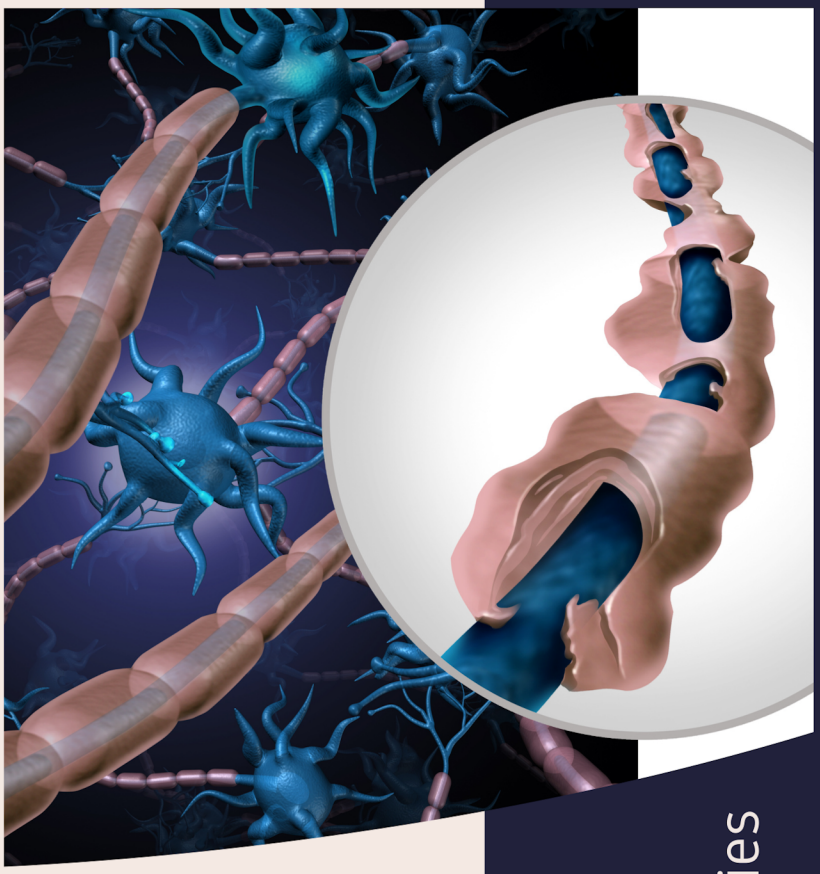
sisters' hope FOUNDATION

Cure ALSP RESEARCH

Clover Genetics



I have ALSP. Now What?

A patient's guide to living with Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia (ALSP).

A Resource Guide for Patients & Their Families

A diagnosis of ALSP is life changing and creates many questions.

WE HOPE THIS PACKET CAN HELP YOU NAVIGATE THROUGH THIS PROCESS.

** Patient Kit Developed in Collaboration with Clover Genetics **

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WHO WE ARE

Sisters: Holly, Heidi, and Heather
Heidi Edwards is the founder of Sisters' Hope Foundation.
She lost her eldest sister, Heather, to ALSP in August of 2020,
and just under a year later, her twin sister, Holly, died from ALSP in July 2021.

Sisters' Hope Foundation is the first, and only, global non-profit organization supporting those affected by ALSP.

The mission of Sisters'Hope Foundation is to support and empower families impacted by CSF1-R - related ALSP by:

- Educating the public to increase awareness around this rare disease
- Advocating for research and funding for improved treatment options
- Building community and support through connecting patients and families impacted by ALSP
- Providing financial assistance and resources to those who need them

Our goal is to create a world where individuals impacted by ALSP have the knowledge and access to the necessary support to improve their quality of life. Our ultimate vision is to witness the first survivor of this devastating disease.

OUR CENTRAL VALUES AND GOALS:

HONESTY & TRANSPARENCY

PATIENCE

ACCESSIBILITY

COURAGE

DID YOU KNOW?

ALSP STATISTICS & FACTS

10,000

is the estimated number of people thought to have ALSP in the USA
(numbers are similar in Europe and Japan)

ALSP makes up

25%

of all adult-onset leukodystrophies

95%

of patients become symptomatic before age 60. However, symptoms can occur as early as age 18.

MEN / WOMEN

are equally affected. However, women are thought to show symptoms earlier than men (at age 40 vs. 47 in men)

LIFE EXPECTANCY
is within an average of

8 YEARS

after symptoms onset
(range: 2-30 years post symptoms)

PREVIOUS NAMES FOR ALSP

Hereditary diffuse leukoencephalopathy with spheroids (HDLS)

Leukoencephalopathy, diffuse hereditary, with spheroids

Adult-onset leukodystrophy with neuroaxonal spheroids

Autosomal dominant leukoencephalopathy with neuroaxonal spheroids

Neuroaxonal leukodystrophy
Pigmentary orthochromatic leukodystrophy (POLD)

CSF1-R-related leukoencephalopathy

ALSP & YOU

Newly Diagnosed with ALSP

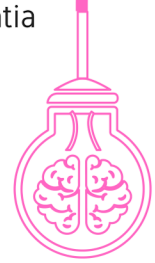
INTRODUCTION TO THE CAUSE AND IMPACTS OF THE DISEASE

Connecting with others living with ALSP can lessen the fear of the unknown and help you and your family prepare for the future by knowing what to expect. Gaining a comprehensive understanding of your diagnosis is a continual journey, but there are proactive measures you can embrace to ensure a fulfilling life for as long as possible.

The term "pathogenic variant" is used to describe what was formerly known as "mutation," which is a specific disease-causing change in the DNA code

Conditions with symptoms overlapping with ALSP:

- Frontotemporal dementia
- Alzheimer's Disease
- Multiple Sclerosis
- Parkinson's Disease
- Schizophrenia
- and others



