SUMMARY OF PETITIONERS' ARGUMENT

NurOwn marries the promise of stem cell therapies with the science of neurotrophic factors. In the 2016 documentary, *"Die Trying: the Battle for ALS Treatments,"* Mayo Clinic's Dr. Tony Windebank described the innovative mechanism of action of Brainstorm's autologous mesenchymal stem cell therapy enhanced with neurotrophic factors (MSC-NTF):[1]

> *"One of the important steps in the Brainstorm trial is that the cells come out of the bone marrow and then they're treated in a way that makes them protective for nerve cells. So they're kind of **enhanced stem cells**... He'll have a spinal tap and that allows us to inject the stem cells into the fluid around the spinal cord. When you have an injury anywhere in your body, those cells will move out of the bone marrow and they go to the area that's injured and they aid the healing process. Now we're taking these healing cells and we're putting them into the nervous system, so we're putting them into a place where they don't usually go."*

(See documentary at 12:45).

Developed by world-renowned neurologist and researcher Eldad Melamed, NurOwn combines the restorative powers of stem cells with the regenerative powers of neurotrophic factors. One neurologist explained that neurotrophic factors are like "Miracle-Gro" for your neurons. But the problem in the past has been the delivery system. Neurotrophic factor trials have failed as oral or IV delivery systems couldn't overcome the obstacles presented by the blood brain barrier. Uniquely, NurOwn uses your body's own stem cells as an innovative delivery system for those neurotrophic factors. Once injected directly into the CSF, your stem cells work like a Fed Ex truck, delivering nano-packages of neurotrophic factors and immunomodulatory cytokines directly to the sites of the motor neurons damaged by ALS.

Almost immediately those "healing cells" go to work. Within a few days, people reported that NurOwn improved how they felt and functioned. And with more doses, we now have proof that NurOwn improves how long they survive. (See details of that survival data starting on page 18 of this Petition).

When people are dying, they know when a drug helps them live. When people are becoming paralyzed, they know when a drug helps them move again. And when people can't breathe without a non-invasive ventilator, they know when a drug helps them breathe again. That's what NurOwn did. Patient experiences and real-world evidence should matter.

When world-renowned neurologists like Anthony Windebank of Mayo and Robert Brown of UMass tell the FDA that they saw some patients regain function for the first time in their 40+ year careers of treating people with ALS -- their clinical observations should matter.

[1] Fanous, A. (Producer: HBO VICE News) (2016). *Die trying - The battle for ALS treatment*. [Video]. YouTube.

At the Advisory Committee meeting for NurOwn, Dr. Windebank presented the NurOwn clinical trial data and then shared his expert opinion about the clinically meaningful impact and "progression-free survival" that he observed when people received NurOwn:

> *"I would now like to provide my clinical perspective on NurOwn …. I think this data is compelling & it should be approved…. While not everyone responds to the treatment, there are clearly a SIGNIFICANT number who do. I have clearly seen some people STABILIZE in a way that I have never seen in any other trial.*
>
> *In fact, in the small number of people who participated in EAP & received 6-9 treatments, there were people who STABILIZED while on NurOwn in the trial. In the interval before they were in the EAP -- which was over a year or more in some cases – these participants deteriorated, then again STABILIZED in the additional treatment period. There were some who IMPROVED their score! Other investigators who have been working 'hands on' with the participants in the trial have seen similar responses...."*

When the data demonstrate a clinically meaningful and statistically significant change on those earlier in ALS progression and one of the world's top biostatisticians opines that the totality of the evidence methodology is most appropriate for rare disease trials – his expert opinion should matter.

When an innovative, small pharmaceutical company identifies two dozen first-in-class CSF biomarkers showing target engagement across biological pathways of neuroinflammation, neurodegeneration and neuroprotection – and no one on placebo had these changes – these plausible mechanisms of action and common sense should matter.

But most importantly, when all 10 people in the Expanded Access program significantly outlived or are outliving the ALS natural history, and the trach-free survival data meets or exceeds the survival data supporting Accelerated Approval in rare cancers, this survival data should matter.

Graphic- Survival Data - NurOwn Phase 3 Trial and EAP Data thru June 2025

NurOwn EAP - Trach-free Survival Data*

		Total EAP Population				EAP - Early vs Delayed Start			
SURVIVAL from	ALS Natural History	Survival Range	EAP Survival		△ months	6/10 Early Start (P3 NurOwn)	△ months	4/10 Delayed Start (P3 Placebo)	△ months
Symptom Onset	30.0	60-103 months	Median	85.0	55.0	85.0	55.0	73.5	43.5
			Mean	80.9		85		74.8	
Diagnosis	18.0	51-87 months	Median	78.0	60.0	78.0	60.0	68.5	50.5
			Mean	73.3		76.3		68.7	

1. Traxinger / Glass (2013). Prognosis and epidemiology of ALS: analysis of a clinic population
2. Chio / Traynor (NIH) (2009). Prognostic Factors in ALS: a critical review
3. Knibb / Al Chalabi (2016). A clinical tool for predicting survival in ALS

* No one in NurOwn EAP received a tracheosotomy
10/10 people in EAP survived / are survivng trach-free ≥ 5 years
6/10 still alive as of June 2025 - without tracheostomy

All of these events are unprecedented in ALS history and they merit an unprecedented response from the FDA. That is the remedy we are seeking in this Citizens' Petition.

The ALS community has long been imploring the FDA to customize its regulatory process. Nearly a decade ago, when Matt Bellina was advocating for Right to Try, he too spoke of the clinical trial obstacles to assessing efficacy in a 100% terminal, rare disease with unmatched heterogeneity:

> *"The current FDA Guidelines are preventing innovation…. The problem with ALS and a lot of these cancers is that* ***everybody's a little different. Everybody manifests a little differently. So, you can't compare two patients against each other****. Our current system with the FDA is not tailored to create drugs for diseases like this.* ***ALS is never going to be cured by a one-size-fits-all drug.****"*

In Commissioner Makary's confirmation hearings before Senator Murkowski and in his interview with Megyn Kelly, he spoke about the regulatory process for rare diseases like ALS:

> *"We have to customize the regulatory process to the condition that we're trying to be able to offer hope for… we cannot require two randomized control trials. We have to customize the regulatory process to what we're trying to do. If our goal is to try to provide safe and effective therapies, and I do believe firmly in that approach, I think we can use some common sense to ask some big questions we've never asked before at the FDA."*

Petitioners believe the OCE's Rare Cancers Program is an apt template for how to address rare, terminal, heterogeneous neurodegenerative diseases like ALS. As a cancer patient himself, former Commissioner Gottlieb understood the need for a modified risk-benefit assessment. In his 2018 speech at the Annual Conference of the American Society of Clinical Oncology, he advocated for urgency and regulatory flexibility when the mortality data is ominous.

