 to 65 years old
- 66 or older

Q20 What is your gender?

- Male
- Female
- Other
- Prefer not to answer

Q21 What race and ethnicity do you identify as? (Please choose all that apply)

- Black or African American
- Asian or Pacific Islander
- White/Caucasian
- Native American or Native Alaskan
- Hispanic, Latino, or Spanish origin
- Middle Eastern or North African
- Other
- Prefer not to answer

Q22 What is the highest level of education or highest degree you have received?

- Some high school
- High school or GED
- Some college
- Undergraduate degree (Associate's or Bachelor's degree)
- Some graduate school
- Graduate or professional degree (Masters's, MD, PhD, etc…)
- Prefer not to answer

Q23 What is your marital status?

- Single
- Married
- Divorced
- Widowed
- Separated
- Prefer not to answer

Q24 Do you have any biological children?

- Yes
- No
- Prefer not to answer

Q25 How many biological children do you have

- 1
- 2
- 3
- 4
- 5 or more
- Prefer not to answer

Appendix D IRB Approval

University of Pittsburgh | Institutional Review Board
Office of Research Protections

APPROVAL OF SUBMISSION (Expedited)

Date:	November 2, 2020
IRB:	CR19100151-001
PI:	Quasar Padiath
Title:	Elucidating the genetics of Demyelinating disorders
Funding:	None

The Institutional Review Board reviewed and approved the above referenced study. The study may begin as outlined in the University of Pittsburgh approved application and documents.

Approval Documentation

Review type:	Continuing Review
Approval Date:	11/2/2020
Expiration Date:	11/1/2021
Expedited Category	(5) Data, documents, records, or specimens, (2)(a) Blood samples from healthy, non-pregnant adults, (3) Noninvasive biological specimens
Approved Documents:	• Screening script, Category: Waiver Script; • Padiath-consent-adult-editable-no footer.pdf, Category: Consent Form; • Padiath-consent-child-editable-no footer.pdf, Category: Consent Form;

As the Principal Investigator, you are responsible for the conduct of the research and to ensure accurate documentation, protocol compliance, reporting of possibly study-related adverse events and unanticipated problems involving risk to participants or others. The HRPO Reportable Events policy, Chapter 17, is available at http://www.hrpo.pitt.edu/.

Continuing review (CR) can be submitted by clicking "Create Modification/CR" from the active study at least 5 weeks prior to the expiration date.

Clinical research being conducted in an UPMC facility cannot begin until fiscal approval is received from the UPMC Office of Sponsored Programs and Research Support (OSPARS).

If you have any questions, please contact the University of Pittsburgh IRB Coordinator, Larry Ivancd.

Please take a moment to complete our Satisfaction Survey as we appreciate your feedback.

Appendix D.1 IRB ADLD Survey Exemption Letter

University of Pittsburgh | Institutional Review Board
Office of Research Protections

EXEMPT DETERMINATION

Date:	February 22, 2021
IRB:	STUDY21020157
PI:	Quasar Padiath
Title:	Assessment and Distribution of Online Educational Materials Regarding Autosomal Dominant Leukodystrophy (ADLD).
Funding:	None

The Institutional Review Board reviewed and determined the above referenced study meets the regulatory requirements for exempt research under 45 CFR 46.104.

Determination Documentation

Determination Date:	2/22/2021
Exempt Category:	(2)(i) Tests, surveys, interviews, or observation (non-identifiable)
Approved Documents:	• ADLD Survey - No skip logic, Category: Data Collection; • ADLD Survey - Visible skip logic, Category: Data Collection; • ADLD Survey Introduction, Category: Recruitment Materials; • HRP-721 Document, Category: IRB Protocol;

If you have any questions, please contact the University of Pittsburgh IRB Coordinator, Larry Ivanco.

Please take a moment to complete our Satisfaction Survey as we appreciate your feedback.

Appendix E ADLD Fact Sheet

What is Autosomal Dominant Leukodystrophy?

Autosomal Dominant Leukodystrophy (ADLD) is an adult-onset condition caused by harmful changes to the *LMNB1* gene, which provides instructions for the Lamin B1 protein.

What is myelin and how does ADLD affect it?

ADLD causes changes in myelin. Myelin is a substance made by special cells called "oligodendrocytes" in the central nervous system (CNS) which is the brain and spinal cord.