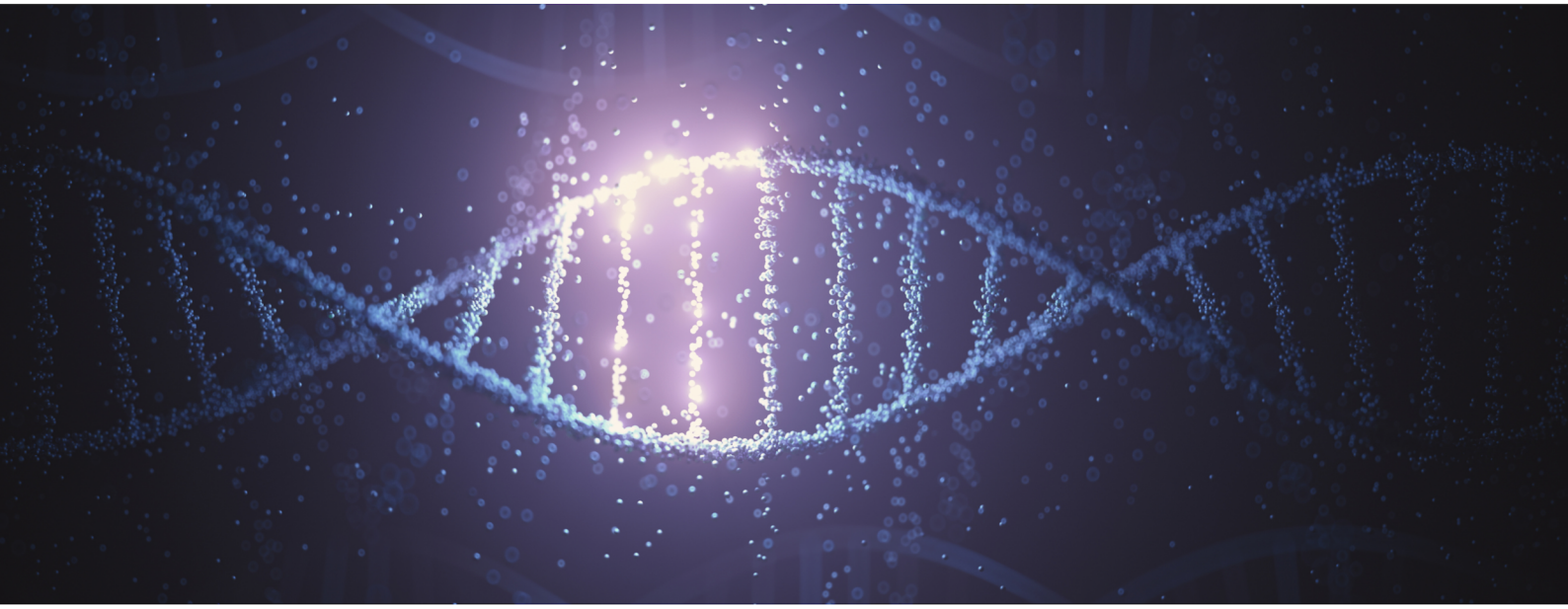
Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is a rare, progressive neurological disease caused by pathogenic variants in the CSF1-R (colony-stimulating factor-1 receptor) gene. These variants cause white matter to waste away. This is called leukodystrophy and it leaves behind lesions of damaged tissue.

ALSP is estimated to account for between 10 to 25% of adult-onset leukodystrophies. Lesions on white matter lead to major changes in personality, thinking, and muscle function.

Eventually, the lesions in the brain caused by ALSP progress to cause dementia, ultimately declining brain function into unresponsive wakefulness syndrome (i.e. vegetative state, impaired consciousness).

Symptoms of ALSP overlap with many other neurological conditions, which makes it difficult to diagnose without genetic testing. As with many rare genetic conditions, the symptoms of ALSP can vary considerably from one person to the next even within the same family.

UNDERSTANDING CSF1-R



UNDERSTANDING CSF1-R

ALSP is caused by an abnormal CSF1-R gene variant that codes for colony-stimulating factor-1 receptors found on many cell membranes, including the central nervous system (CNS), which includes the brain and spinal cord. This receptor plays a role in cell growth and cell specialization where cells take on specific functions in the body. Without a normally functioning CSF-1 Receptor, structural changes to the nerve cell, or neuron, occur eventually. The portions of neurons that transmit signals to the next neuron are called axons and they are typically coated in a white covering, called the "myelin sheath". In leukodystrophies, such as ALSP, this myelin is destroyed, damaging the neurons and their function. Immune cells, called macrophages and microglia, are also impacted without functioning receptors leading to macrophages destroying myelin and microglia unable to maintain healthy brain cells.

Inherited variants in CSF1-R associated with ALSP are inherited in an autosomal dominant fashion. This means only a single copy of the disease-causing genetic variant is necessary to cause ALSP. The altered gene can be inherited from either parent in an autosomal dominant fashion, or it can be the result of a new variant in the affected individual, known as a de-novo variant.

If the gene is inherited in an autosomal dominant fashion, there is a 50% chance the affected individual will pass the altered gene to their child, with the risk of inheritance being the same for all genders.

De-novo variants are those that happen by chance and have never before been present in the family. De-novo cases are also referred to as a sporadic rather than an inherited case of ALSP.

DISEASE PROGRESSION

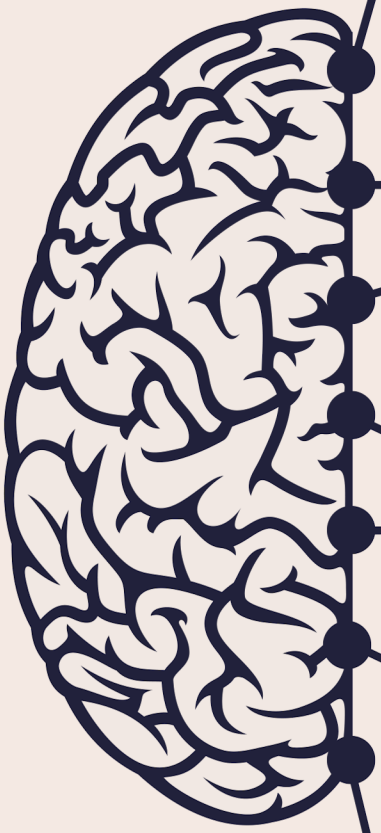
SIGNS AND SYMPTOMS OF ALSP

EARLY SYMPTOMS

ALSP may initially cause psychological, cognitive, behavioral, or motor changes, such as difficulty walking, falling, and slow movements. As the condition progresses and brain lesions become more severe, the combination of psychological, cognitive, and motor symptoms also increases in severity. The speed and initial symptoms of the disease vary among individuals, even between family members with shared familial inheritance.

PSYCHIATRIC CHANGES

ALSP can cause psychiatric changes like alterations in personality, the onset of anxiety, depression, apathy, irritability, disinhibition, and food cravings. The condition can also lead to cognitive impairments, such as dementia, memory loss, aphasia, apraxia, poor attention, judgment, problem-solving, and impulse control.