> *"There are critics who say we should hold drugs back from the market, & demand more pre-market studies proving overall survival endpoints, before we consider approving new drugs. I disagree. And I suspect some of the patients who face long odds -- for whom available therapy gives them just a slim chance of long-term survival -- might also disagree.*
>
> *I had Hodgkin lymphoma. I had a very curable tumor. At the time of my diagnosis, I was told my odds of a cure were 90% or better…. So, I understand why demanding large, pristine studies ultimately serves the interest of patients like me. But my situation was very different than being diagnosed with cancer & being told your chance of surviving five years is 50%, or 30%, or just 10%. Available therapy isn't very promising if that's your circumstance. The ability to access novel treatments becomes more urgent in these circumstances.* ***Waiting 3 more years for another large, prospective, randomized trial to be completed – to confirm highly promising results already observed in an earlier clinical trial -- may not sound as compelling to the patient who faces these long odds."***

People in the ALS community are facing even more daunting odds — they have a 100% chance of dying. Over 50% will die within 18 months and less than 20% have a chance of living five years.

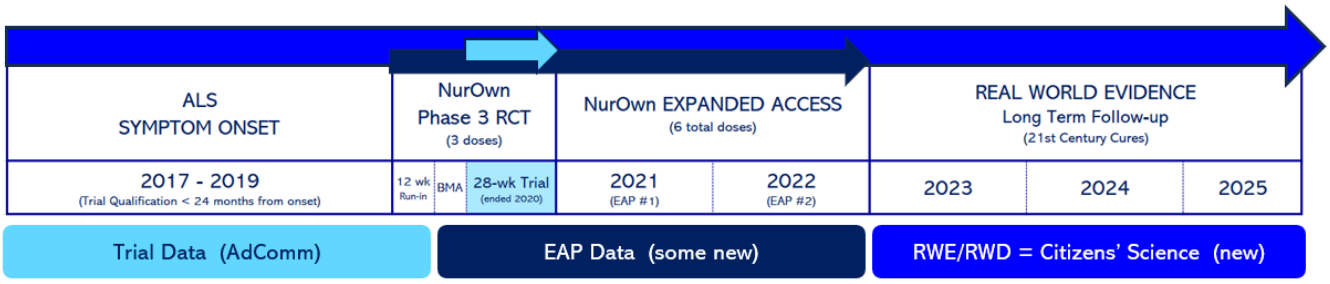
People with ALS can't wait another 3-5 years for yet another double-blinded, randomized controlled trial (RCT). Generations of people with ALS have already died waiting. Now is the time to change that inhumanity. Brainstorm's stem cell therapy is the way forward for thousands of people battling ALS.

In the keynote address at the National Organization for Rare Disorders (NORD) Rare Disease Scientific Symposium earlier in June 2025, Dr. Prasad outlined a framework aimed at accelerating access to therapies for rare diseases. He emphasized the FDA's commitment to approving promising therapies "at the first sign of promise," utilizing surrogate endpoints and regulatory flexibility to bypass traditional efficacy requirements for initial approvals, while relying on real-world data (RWD) to evaluate post-market outcomes. Petitioners submit that this policy framework is directly applicable to the FDA's review of NurOwn.

NurOwn has demonstrated evidence of efficacy in some people for over a decade. The ALS community desperately needs CBER to act on Commissioner Makary's promise to use both common sense and gold standard science; to emphasize urgency and regulatory flexibility; and to honor the spirit of Right to Try by ensuring people dying of ALS have access to promising therapies, while the FDA continues to study the promising therapy in rigorous and informative post-approval monitoring.

We respectfully urge the FDA to apply these principles to its evaluation of NurOwn. We are asking the FDA to consider the "totality of the evidence" from the short 28-week trial; the new evidence from the Expanded Access program; the unblinded real-world data and patient experiences spanning 6 to 8 years; and especially the new survival data that surpasses survival data of cancer therapies granted accelerated approval.

<u>Graphic</u> - NurOwn Totality of the Evidence from Phase 3 and EAP



Following is a summary of both unprecedented new and existing "substantial evidence" supporting our request for NurOwn's approval:

1. New EAP data demonstrating a 5.5 month Improvement in OS as of 2022
2. New EAP data demonstrating a 100% five-year survival rate far in excess of the 20% median ALS natural history
3. New and unprecedented data demonstrating years of improvement over median trach-free survival, as of June 2025
4. New, long-term respiratory function data that demonstrates a significant preservation of breathing function as evidenced by improvements in Forced Vital Capacity and significant extensions in Time-to-Event data for non-invasive ventilation
5. New long-term functional data that demonstrates a significant slowing in ALS progression (as much as 85%), outperforming any ALS therapy currently on the market
6. New survival data that far exceeds the survival data used to support accelerated approval of many cancer therapies
7. New, long-term progression free survival data that significantly outperforms any ALS therapy currently on the market
8. New, long-term functional data that demonstrates an ORR that meets or exceeds the ORR used to support accelerated approval of many cancer therapies
9. New EAP Neurofilament light data that demonstrates a significant decrease in neurodegeneration, and demonstrates a dose-dependent response in both the magnitude of change as well as the durability of those changes
10. Biomarker data that demonstrates target engagement and a plausible mechanism of action supporting accelerated or conditional approval
11. Biomarker data that demonstrates target engagement across ALS disease progression – regardless of ALSFRS-R score – but only in the NurOwn-treated arm, with no similar biological changes evidenced in the placebo arm
12. "Totality of the evidence" demonstrating that NurOwn had a dose-dependent response, with those who received the most doses of NurOwn the earliest in their ALS progression demonstrating the largest magnitude and longest durability of functional response
13. Expert opinions from world-renowned neurologists who opined that NurOwn caused unprecedented stabilization (and some improvements) in ways they had never seen in their 40-plus years as physician-scientists conducting ALS clinical trials
14. Expert opinions from treating neurologists, pulmonologists, respiratory and physical therapists who had never seen similar slowing, stabilization or improvements in function as they observed in clinic with their ALS patients who participated in the NurOwn trial
15. Real-world evidence, real-world data and newly unblinded lived patient experiences and PROs documenting that NurOwn interrupted, slowed and halted their lethal ALS progression and in some ways, improved how they felt and functioned
16. "Totality of the evidence" including dozens of "n of 1" case studies that demonstrate that NurOwn had a "clinically meaningful" impact on how people felt, functioned and survived

Just as the FDA recently did for Stealth Bio's drug, we are asking the FDA to invite Brainstorm to resubmit its BLA so Dr. Prasad's team at CBER can take a fresh look at and consider the "totality of the evidence" from the last 10 years – NOT just the evidence from the 28-week trial.