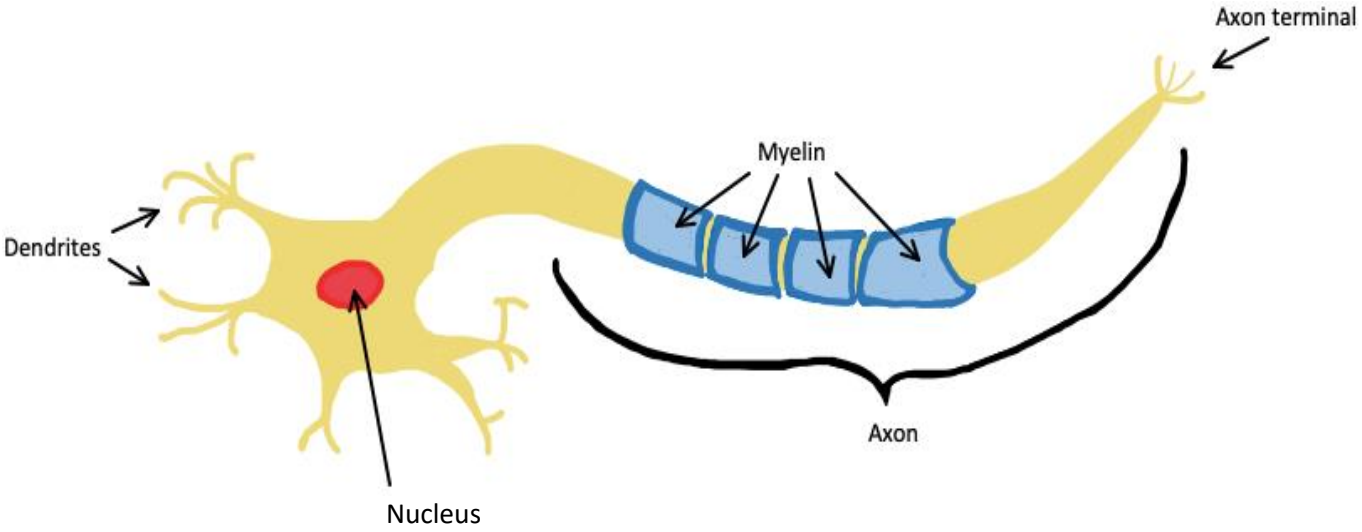
Myelin is used to coat the axons of neurons in the CNS, and acts as an insulator, which speeds up the communication from one neuron to the next.

If a person has damage to the myelin, and the body can't fix it, then a person might experience health problems.

ADLD is a "demyelinating" condition, meaning that people with ADLD lose the myelin coating on their neurons over time.

What is a neuron?

A neuron, or nerve cell, is a type of cell found in the nervous system. Neurons help us sense the outside world through our senses of touch, smell, sight, taste, and hearing. Neurons also tell our bodies how to move. Neurons do this by acting like electrical wires in the body. Like electrical wires, they use electrical signals to send messages from one neuron to the next. Myelin is like the insulating coating on electrical wires, helping to make sure that the signal goes quickly to where it is supposed to go.



What are the symptoms of ADLD?

Often the first symptoms a person with ADLD might experience are a lack of bladder control, difficulty with bowel movements (constipation), men may have difficulty getting an erection (erectile dysfunction), and low blood pressure due to position of the body (orthostatic hypotension).

These symptoms are often followed by impaired balance or coordination (ataxia), and shaking when moving (intention tremor). Emotional, behavioral, and memory problems may also be a later sign of ADLD.

Specific changes to the brain and spinal cord can also be seen in individuals with ADLD, many years before they experience other symptoms.

What is the treatment for ADLD?