IMPACTED PYRAMIDAL SYSTEM

Within the brain, ALSP causes degeneration in the pyramidal tracts, which control nerve fibers responsible for voluntary movement. The resulting symptoms vary spanning overactive reflexes (hyperreflexia), stiff muscles (hypertonicity), muscle spasms (spasticity), weakness of one side of the body (hemiparesis), or all four limbs (quadriparesis), reduced coordination, changes in vision, difficulty walking, swallowing, and slurred speech. Additionally, it can lead to heightened emotional responses, including inappropriate laughing or crying.

PARKINSON'S-LIKE SYMPTOMS (a.k.a. Parkinsonism)

Symptoms associated with Parkinson's disease like increased muscle stiffness, tremors, slow movement (bradykinesia), shuffling gait, and reduction or loss of facial expression, are also symptoms of ALSP. Parkinsonism is not helped by medications that increase dopamine levels, which would improve symptoms in Parkinson's disease, therefore excluding Parkinson's disease from the diagnosis.

SENSORY CHANGES

Changes to sensory nerves make it more difficult for patients to sense pain, touch, vibration, and changes in body position. Frequently, patients struggle to recognize the right or left sides of their bodies.

SEIZURES

Approximately 30% of patients diagnosed with ALSP experience seizures.

LATE STATE SYMPTOMS

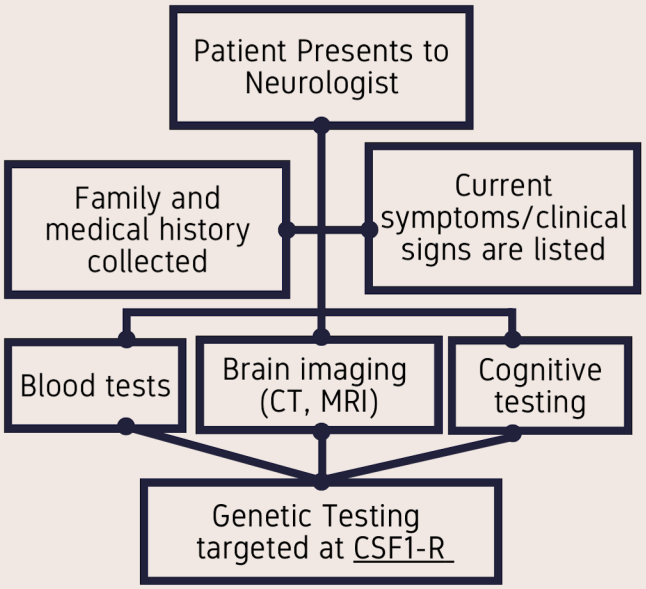
The progression of the disease forces patients into a position where they can no longer walk or speak and require total supportive care to complete all daily living functions. Loss of independent control of bladder and bowel sphincter function is common at this stage. Pneumonia is the most common cause of death in ALSP patients.

DIAGNOSIS & GENETIC TESTING

How is ALSP Diagnosed?

The diagnosis of ALSP is typically made by a neurologist and is confirmed through genetic testing to identify a CSF1-R gene variant.

Family history, clinical signs, cognitive testing, and brain imaging can also help raise suspicion for the disease. MRI and CT scans can show specific patterns of brain deterioration, such as white matter lesions in the frontal and parietal lobes of the cerebrum, thinning of the corpus callosum, and small calcifications.



GENETIC TESTING

Genetic testing offers benefits regardless of the results. It can remove uncertainty and help informed decision-making.

A negative result can spare patients from unnecessary checkups and screenings, while a positive result can guide them toward available prevention and treatment options.

Early diagnosis of ALSP offers investigational treatments, observational studies, and clinical trials.

There are now treatment options available and neurologists can offer testing options through numerous genetic testing labs.

PLEASE NOTE:

Genetic counseling is recommended for patients and families to understand ALSP genetics and progression and to receive psychosocial support.

For more information, please visit: www.CloverGenetics.com

Genetics Support Program

What is this program?

This is a genetic counseling and testing program where eligible individuals may qualify for ALSP genetic counseling and testing services. These services are provided by the qualified genetic counselors of Clover Genetics in collaboration with referring physicians, while the cost is covered by Sisters' Hope Foundation.

Who qualifies?

Eligible patients are those who meet the following criteria:

- ✓ Over the age of 18
- ✓ Has a family history of ALSP
  OR
- ✓ Showing symptoms of ALSP
  AND
  Has established care with a neurologist

- To determine eligibility, please visit: www.CloverGenetics.com/alsp
  Find a link to the qualification checker at the bottom of the page, or scan the QR code to the right for direct access.

- Final qualification decisions will be made by Sisters' Hope Foundation following your registration for genetic counseling services using your eligibility code.

The Process

1. Patient reviews eligibility criteria
2. Patient completes online qualification checker for their registration code
3. Physician faxes referral form and clinical notes to (412)465-6050
4. Patient schedules genetic counseling and discusses genetic testing options
5. If appropriate, Clover Genetics will coordinate genetic testing in collaboration with the patient's physician team
6. Follow-Up Appointment:
   Discuss results, familial Implications, and next steps. A report is faxed to the referring provider.

TREATMENTS, TRIALS & RESEARCH

STANDARD THERAPIES

No FDA-approved treatments exist for ALSP at this time. Symptom management is the current focus for patients, as brain damage is not reversible. Medications such as anti-epileptics, muscle relaxers, and antibiotics may be prescribed to manage seizures, spasticity, and infections, respectively. Anti-depressants may be used for psychological symptoms but have limited effectiveness. Anti-psychotics may be prescribed for aggression, but side effects can be problematic. Nutritional supplements and physical therapy may be recommended to slow overall decline and maintain optimal health. Research is ongoing to identify more effective treatments.

INVESTIGATIONAL THERAPIES

As of the beginning of 2022, bone marrow transplantation is the first and only available potential treatment to modify the ALSP disease course. Results vary between each patient, but in some cases, bone marrow transplants have slowed the progression of motor and cognitive symptoms of the disease. Bone marrow transplants are thought to be beneficial for some individuals with ALSP by providing new immune cells from donors with normal CSF-1 receptors to develop and increase levels of microglia in the brain.

OBSERVATIONAL STUDIES

Vigil Neuroscience is conducting a Natural History Study. More information can be found by scanning the QR code to the left, or by contacting trials@vigilneuro.com

The Myelin Disorders Biorepository Project (MDBP) collects and analyzes clinical data and biological samples from leukodystrophy patients worldwide to support research. Scan the QR code on the right to learn more.