In their OpEd for JAMA Viewpoints, Doctors Prasad and Makary said:

> *"The FDA must have the courage to create new pathways for therapeutic developers to respond to the current forest fire that is worsening the health of the US population. We will rapidly usher to market new products with transformational potential."*

There is no forest fire creating more death and destruction than ALS. It is cheating people out of the decades of life they still had left to live and replacing their last years with inexplicable suffering as their paralyzed bodies slowly become their own coffins. NurOwn has not just the "potential" for transformational changes but based on the survival data and RWE/RWD we have submitted herein, it has already caused transformational changes.

Petitioners ask the FDA to honor Secretary Kennedy's pledge to end the war on stem cell therapies. Please rush NurOwn to market with a Phase 4 post-marketing study and patients' mandatory participation in a biorepository, with a disease-wide natural history and exposome database.

PETITIONERS

"A healthy person has a thousand dreams. The sick person only has one."
~ Secretary Robert F. Kennedy Jr.
(April 22, 2025)

For thousands of people battling ALS, that dream is to get a mesenchymal stem cell treatment called NurOwn. As Dr. Prasad has said: the American people are the FDA's *"number one stakeholder."* Nowhere are the stakes higher than among the people dying of ALS. As such, Petitioners are imploring the FDA to help make their dream of getting NurOwn become a reality.

The first group of Petitioners represent the class of people with ALS who received 3 doses of NurOwn in the Phase 3 trial and up to 6 more doses in the Expanded Access Program ("EAP"). Petitioners Matt Klingenberg, Josh Smith, Eric Stevens, and Roberto Muggli received the most doses in the US. When they screened for the trial, all four men were early in ALS progression, with an ALSFRS-R score above 40 on the 48-point functional rating scale. NurOwn worked on all. None got more. Roberto died waiting.

The second group of Petitioners represent the class of people who received 3 doses of NurOwn during the Phase 3 trial but not during the Expanded Access Program. Both Kade Simons and Justin Rogers were initially fast progressors. They began the trial screening with an ALSFRS-R score above 35 on the 48-point functional scale. NurOwn worked on them. They never got more. Both Kade and Justin died waiting.

The third Petitioner, Lesley Krummel represents the class of people who received NurOwn during the Phase 3 trial and were chosen to receive more in EAP, but their invitations to participate in EAP were withdrawn after the FDA's statement in March 2021. Lesley began the trial screening with an ALSFRS-R score above 40 on the 48-point functional scale. NurOwn worked on her. Lesley improved. But her EAP dosing was cancelled. She never received more. She has now declined and is dying waiting.

All the above Petitioners collectively are hereinafter referred to as " NurOwn Petitioners." They were in the subgroup of trial participants – earlier in ALS progression – where the clinical data met statistical significance on both the trial's primary and secondary endpoints. All these people told the FDA that NurOwn caused "clinically meaningful" improvements in how they "felt and functioned." But at the time of the NurOwn Advisory Committee ("AdComm") meeting in September 2023, the Phase 3 trial was still blinded; both the FDA and AdComm members appeared reluctant to give credence to the patient experiences and real-world evidence as outlined in 21st Century Cures.

But when the NurOwn Phase 3 trial was unblinded months after the AdComm, it was both validation and vindication. Everyone who testified that they could feel NurOwn working in their body was correct. All the above NurOwn Petitioners received confirmation from their trial sites that they received NurOwn in the Phase 3 trial. This is new information that the FDA has never considered.

Now, with this new proof in their possession, each of the above named NurOwn Petitioners can justifiably assert that NurOwn helped them "live better and live longer." Specifically, NurOwn:

- slowed or halted their lethal progression
- restored lost function in some
- caused long periods of progression-free survival (PFS)
- caused an increase in "trach-free" survival (TFS) that exceeds ALS natural history by 2x-3x
- caused a long-term slowing of ALS decline that was as much as 75-85% decrease
- caused an increase in overall survival (OS) that exceeds the disease's natural history

Many other unblinded Phase 3 trial participants experienced similar beneficial results when they received NurOwn. We hope that they will join in support of this Citizens' Petition.

The fourth Petitioner is Terri Pickering Saenz. She represents the people who participated in the NurOwn Phase 2 trial. Terri received one dose of NurOwn in 2015. She and many other people in Phase 2 reported that NurOwn improved how they "felt and functioned," albeit not with the same magnitude or durability as people in the Phase 3 trial and EAP who received more doses. For the last decade, Terri has been dying waiting for more NurOwn.

The fifth Petitioner is Mayuri Saxena. Mayuri was not in the NurOwn trial, but as a SOD1 carrier she tried repeatedly to get into the Tofersen expanded access program. She represents the thousands of people with ALS who have repeatedly and unsuccessfully tried to get access to investigational therapies via EAP or Right to Try but were refused access by drug sponsors. Today, Mayuri exemplifies the irreparable harm that results when access to a promising therapy is delayed. For years, she has

been unable to move, eat, drink or swallow. Today she is trached and on life support. She uses a feeding tube to eat, a suction device to remove excess mucus, a Tobii to talk, and a ventilator to breathe. She is now even losing the ability to use eye gaze to communicate. Her ALSFRS-R functional score is 0 on the 48-point scale. Her body is "locked in," but her mind is still as brilliant as ever.

The sixth group of Petitioners represent the class of people with ALS who were not eligible to participate in the trial and could not get NurOwn despite their valiant efforts. Petitioner Tara Collazo screened for the Phase 3 trial but was progressing too slowly to qualify; she is now a quadriplegic. Petitioners Patty Manhardt and Jamie Rose Berry were diagnosed too late to qualify for the Phase 3 trial; both died waiting. Anesthesiologist Shahriar Minokadeh, MD ("Shah") had ALS too long to qualify for either the Phase 2 or Phase 3 trial; he also tried unsuccessfully to get into the NurOwn "hospital exemption" program for cell therapeutics in Israel. Dr. Minokadeh has lost all limb function and now must use a trach to breathe.