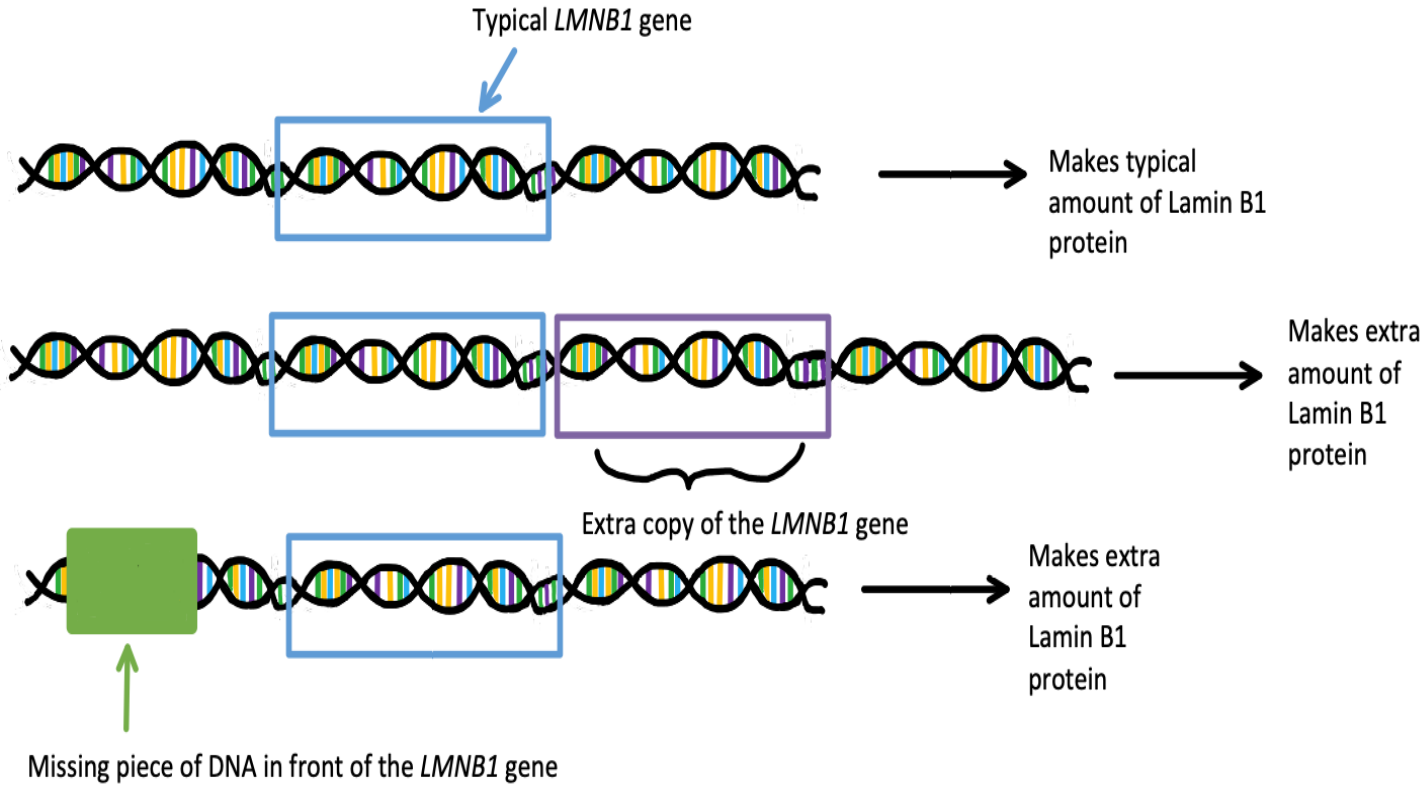
Currently, there is no specific cure or treatment available for people with ADLD. Treatment is based on the symptoms a person is experiencing and is focused on managing symptoms. This may involve a number of specialized doctors.

What is the cause of ADLD?

Our body is made up of many cells, and in the cells, there is DNA, which is the genetic information that is passed from parent to child. Specific parts of this DNA are called “genes.” Genes are the segments of DNA that act as an instruction manual for the body to make substances called “proteins.” Proteins have many different important jobs including helping our body to grow and work properly. The Lamin B1 protein has many different jobs and is thought to be needed for neurons to develop properly, and for oligodendrocytes to build and maintain the myelin.

We typically have two copies of our genes, one inherited from our mother, and one from our father.