CLINICAL TRIALS

Current clinical trials are accessible at: https://www.clinicaltrials.gov.

For information about clinical trials being conducted at the NIH Clinical Center in Bethesda, MD, contact the NIH

Patient Recruitment Office: Toll-free: (800) 411-1222, TTY: (866) 411-1010, Email: prpl@cc.nih.gov.

Information about clinical trials sponsored by private sources, visit: https://www.centerwatch.com.

European clinical trials can be found at: https://www.clinicaltrialsregister.eu/.

MEDICAL EXPENSES

MEDICAL EXPENSE & TRAVEL REIMBURSEMENT PROGRAM

Sisters' Hope Foundation provides financial assistance to ALSP patients. The program operates as needed and provides financial support for medical expenses like co-pays, deductibles, and services not covered, or services denied, by insurance companies, including medical travel expenses.

What we can help with:

- Treatment-related co-pays, deductibles, and services that are not covered by insurance
- Prescription and over the counter medication related to prescribed treatment
- Medical equipment including canes, walkers, wheelchairs, and incontinence products
- Travel expenses directly related to a clinical neurology appointment within the United States or within a pre-approved location.
  - May include; airfare, hotel, rental car or rideshare, food and drinks.

Eligibility Criteria

To be eligible for Financial Assistance, you must:

- Be a citizen or permanent resident of the U.S. or U.S. territory. Exceptions may apply and will be approved on an as needed basis.
- Have medical insurance and provide proof of insurance.
- Have an ALSP diagnosis confirmed by a positive genetic test report providing proof of a CSF1-R variant.

Exlusion Criteria

- Due to the extremely high cost of certain medical procedures including bone marrow transplant, SHF is not able to offer financial assistance when insurance denies coverage for this procedure.
- Medical insurance premiums are not an eligible expense for reimbursement.

***Note:**

These programs are for patients and their families who reside in the United States, but exceptions will be reviewed. SHF's ability to help outside of the US is limited, but all requests will be thoroughly reviewed and considered.

HOW TO APPLY

HOW TO APPLY

1 Collect the following items:

- ☐ Proof of ALSP diagnosis provided by genetic testing.
- ☐ Proof of Medical Insurance, including Medicare/Medicaid.
- ☐ Name of treating physician.
- ☐ Direct payment to medical provider **OR** Reimbursement for payment
  - ○ Proof of payment (receipt, bank or credit card statement, cleared check).
  - ○ Copy of unpaid invoice, bill that includes the exact treatment or service.
  - ○ Copy of Explanation of Benefits (EOB) from your medical insurance company.
  - ○ Copy of unpaid invoice, bill that includes the exact treatment or service.
  - ○ Copy of Explanation of Benefits (EOB) from your medical insurance company.

2 E-mail the foundation:

- ☐ heidi@sistershopefoundation.org and provide all the items you've collected above

3 Decisions

- ☐ You will be notified via email when a financial determination has been made. The financial assistance program is made possible by sponsors and donations to SHF.
  Financial assistance is not guaranteed and is available on a first-come, first-served basis.

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This information will not be shared and is for verification purposes only.

Benefits and Taxable Income

As a charity, SHF is exempt from federal income tax and individuals who receive assistance from a charity to meet their personal needs do not generally have to pay federal income tax on the value of the assistance they receive. It should not affect your ability to receive financial assistance from the government or affect your income taxes. Any questions or concerns should be discussed with a tax professional.

Frequently Asked Questions

What is a Co-Pay?

A set fee for covered health services that you pay after meeting your deductible. The amount varies depending on the specific service within your insurance plan.

What are some expenses that are necessary and may be eligible for reimbursement?

Expenses for ALSP may include co-pays, deductibles, and co-insurance for CT and MRI scans, treatment-related costs, prescription drugs, incontinence products, and mobility aids. Visits to a specialist neurologist may also be necessary.

Who will be my care team?

You have complete freedom to choose doctors, providers, suppliers, insurance companies and treatment-related medications.

Please note:

As a non-profit organization, our program depends on sponsor generosity and may be modified or discontinued if funds become limited or unavailable.

STAY CONNECTED

REMAIN INFORMED & GET INVOLVED

"The future is not guaranteed to any of us; especially those suffering from a rare, neurodegenerative disease. Even when treatment options are available, complications may arise. Planning and preparing for the future can alleviate undue stress, which is important for you and your loved one."

~ Heidi, President & Founder, Sisters' Hope Foundation

STAY CONNECTED AND UP TO DATE

Visit https://www.sistershopefoundation.org created for those diagnosed with ALSP, their caregivers, family members, physicians, and others interested in staying updated on the newest information available for ALSP. Follow our social media pages and sign up for the SHF Newsletter to be informed of guest speakers and presentations.

- Social Media:
  - Facebook: @SistersHopeFoundationALSP
  - Twitter: @SistersHopeALSP
  - YouTube: Sisters Hope Foundation
  - TikTok: TikTok.com/sistershopefoundation
  - LinkedIn - Sisters' Hope Foundation: https://linkedin.com/company/sisters-hope-foundation
  - LinkedIn - SHF Founder, Heidi Edwards: https://www. linkedin.com/in/heidiLedwards
  - Instagram: sistershopefoundationalsp
  - Pinterest: Pinterest.com/SistersHopeFoundation
- Support Groups;
  - Available virtually each month via Zoom or our online community (Facebook = @SistersHopeALSP).
  - Family and Caregivers Support Group for HDLS/POLD and ALSP (https://www.facebook.com/groups/196377142318807)

GET INVOLVED

For those living with ALSP, getting involved and raising awareness about the disease has proven to be a powerful way to enhance their sense of purpose and connection to others. You, too, have the chance to transform your experiences into a source of inspiration for others and make a meaningful impact in the fight against ALSP. Sisters' Hope Foundation provides numerous opportunities to join the fight, raise awareness, and contribute to the cause:

1. Advocate for the condition and raise awareness
2. Become a leader, chair a committee, volunteer at an event
3. Support fundraising or host your own fundraising events

Contact Sisters'Hope Foundation to learn more about programs available for people living with ALSP: info@sistershopefoundation.org