The seventh Petitioner is Navy pilot Nick Warack. He represents the class of veterans with ALS, a service-related disease. Nick learned of the NurOwn trial too late to qualify. Along with Navy pilot Matt Bellina and thousands of others, Lieutenant Commander Warack served post-9/11 and had a significantly heightened risk of getting ALS.

The final group of "John Doe" Petitioners represent the class of approximately 33,000 people living with ALS in the US and the approximate 6,000 more who will be diagnosed each year in the future. Tens of thousands will die waiting for the completion of a Phase 3B trial. For all of these people still fighting ALS today, the ALS clock is a ticking time bomb. They cannot wait multiple years until the Phase 3B trial is fully funded, enrolled, completed, and then wait another year as the NurOwn BLA meanders its way through the FDA approval process. They need the FDA to act with the same urgency as ALS is killing their motor neurons.

You can find more details about each Named Petitioner starting at section "H" on page 91 below.

EMERGENT FACTS:
New Survival, Respiratory, and Neurofilament Light Data from Phase 3 and EAP

"ALS is notoriously difficult to treat….
One of the major challenges is the heterogeneity"
~ Dr. Merit Cudkowicz, MD

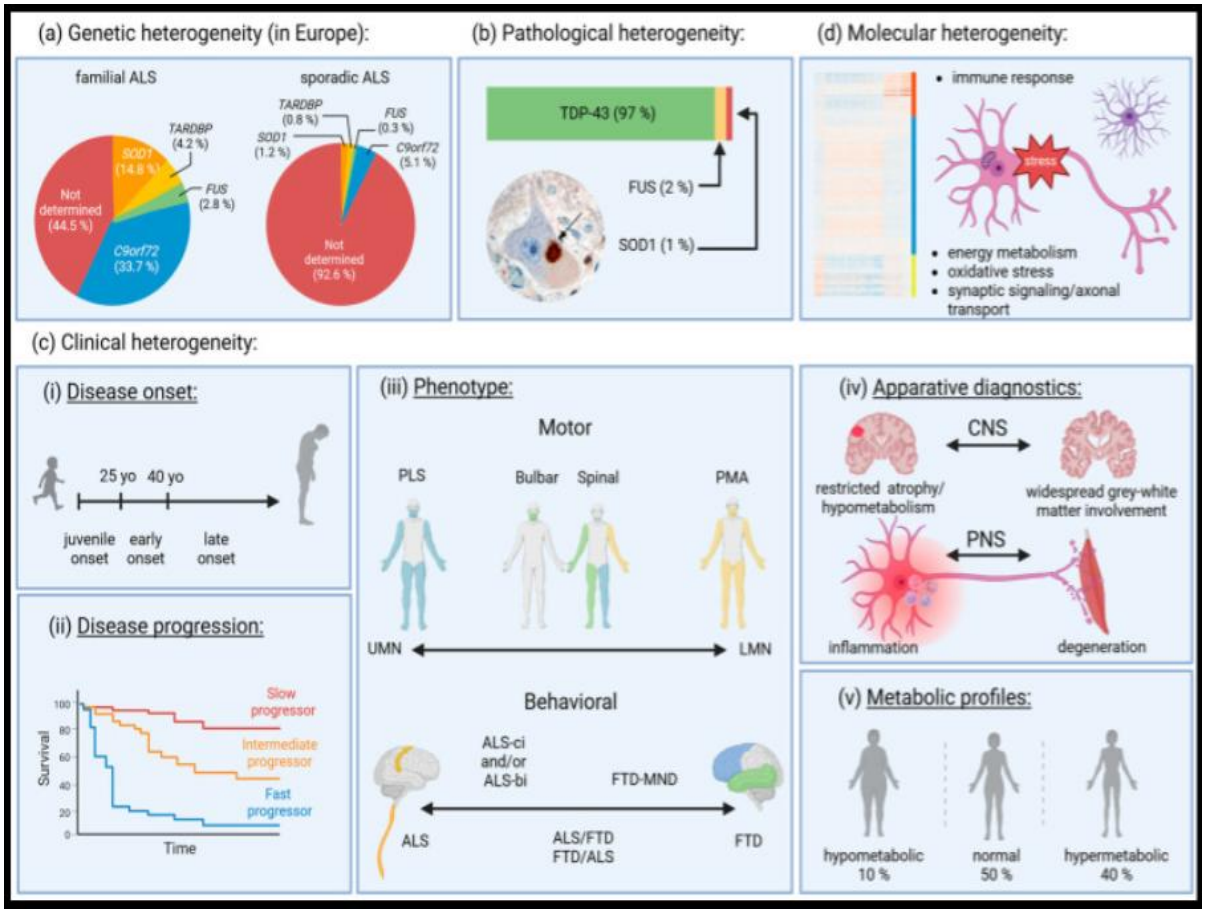
ALS is a 100% fatal, heterogeneous, rare neurodegenerative disease. As motor neurons die, the brain can no longer communicate with the voluntary muscles, which slowly become paralyzed. For reasons researchers don't fully understand, ALS impacts only the motor neurons, not the sensory neurons. Thus, people with ALS still feel cramping, sensations, fasciculations and pain, but they can't move to respond to them. Ultimately, people lose the ability to walk, talk, move, eat, drink, swallow, and eventually, breathe. Despite ALS being a clinical diagnosis with vastly heterogeneous phenotypes and cellular pathology, in the end, all people with ALS experience respiratory symptoms and almost all inevitably die from respiratory failure.[2]

A. ALS is a Vastly Heterogeneous, Terminal Rare Disease

ALS is a vastly heterogeneous disease in phenotype and genotype, and in pathology and penetrance. That's what caused Dr. Billy Dunn, CDER'S former Neuroscience Director, to concede that the biggest hurdle slowing ALS drug approvals is its complexity, calling heterogeneity *"the death of many clinical trials."* This graphic outlines some of that heterogeneity:[3]

[2] Andrews JA, Meng L, Kulke SF, Rudnicki SA, Wolff AA, Bozik ME, Malik FI, Shefner JM. Association Between Decline in Slow Vital Capacity and Respiratory Insufficiency, Use of Assisted Ventilation, Tracheostomy, or Death in Patients With Amyotrophic Lateral Sclerosis. JAMA Neurol. 2018 Jan 1;75(1):58-64.
[3] Tzeplaeff, L., Jürs, A. V., Wohnrade, C., & Demleitner, A. F. (2024). Unraveling the heterogeneity of ALS: A call to redefine patient stratification for better outcomes in clinical trials. Cells, 13(5), 452.