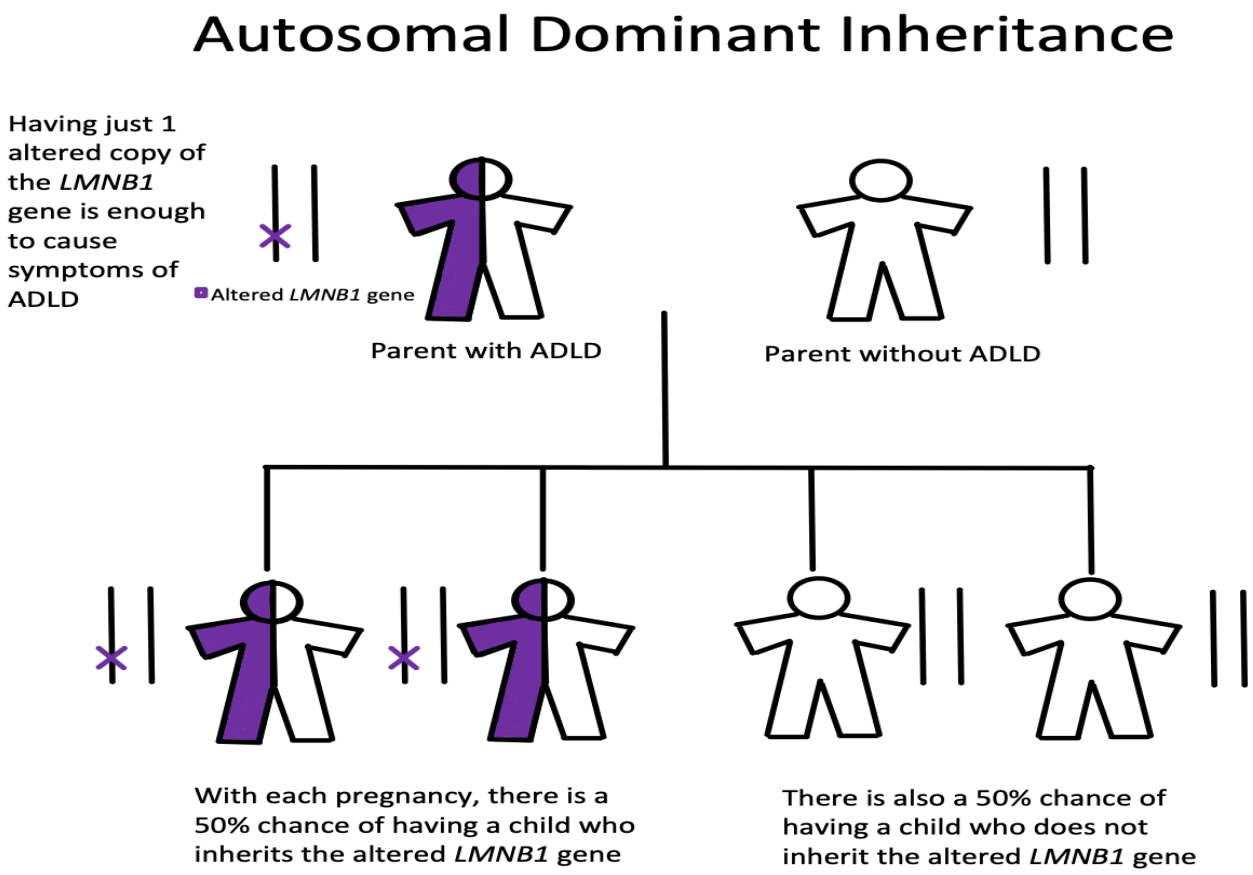
ADLD is caused by harmful changes involving the *LMNB1* gene. This change is often an extra copy (duplication) of this gene, but sometimes, a missing piece of DNA (deletion) in front of the *LMNB1* gene. These changes cause extra Lamin B1 protein to be made, and too much of this protein is thought to interfere with how oligodendrocytes work.



How is ADLD inherited?

ADLD is passed through families in an "Autosomal Dominant" manner. This means that both men and women can have changes to the *LMNB1* gene. This also means that having a change such as a duplication or deletion in just one of the copies of the gene is enough for a person to experience symptoms and be diagnosed with ADLD.

As seen in the picture below, when one parent has ADLD, there is a 50% chance with every pregnancy that the child will inherit the changed or altered *LMNB1* gene, regardless of whether the child is a male or female. This also means that there is a 50% chance that the child will not inherit the altered gene. When a person has ADLD and received the changed *LMNB1* gene from a parent, his/her brother or sister has a 50% chance for also having the changed *LMNB1* gene.



What current research is taking place?

Much of the current research is trying to understand what exactly causes a duplication or deletion to happen in the *LMNB1* gene. Additionally, animal models, which are non-human animals, such as a mouse, have been developed to mimic certain aspects of ADLD, and hopefully will help find possible treatments or a cure for ADLD. Medical advances happen every day, but no one knows how long it may take to find a cure for ADLD.

Are there any clinical trials for ADLD?

Clinical trials are experiments to see if a new treatment like a drug, or medical device, is safe and helps to treat people. Currently, there are no available clinical trials for people diagnosed with ADLD. This may change in the future, and www.clinicaltrials.gov offers an updated list of available clinical trials.

Additional Resources

https://medlineplus.gov/genetics/condition/autosomal-dominant-leukodystrophy-with-autonomic-disease/

This resource provides an overview of ADLD.

https://www.facebook.com/groups/670655456431287/

This resource is the ADLD Facebook support group. This site helps connect patients, family members, caregivers, and researchers, and allows for people to share their thoughts and experiences. It is specifically intended for people who have ADLD, have a family member with ADLD, or care for a person with ADLD.

Terms used

Axon – The part of the neuron that sends an electrical signal.

Axon terminal – The end of the axon. This part is close to the dendrites of other neurons, so that they can receive the signal.

Central Nervous System – The brain and spinal cord.

Deletion – A missing piece of DNA.

Dendrite – The part of a neuron that receives signals from the axon terminal of another neuron.

DNA – The genetic information that is passed on from parent to child.

Duplication – An extra copy of DNA.

Gene – Part of DNA that provides instructions on how to make substances called proteins.

Myelin – A substance that surrounds the axons of neurons. Myelin helps the signal move quickly from one neuron to the next and prevents the signal from accidentally going to unintended neurons.

Neuron – A cell found in the nervous system that helps us sense the outside world and help tell muscles how to move.

Nucleus – The control center of the cell. This is also where DNA is found.

Oligodendrocyte – Specialized cells that make and maintain the myelin that coats axons in the central nervous system.

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