LIVING MY BEST LIFE DAILY

HOPE FROM A CARRIER

I have ALSP - Patient story | Serena, carrier of CSF1-R gene variant

My story begins with my younger brother's diagnosis of HDLS/ALSP when he was 54. His most noticeable symptom was seizures. Family that lived nearby eventually took him to the Mayo Clinic in Rochester, MN when other changes became apparent. No diagnosis was given during that trip. A relative saw an unopened letter on his kitchen table and questioned him about it. The relative received permission from him to open it and learned of his diagnosis. Not long after I learned of the letter's contents. When I called my brother to visit with him about the contents of the letter, he was very hazy as to what his diagnosis was. That was when I started researching what HDLS/ALSP meant for my brother and the rest of our family. Four to five years ago there was very little information available about HDLS/ALSP for patients and their families that was not research findings phrased in medical terminology. What little I found gave me a sense of impending doom. What an awful disease. Not only would it take your body, but it would also take your mind. After onset, life expectancy on the average was seven years. No treatment. No cure. No way to prevent it. Worse yet, it was autosomal dominant. The children of a parent that had the mutated CSF1-R gene had a 50/50 chance of passing it on. Yikes! I started reading research papers/findings. I learned more about the disease. The more I read, the less Greek the terminology seemed. What at first seemed incomprehensible became understandable. If I came across a term I didn't know, I looked it up. I concluded that if I had a difficult time finding information, so would others in my family's shoes.

Prior to my brother's diagnosis, two of our first cousins had become nursing home residents. Each entered a nursing home at 64 years of age for differing reasons. Our cousin, who I will refer to as J, had the diagnosis of frontal lobe dementia thought to have been caused by excessive exposure to pesticides. Which made perfect sense as he was a farmer. It was after my brother's diagnosis that my cousin's family began to wonder if J had HDLS/ALSP. They planned to have him tested. His blood test indicated that he too had the mutated CSF1-R gene. With J's diagnosis it was now known that the disease was being passed down the paternal side of our families. J's dad and our dad were brothers. J's diagnosis also verified that my brother's gene wasn't a new variant.

Families cope with the news that there may be a genetic disease in the family in various ways. When families live in a small, rural community it is especially interesting. Some family members will openly discuss the disease. With others it becomes a family secret. Not to be acknowledged or spoken of. The grown children and grandchildren are not informed. Other family members are kept in the dark. The disease does not exist. If the topic of the disease is brought up…. deny that the disease has affected you and yours. I get why this happens. Family members who are young need not be traumatized. Nosy neighbors and community members don't need to know all your business. No one wants to carry the stigma of a genetic disease. I saw it happen both ways with my relatives. Some openly discussed the disease. Others denied that their family member/s had HDLS/ALSP. Right or wrong, I chose to openly speak of the mutated gene and of the disease associated with it. My adult children learned early on that their uncle had a genetic disease and that I had a 50/50 chance of also having the gene and the disease.

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A few years down the road various health concerns caused me to wonder if I too had the disease. My husband and I priced long-term care insurance and term life insurance. We discussed what would happen if I had the gene. We discussed what assisted care options were available to us where we lived. Serious conversations for a couple married only a few years. Even though I had suspicions, I hesitated when it came to verifying one way or another as to whether I had the mutated CSF1-R gene. Finally, I asked my physician to plan for me to be tested. Initially, he was hesitant. It was not until I provided him with more specifics about my brother's diagnosis was, he willing to refer me to a genetic counselor. A disease as rare as ALSP means you become an educator when you meet with your healthcare provider. Interaction with a genetic counselor is interesting to say the least. I could tell that she was trying to determine if I could mentally cope with the knowledge of knowing the test results if they came back positive. At the end of our online virtual consultation, she approved my being tested. A test kit arrived at the medical clinic near me. Blood was drawn and sent back to the lab where the kit was ordered from. It seems like it took months for my results to arrive at the genetic counselor's office. Our conversation was brief. The result of the test was positive for the mutated CSF1-R gene. No matter how prepared you think you are prepared to hear the worst, the worst still is a hard hit. I am going to be honest; I had hoped that the test result would come back negative. I coped, but my coping was to make end of life plans. I confided in J's sister about my results. I told her that I intended to contact Mayo in Rochester which is the hospital where my brother receives care. She suggested Florida Mayo as she had read that it was the Mayo Clinic researching the disease. I started searching and came up with the name of the neurologist /researcher at the Florida Mayo who was researching HDLS/ALSP. Between my cousin and I we contacted Dr. Wszolek and his assistant. My cousin helped her family make arrangements for her siblings' brains to be donated to Mayo. Yes, you heard correctly the term siblings. Around the time I was tested, J's sister who went into the nursing home at 64 was tested. She too, was found to have HDLS/ALSP.

I called Florida Mayo to make an appointment with Dr. Wszolek. I dont recall all the details but with some effort I was able to make the trip to Florida Mayo as part of a research project in June of 2021. Expect the following when you go through an assessment to determine if you have the disease. Blood is drawn, urine is taken (I was handed a jug to fill over a 24-hour period), a spinal puncture is done, an MRI (possibly with contrast) and a CT scan done, a mental assessment is given by a psychiatrist (I think it was the Montreal Dementia test), The neurologist also administered a physical exam and spent time visiting with me. I should mention that by the time I arrived at Mayo in June I had processed and had come to terms with my mortality. I had made my peace with what my future held. If anything, my belief in God had been strengthened.

It was around this time that I reached out to the Sisters'Hope Foundation. Heidi quickly responded. It helped to have support from another family who had knowledge of the gene and the disease. It was a comfort to communicate with someone whose family knew intimately the same disease.

The results of the tests came back as a surprise to me and my husband. They were, I think, also a surprise to Dr. Wszolek. Dr. Wszolek informed me that I was only the second person he knew of that had the gene, but not the disease. There was no sign in my brain of the disease. July 2021 Dr. Wszolek visited my hometown where my brother and many of my cousins live. He spent time at the local nursing home where my two cousins reside. He ran some tests on them. Later that afternoon Dr. Wszolek met with myself, my brother, our children, our cousins, their children, and grandchildren. Interestingly, nursing home staff from the nursing home where my cousins resided also attended Dr. Wszolek's presentation regarding the mutated CSF1-R gene and the disease ALSP/HDLS.