Graphic - ALS Heterogeneity

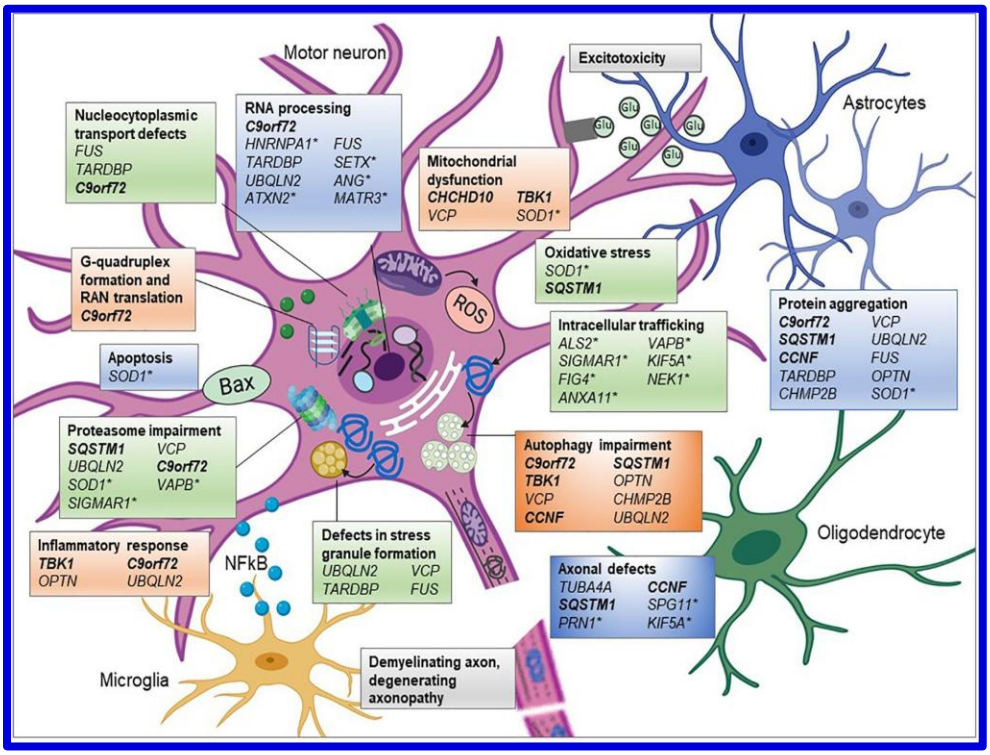


In the 2016 documentary, *"Die Trying: the Battle for ALS Treatments,"* ALS patient and VICE Producer Angelina Fanous said a *"one-size-fits-all system"* won't work for a heterogeneous neurodegenerative disease like ALS.

1. Cellular Heterogeneity

A 2023 article in Nature Reviews Drug Discovery underscored the need for multi-targeted approaches for ALS therapeutic development.[4] The failure of many single-agent trials reflects ALS's complexity, involving diverse cellular pathology. The consensus among researchers is that the heterogeneity of ALS — spanning genetic mutations and diverse pathological mechanisms — likely necessitates a cocktail of drugs targeting multiple aspects of the disease. As a result, the complexity of ALS likely requires better stratification of the patient population and a multi-drug approach to achieve meaningful therapeutic outcomes.

Graphic - ALS Cellular Heterogeneity



2. Genetic Heterogeneity

In addition to cellular heterogeneity, ALS is vastly diverse in genotype. Approximately 10-15% of cases are directly caused by 40+ genetic mutations;[5] but 85-90% of cases are sporadic of unknown etiology. The diagram above illustrates the varied pathophysiology affecting neurons and their glial cells in both sporadic and genetic forms of ALS, with boxes highlighting the genes associated with each pathological process. Notably, sporadic ALS displays similar pathological features despite its unclear origins.

[4] Mead, R. J., Shan, N., Reiser, H. J., Marshall, F., & Shaw, P. J. (2023). Amyotrophic lateral sclerosis: A neurodegenerative disorder poised for successful therapeutic translation. Nature Reviews Drug Discovery, 22(3), 185–212.

[5] Chiò, A., Logroscino, G., Traynor, B. J., Collins, J., Simeone, J. C., Goldstein, L. A., & White, L. A. (2020). Global epidemiology of amyotrophic lateral sclerosis: A systematic review of the published literature. Neuroepidemiology, 54(4), 300–310.

ALS can be both a polygenic and oligogenic disease. In fact, there are several reports of patients carrying two or more mutations of different ALS-related genes.[6] The distinction between ALS as an oligogenic or polygenic disease lies in the number and interaction of genetic factors contributing to its development. Oligogenic ALS involves a smaller number of genetic variants (typically 2–3 key mutations or rare variants) that interact to significantly increase disease risk or influence progression. For example, a patient might carry a rare mutation in a major ALS gene (e.g., C9orf72) alongside a modifier gene like SETX.

Polygenic ALS, on the other hand, arises from the cumulative effect of many common genetic variants (often single-nucleotide polymorphisms, or SNPs), each with a small individual effect, contributing to overall disease susceptibility in a more gradual manner, as seen in genome-wide association studies (GWAS) of sporadic ALS. While oligogenic cases are more common in familial ALS and linked to severe phenotypes, polygenic influences are prevalent in sporadic ALS, highlighting the complex genetic architecture of the disease.[7]

In a study of 391 patients with ALS that assessed variants in 17 genes, 3.8% had variants in more than one gene.[8] In that series, the burden of rare variants in known ALS genes significantly reduced the age at onset of symptoms. People with oligogenic expression are often faster progressors.[9] Petitioners Mayuri Saxena and Jamie Rose Berry are two examples of people with oligogenic heterogeneity. Both oligogenic and polygenic heterogeneity in ALS can significantly influence trial design and outcomes by introducing variability in disease progression and treatment response. Oligogenic ALS often leads to faster disease progression, thus necessitating stratification of participants by genetic profile to ensure balanced cohorts and accurate assessment of therapeutic efficacy, as highlighted by Iacoangeli et al. (2025). But this stratification is difficult to do with the many ultra-rare ALS variants with differing penetrance.

Polygenic ALS, driven by the cumulative effect of numerous common variants, contributes to a broader spectrum of disease severity in sporadic cases, requiring larger sample sizes and genetic risk scoring (GRS) to account for subtle genetic influences on outcomes (Feldman et al., 2022). This complex heterogeneity complicates endpoint selection, such as survival or functional decline, and underscores the need for personalized trial designs, including biomarker-driven approaches, to mitigate confounding factors and enhance the reliability of clinical results.