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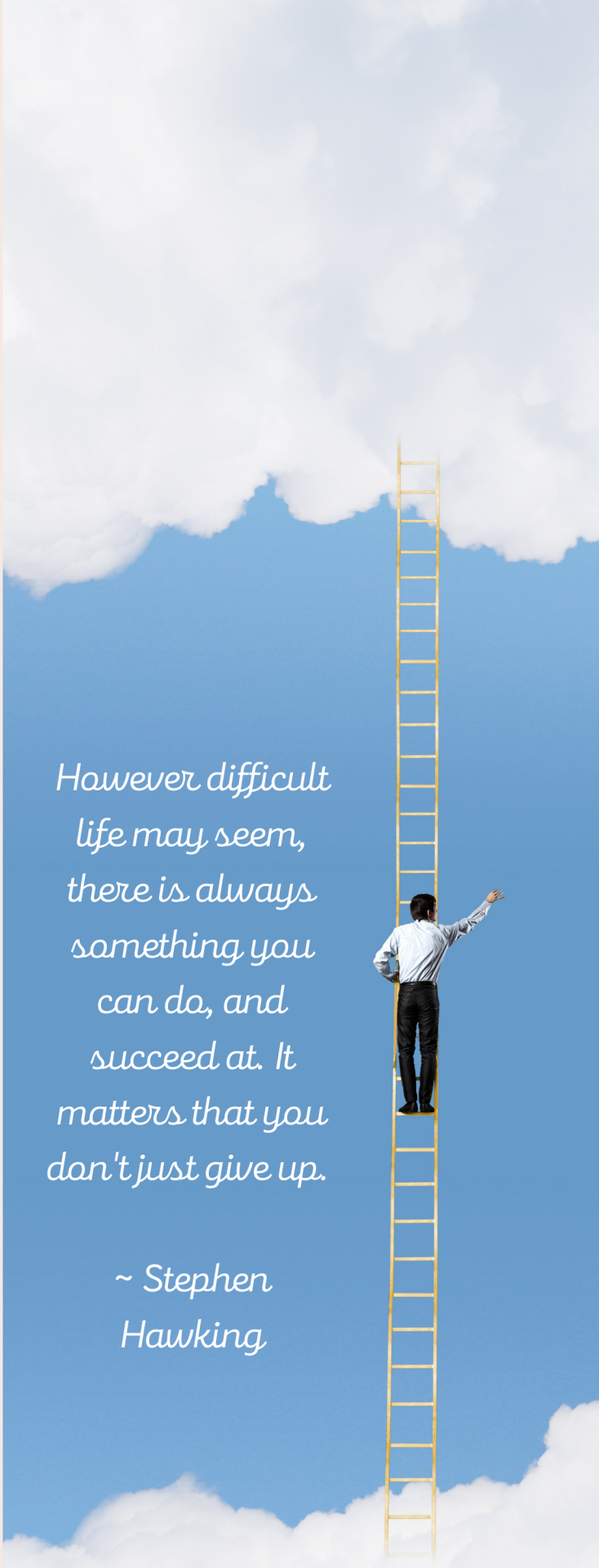
November 2021 cousin J died at the age of 72. His obituary stated that he died of a genetic disease.

In January of this year, I returned to Florida Mayo as part of another research project. It is a two-year natural history study. Once again, the test results were good. Dr. Wszolek and his colleague, Dr. Tipton, both stated that I may never develop the disease. At this point I am referred to as an asymptomatic carrier of the CSF1=R gene. My brother is now also part of the natural history study of CSF1-R gene and HDLS/ALSP. My brother still can live on his own. He has family and friends nearby that assist him as needed. One of the advantages of living in a tight knit rural community. My brother and I both believe that doing something is better than doing nothing. Perhaps through us, more can be learned as to how this genetic disease can be treated. My brother and I both have adult children. My brother also has grandchildren. We have a reason to assist where we can further the research and development of a successful treatment of ALSP. Prior to my examination at Mayo, I presumed my life with the CSF1-R gene meant that I soon would become mentally and physically incapacitated with a life expectancy of approximately seven years. I have the gene, but apparently not the disease. I am considered an asymptomatic carrier which is not typical for someone of my age (63). Dr. Wszolek finds my disease resistant state an intriguing puzzle. What has protected me from developing the disease? My son posed an interesting question, could there be others out there with the gene who havent been tested to learn if they have the gene? If my brother hadnt been found to have the disease, I would not have taken the genetic test. Maybe, it means others are out there living with the gene, and who may never develop the disease.

I know firsthand that when you or your family member is found to have the CSF1-R mutated gene and/or ALSP that there will be despair. I have a few words of hope for those who are new to the mutated CSF1-R gene and ALSP/HDLS. This is a fairly new disease where research and treatment are concerned. What is amazing is that there is research into this seemingly rare disease. That alone is hopeful. Do not lose faith that a treatment will be developed. If the present treatment/s that are currently in various stages of development are successful, then the future of those with the CSF1-R gene, and the disease, adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) suddenly becomes so much brighter. I have been reminded that tomorrow is not promised to any of us. Take each day as a gift. Live your life fully while you are able.



LOVE, LOSS AND THE POWER OF KNOWLEDGE

PERSPECTIVE FROM AN ASYMPTOMATIC YOUNG ADULT

A 19 year old Patient story | Mason, carrier of CSF1-R gene mutation

One of the realities of growing up and becoming an adult is the day when children are faced with the need of their parents who may be in failing health or require some type of health-related care, and the child's commitment to caring for that parent. Roslyn Carter is a former First Lady of the United States and founder of the Roslyn Carter Institute of Caregiving and has a famous quote on caregiving: "There are only four kinds of people in the world. Those who have been caregivers. Those who are currently caregivers. Those who will be caregivers, and those who will need a caregiver."

Of course, most of us kids feel that we wont be put into a position of having to care for our parents and accepting those responsibilities until late in our lives; maybe when we have started our own families and have a more stable life. In my case, this responsibility came at a much earlier age than most.

When I was 16, my mom began to have difficulties with her speech. It was very minor, and I didnt really notice it at first. When I did, it didnt alarm me, and I thought that maybe she was just tired from work. At that time, it never occurred to me that there could be something medically wrong with her. She started misplacing words or mispronouncing words that began with an "s" or a "c". My mom and I had a great relationship, and we would often make fun of each other in a harmless way, especially when one of us had a slip of the tongue, but this seemed different because it was occurring more often than in the past. When I asked her about it, she would just chalk it up to being tired from work or the effects of her asthma, and at the time I accepted and didnt pressure her any further. After a few months passed her word slip ups not only happened more often, but they seemed to be getting worse and she was having a hard time with her speech in general. During this time, she would mumble through entire sentences and not enunciate any words at all; it was clearly different than it had been even a few months before. She did not think anything was wrong and continued to blame work fatigue or asthma as the cause. Everything else in her life seemed normal: she was still working, driving, and taking care of herself and me. I agreed with her until my Aunt Heidi, who is also my mother's twin sister, asked me if I noticed anything different about my mother's behavior, particularly her speech. I shared my observations with my aunt, and I suddenly became more concerned because someone else noticed these changes. We finally got Mom to agree to a check-up and took her to the hospital. She was given an MRI and CT which resulted in the observance of some abnormalities that they were unable to accurately identify but knew that under normal circumstances should not be observed. Although the doctors were not forthcoming with specific information, given our family's history, my aunt and I had a guess of what might be wrong. My grandmother, great aunt, great uncle, my mother's older sister, and my Aunt Heather all were diagnosed and died from complications from adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP). Both Aunt Heidi and I were sure my mother was showing the beginning signs of this disease. A few months later, she was diagnosed with ALSP after receiving the results of her genetic test. Two months later, she had a seizure at work. It was a focal seizure that only affected the left side of her body. While in the hospital with her seizures she was given an anti-seizure medicine and sent home a few days later.

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Sisters: Holly, Heather, and Heidi

This entire incident made me very anxious because I felt this was the next step in her battle with ALSP and I knew from watching my grandmother's journey with the disease that our lives were about to change in a big way. It began to be clear that my mother's disease was progressing quickly, and she would need some type of caregiver assistance. As her only child I knew it would become my responsibility.

This was all happening at the time when COVID-19 became widespread and was starting to shut everything down, which meant I was home from school full-time. I was still responsible for my schoolwork, but my mother's needs became a priority, and I chose to spend time away from schoolwork caring for her. Most of my work was doing domestic chores like cleaning, cooking, doing the dishes, walking the dog, and taking my mother on errands. Due to the seizures her license was revoked. Caring for my mom was all new to me and at times I questioned whether I could do everything to help her while I also focused on school. I realized that I had no other choice. she needed help, I was available, able and an only child, end of story!

As soon as things appeared to be settling into a manageable routine for the two of us; everything blew up. My mother had completed all her initial testing, including an MRI and memory and cognitive tests at University of Pennsylvania. They informed us of a bone marrow transplant program at the University of Minnesota Medical Center available to my mother and my Aunt Heather. Heather had been diagnosed with ALSP before my mom and was in the final stages of her battle with the illness. The bone marrow transplant was not a cure and had some risk involved, but as a family we felt it was worth Heather entering into the program. One month into the transplant program, Heather had a heart attack which put her in the ICU and during which her body rejected the bone marrow. Based on Heather's difficulty with the transplant I felt strongly about my mom not being involved. Sometimes being a caregiver means having hard discussions with the people you love and want to protect. I told my mom that if she entered the bone marrow program it is likely that she would suffer the same fate as her sister and after spending four months alone in Minnesota she would likely die away from home. The alternative would be to go back home and be around family and friends for her final days. My mom decided to come home. While living back home, Mom had good days and bad. The good days were spent with those that loved and cared for her doing things she enjoyed like going to the beach, being outside, and sitting on the couch and watching lots of TV. The worst day happened when Aunt Heather passed away while still at the University of Minnesota Medical Center; ironically this would have been the same day that my mom was to begin the bone marrow transplant program.

Part of what made my mom's last days more enjoyable was when one of Aunt Heidi's neighbors, April, joined us as a caregiver. She was great, had a ton of energy and compassion, and helped me out a bunch. And while my mom seemed to respond in a positive fashion to this new situation, this was perhaps the hardest time for me. COVID lockdown inside a small space, cold weather which kept us inside, my mom's progressive disease, isolation from my friends, and the ongoing pressures all caregivers experienced were a huge emotional burden for me. I had nobody to talk with or activities to help alleviate the emotional strain.

The progression of the disease became obvious when the day after my Aunt Heidi launched Sisters' Hope Foundation to help support ALSP patients and their families, My mom became quite sick in the aftermath of the event. The next day April and I noticed that Mom had slept in later than usual. After spending the week in the hospital, my mom returned home on hospice care.

One of the things that was a departure from all the stress of caring for my mom was my upcoming graduation from high school; an event she desperately wanted to attend.

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Holly, Heather, and Heidi

All my mom wanted to do was see her only son graduate from high school. She lived for this moment, knowing she succeeded in raising her only child and set him up for his future. She was able to attend my high school graduation, with assistance. It was not without its challenges but ended up being a good time and wonderful memory for me. She was excited, but I wasnt sure if she would make it as her condition continued to worsen, including more frequent seizures and the addition of home hospice to her care. She made it to my graduation and for that I was extremely grateful, but bittersweet at the circumstances. Its interesting as I think back about that particular chapter in our lives and how we both began to detach ourselves from different aspects of our lives. Mom from her present physical being which had changed so drastically in the space of a couple of years and me letting go of the person she had become. I couldnt think of her in the present and kept remembering her past self. A few weeks after attending my high school graduation my mom passed away on July 20, 2021.

I took my moms death hard, especially how she died and watching her slip away the way she did. It also came at a time in my life where she and I had become good friends and we would have had so much more to share had she lived. One of the hard lessons I learned throughout this experience was the ongoing effect ALSP had on our entire family and how I might also become symptomatic one day. One of the people who was a huge help to me in the final days of my moms life and the weeks after she died, was my Aunt Heidi. She and I talked a lot and one of the things we discussed was whether or not I would want to know if I carried the Variant. From what we know about ALSP, it could be 20 or 30 years before I become symptomatic. I felt strongly that I needed to know for sure. I decided to get tested to see if I carried the CSF1-R variant which causes ALSP. The process was surprisingly quite simple: I received an at-home test where I swabbed the inside of my mouth and sent it to a lab in California. During the approximate two weeks while I waited for the results, everyone was encouraging and telling me that I would test negative, but somehow, I knew, deep down, that I carried the variant. It was just a suspicion and gut feeling. I knew from familys experience that if you tested negative, the lab would share that information with a simple phone call. Those who tested positive received a message to schedule a Zoom call to review the results. My fear and inclination came true when I received an invitation for a Zoom call with the genetic counselor.