Even familial and sporadic ALS are impacted by genes that modify risk factors, impacting the onset, expression and progression of ALS. Besides “causative” genes, several other genes have been reported to modify ALS phenotype suggesting that variants in these genes modify the Gene-Time-Environment

[6] Lattante, S., Ciura, S., Rouleau, G. A., & Kabashi, E. (2015). Defining the genetic connection linking amyotrophic lateral sclerosis (ALS) with frontotemporal dementia (FTD). Trends in Genetics, 31(5), 263–273.
[7] Iacoangeli, A., … Cooper-Knock, J., … Glass, J. D., … Hardiman, O., … (2025). Oligogenic structure of ALS has genetic testing, counselling and therapeutic implications. Journal of Neurology, Neurosurgery & Psychiatry. Advance online publication.
[8] Cady, J., … Miller, T. M., Mitra, R. D., Ravits, J., Harms, M. B., & Baloh, R. H. (2015). Amyotrophic lateral sclerosis onset is influenced by the burden of rare variants in known ALS genes. Annals of Neurology, 77(1), 100–113.
[9] Iacoangeli, A., … Cooper-Knock, J., … Glass, J. D., … Hardiman, O.,… Farhan, S. M. K. (2025). Oligogenic structure of ALS has genetic testing, counselling and therapeutic implications. Journal of Neurology, Neurosurgery & Psychiatry.

theory that is unique to each person with ALS. Some examples of these "modifier" genes are: *UNC13A, ATXN2,*[10] and *CAMTA1.*[11] As Stanford's Aaron Gitler explained at this ALS One Research Symposium, UNC13A is the most common genetic risk factor across the sporadic ALS community. Dr. Gitler added that the two seminal NATURE studies about UNC13A connected the most common genetic risk factor (UNC13A) seen in approximately 60% of sporadic ALS[12] with the most common ALS pathology (TDP-43) that affects approximately 97% of people with ALS.

Van den Berg (2009) confirmed that people with at least one copy of the C allele have faster ALS progression, more frequent bulbar onset, higher incidences of ALS-FTD, lower FVC at diagnosis and resultantly, shorter survival. Thus, UNC13A variants could influence clinical trial outcomes by modifying disease severity, survival, or treatment response. While stratifying trial participants by UNC13A genotype could account for potential variability in efficacy or progression rates, Petitioners are unaware of any ALS trials that randomize patients based on their UNC13A status, and only a few who have assessed the possible impact.[13] Moreover, UNC13A is only 1 of 66 mis-splicing genes identified by Gitler's lab, further increasing the potential for heterogeneity to be impacting trial outcomes.

3. Heterogeneity by Age of ALS Onset

There is vast heterogeneity in age of onset as well. ALS is a disease typically associated with aging as the average age of diagnosis is 55 and the median is 58.[14] However, as demonstrated by many of the Petitioners, ALS does afflict people in their 20s and 30s. And recently the NIH identified some cases of pediatric ALS caused by a de novo mutation in SPTLC2. Sadly, there are no natural history studies evaluating why so many people are being diagnosed decades earlier than the average.

4. Heterogeneity by Speed of Progression

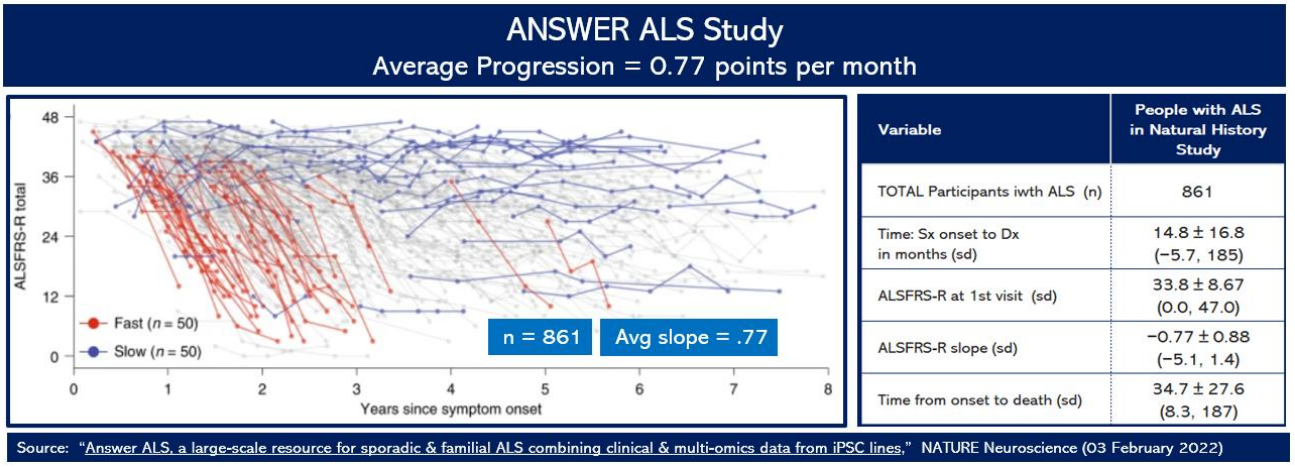
The Answer ALS study provides a comprehensive analysis of ALS progression and demographics, integrating clinical, multi-omics, and induced pluripotent stem cell (iPSC) data from over 850 sporadic

[10] Chiò, A., Calvo, A., Moglia, C., Ossola, I., Brunetti, M., Sbaiz, L., Lai, S. L., Abramzon, Y., Traynor, B. J., Restagno, G., & Al-Chalabi, A. (2015). ATXN2 polyQ intermediate repeats are a modifier of ALS survival. Neurology, 84(3), 251–258.
[11] Fogh, I., Lin, K., Tiloca, C., … Chiò, A., ... Hardiman, O. (2016). Association of a locus in the CAMTA1 gene with survival in patients with sporadic amyotrophic lateral sclerosis. JAMA Neurology, 73(7), 812–820.
[12] van Es, M. A., Veldink, J. H., … van den Berg, L. H. (2020). The distinct traits of the UNC13A polymorphism in amyotrophic lateral sclerosis. Annals of Neurology, 88(4), 796–806.
[13] While Brainstorm has published the UNC13A distribution in its Phase 3 trial, the trial sites have not yet released the UNC13A test results to the trial participants so we don't yet know which participants may have been a "C" allele carrier.
[14] Chiò, A., Logroscino, G., Traynor, B. J., … Goldstein, L. A., & White, L. A. (2020). Global epidemiology of amyotrophic lateral sclerosis: A systematic review of the published literature. Neuroepidemiology, 54(4), 300–310

and familial ALS patients. This large-scale database highlights ALS heterogeneity and identifies key factors influencing ALS progression.[15]