I have decided to just live my life as best I can, which means continuing my plans to attend and graduate from college – something my mom and I both shared. I also decided to enroll in an ALSP Natural History Research Study at the Mayo Clinic in Jacksonville, Florida, close to my fathers home. I had an MRI and some bloodwork which I will repeat every six months. The goal of this study is to compile data of people who have tested positive and use that information for future research and hopefully drug development programs. Taking part in the Natural History Study also allows doctors to monitor me for any disease related changes. If and when this occurs, we will be able to take immediate action. I am the first person in my family to receive a positive CSF1-R genetic test and have no symptoms. I have lost five family members to this disease, and they have taught me that knowing my genetic status is no longer a death sentence. I am now in control of my future. A future where as soon as the doctors observe changes in my exam and MRI, I have an option available, and hopefully more options in the future.

Its important that patients and caregivers share their stories with one another. Connecting with others who are going through what my family experienced is sometimes the knowledge they need and knowing there are others in the same situation is comforting. My mom lived life to the fullest, she loved me with every ounce of her being and she would want me to advocate every day for early detection of this disease, so I have a fighting chance of living a long and fulfilled life.

SHARING YOUR DIAGNOSIS

**Inspired by the Michael J Fox Foundation for Parkinson's Disease.

"I have no choice about whether or not I have Parkinson's. I have nothing but choices about how I react to it. In those choices, there's freedom to do a lot of things in areas that I wouldn't have otherwise found myself in."

- Michael J. Fox

Discussing ALSP openly is a personal decision that depends on your personal comfort, the individual involved, and the specific circumstances. However, disclosing your diagnosis can alleviate some of the associated burdens. An ALSP diagnosis rarely solely affects the person diagnosed. Family and friends can find it challenging to come to terms with their loved one's diagnosis. It is crucial to acknowledge that while the symptoms of ALSP may be experienced individually, the emotional impact extends beyond just yourself. Communicating effectively can minimize misunderstandings and promote common ground.

Your Partner/ Spouse

You and your partner are a team. Neither of you can truly predict how this diagnosis will impact you as individuals or as a couple. Even if you have friends or family members who have ALSP, your own experience will be unique and distinct. Be open and honest about your diagnosis and its implications. Confronting the challenges of the disease together can strengthen your relationship and make it more resilient.

Your Children

When discussing your ALSP diagnosis with your children, it is crucial to be reassuring. Even if your symptoms are subtly noticeable, your children are probably already worried, regardless of whether they mention it or not. The maturity of your children will dictate how open you can be with them about the situation.

Teenagers already experience a lot of emotional and physical changes. Therefore, it's important to be transparent, open to questions, and honest in your responses. If you don't have an answer, be willing to share this; you can research online together to find the information needed. Empowering teenagers with a sense of control can help them navigate this new aspect of their lives.

It is crucial to balance acknowledging the reality of ALSP as a progressive and incurable condition, while also recognizing your current, potentially mild, symptoms. However, it's also important to embrace the optimistic reality that scientists are making remarkable strides towards breakthroughs.

Keeping a positive outlook for both yourself and your children is important. The uncertainty around ALSP can feel overwhelming. Positivity, a desire to learn about the condition and finding ways to cope with your new diagnosis can significantly contribute to making your ALSP journey easier for you and your loved ones, both physically and psychologically.

Friends and Acquaintances

Your friends' reactions to your diagnosis will vary. Those with family affected by ALSP, or a similar disease, may have particularly varying levels of understanding based on their own experiences and may not know what your diagnosis means for you.

Your friends may offer assistance without knowing your specific needs. To improve everyone's comfort, it helps to provide clear communication about the type of help you require, such as a ride to an appointment or picking up groceries. If you don't need assistance at the moment, it's perfectly fine to politely decline by saying, "No thanks; not now."

Some individuals might worry about asking you how you are doing, while others may ask, but prefer not to delve into the details. Sharing in a few words how you feel and then changing the topic, can put them at ease.

Parents

Sharing your diagnosis with your parents won't be easy, as it can be equally difficult for them to process the news. Parents can feel a lot of guilt for not being able to shield you from the disease, leading to frustration and a sense of powerlessness. Their initial reaction may be denial, which might feel to you like a betrayal. However, be patient. With time, they'll be as supportive as they can be.

ALSP will occupy your thoughts frequently. Joining a support group or talking to a counselor can provide an outlet for discussing your diagnosis and well being at length, should you feel the need to do so.

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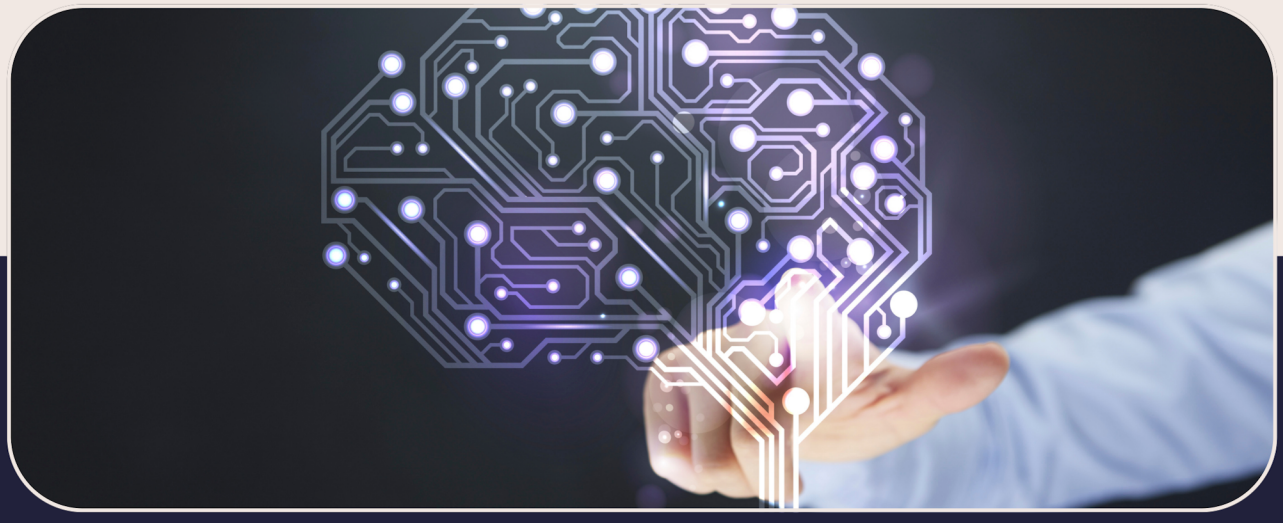

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