People with ALS lose function at different speeds of progression also called "change in slope." In ALS, a bounded scale called the ALS Functional Rating Scale (ALSFRS-R) is the patient-reported clinical outcome assessment used to assess change in function and ALS progression. Until recently the commonly accepted mean change in slope was 1.02 points per month, a statistic derived from the placebo arms of the PRO-Act clinical trial database. But the Answer ALS study of 861 people with ALS documented the now-commonly accepted mean rate of decline as 0.77 points per month.[16]

Graphic - Answer ALS Study Change in Slope diagram - Slow & Fast Progressors



In this 2023 study,[17] researchers compared key events in ALS progression in populations across the US, UK and EU. They stratified those time-to-event data by speed of progression:

- > 0.77 points/month = Fast Progressor
- 0.36 - 0.77 points/month = Intermediate Progressor
- <0.36 points/month = Slow Progressor

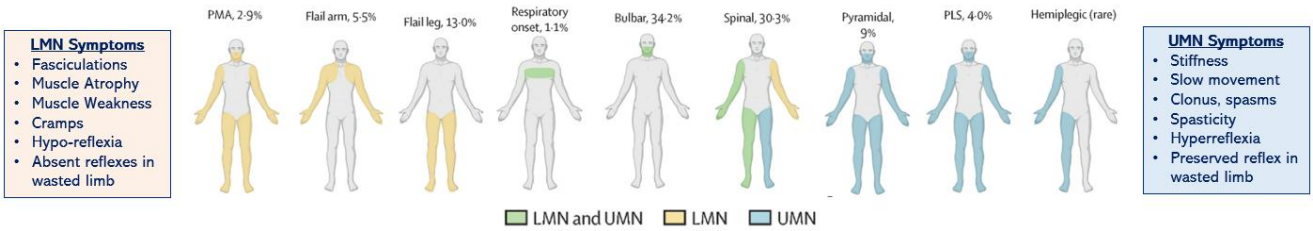
Comparatively, to qualify for the NurOwn trial, everyone had to have lost 3 points in the 12-week run-in period. As such – before receiving NurOwn – most of the people in the NurOwn trial would be characterized as "fast progressors." None would have been slow progressors as the trial sites screened to exclude those people (like Petitioner Tara Collazo).

[15] Baxi, E.G., … Ajroud-Driss, S., Baloh,R., Heitzman, D., Miller, T., Glass, J.D., … Cudkowicz, M.E., Maragakis, N., Finkbeiner, S., Berry, J., Fraenkel, E., Svendsen, C.N., & Rothstein, J.D., et al. (2022). Answer ALS, a large-scale resource for sporadic and familial ALS combining clinical and multi-omics data from induced pluripotent cell lines. Nat Neurosci 25, 226–237.
[16] Similarly the slope before baseline in the Healey ALS platform trials documented ALS progression that aligns with the Answer ALS database: (a) Zilucoplan = 0.75; (b) Verdiperstat = 0.77; (c) CNM-AU8 = 0.72; (d) Pridopidine = 0.75.
[17] Gebrehiwet, P., Brekke, J., Rudnicki, S. A., Mellor, J., Wright, J., Earl, L., Ball, N., Iqbal, H., Thomas, O., & Castellano, G. (2024). Time from amyotrophic lateral sclerosis symptom onset to key disease milestones: Analysis of data from a multinational cross-sectional survey. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 25(3-4), 345–357.

5. Heterogeneity by Site of ALS Onset

ALS heterogeneity can be classified by the site of onset, which influences not only phenotype of initial symptoms, but ALS progression as well. (Feldman et al., 2022).[18] These distinctions are significant as they impact symptom presentation and progression and thus, this heterogeneity can impact trial outcomes.

Graphic - ALS Heterogeneity by Site of Onset



The three most common types of ALS are:

(1) limb-onset: the most common, starting in arms or legs
(2) bulbar-onset: affects speech and swallowing muscles, often more rapid progression
(3) respiratory-onset: the rarest, beginning with breathing difficulties.

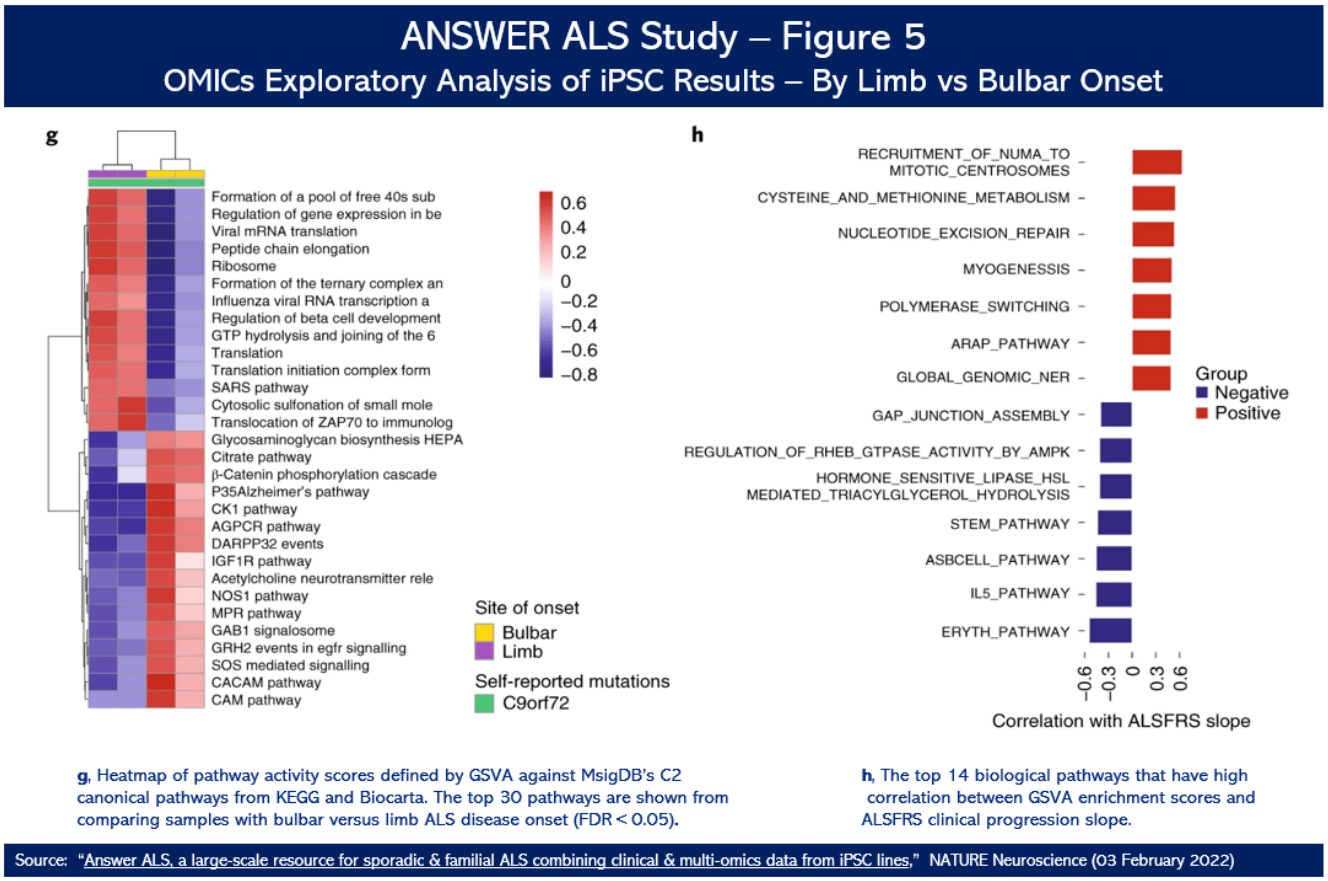
The differences between limb onset and bulbar onset aren't just what is evident from the outside. Rather, they reflect the vast heterogeneity about what is going on inside the diseased motor neurons in people with ALS.

Figure 5g below from the Answer ALS study is a heatmap that illustrates 30 of the top biological differences in the biological pathways between patients with bulbar versus limb onset ALS. This Gene Set Variation Analysis (GSVA) methodology looks at how active a biological pathway is in a patient's cells (specifically, motor neurons grown from iPSCs). An enrichment score is a number GSVA calculates for each pathway, showing how "turned on" or "turned off" that pathway is.

Higher scores mean the pathway is more active (e.g., genes in that pathway are working harder). These scores are what the heatmap visualizes, with colors indicating higher or lower activity (e.g., red for high activity, blue for low). For example, a high GSVA score for an inflammation pathway might mean that inflammation is very active in a patient's neurons, potentially damaging them.

[18] Feldman, E. L., Goutman, S. A., Petri, S., Mazzini, L., Savelieff, M. G., Shaw, P. J., & Sobue, G. (2022). Amyotrophic lateral sclerosis. The Lancet, 400(10360), 1363–1380.

Graphic - Answer ALS Study Figure 5 - Biological Pathways in ALS



Whereas Figure 5g illustrates 30 of the top biological differences in the biological pathways between patients with bulbar versus limb onset ALS, Figure 5h identified 14 key biological pathways where the level of activity (measured by GSVA scores) is strongly linked to how quickly ALS worsens (measured by the ALSFRS-R change in slope). In the context of clinical trial outcomes, these pathways are important because they may help explain why some patients decline faster. [19]

A summary of some of these pathways can be found at Exhibits. You will note that many of these pathways relate to neuroinflammation or neuroprotection – pathways on which NurOwn has a disease modifying impact. For example:

[19] Answer ALS is an innovative research-based non-profit founded by Johns Hopkins' Jeff Rothstein, MD PhD. It has collected biosamples from over 1000 people and is generating iPS cells from each patient, creating thousands of new and different iPS brain cell lines and performing the most comprehensive biological analytics ever—including DNA (genomics), RNA (transcriptomics) and protein (proteomics) analysis—to yield a personalized but open-access database of thousands of petabytes of new ALS-specific information. Then, in collaboration with experts in machine learning and big data informatics, this OMICs data will be mined to uncover ALS causes, subtypes, drug targets and biological pathways gone awry. It will serve as the foundation for new clinical trials, suggest new ways to subgroup patients to better discover successful drugs and to find drug-responsive biomarkers or diagnostics.

- IGF1R Pathway (Insulin-like Growth Factor 1 Receptor Pathway)
  Reduced IGF1R activity impairs neuroprotection. Dysregulation can amplify inflammatory responses in microglia and astrocytes (the brain's immune cells), while disrupting growth factor balance needed for motor neuron maintenance.[20]

- IL5 Pathway
  Overactive IL5 signaling is linked to immune responses that exacerbate neuroinflammation, contributing to motor neuron loss in ALS.[21]

- NOS1 Pathway (Nitric Oxide Synthase 1 Pathway)
  Overactive NOS1 produces toxic nitric oxide, causing oxidative stress and neuroinflammatory damage to motor neurons.[22]

- GRB2 Events in EGFR Signaling
  Dysregulated GRB2 events enhance neuroinflammation by promoting inflammation and growth factor imbalances, worsening motor neuron damage.[23]

- Cysteine and Methionine Metabolism
  Dysregulated cysteine and methionine metabolism impairs antioxidant defenses, increasing oxidative stress and indirectly promoting neuroinflammation while reducing neuroprotection.[24]

Petitioners include these graphics and pathways, not to have a complex scientific discussion about the biological processes involved in ALS, but instead to illustrate several points:

(1) the graphics exemplify why drug development in ALS is so difficult and why the ultimate treatments for ALS will likely take a drug cocktail that will be personalized to each person's own pathology;[25]

(2) there is no possible way to stratify a trial population and randomize for these multiple heterogeneous pathways; but using AI, researchers could analyze thousands of samples in Phase 4 biorepository to help identify why some patients are responding to certain therapies but not others; and

[20] Sakowski, S. A., Feldman, E. L., & Appel, S. H. (2012). Insulin-like growth factor-I for the treatment of amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis, 13(1), 1–7.
[21] Wood, H. (2020). Neuroinflammation in ALS: Cause or consequence? Nature Reviews Neurology, 16(2), 71.
[22] Tronel, C., & Rochefort, G. Y. (2014). Nitric oxide synthase in neurodegenerative diseases: From mechanisms to therapies. Molecular Neurobiology, 49(3), 1396–1407.
[23] Le Pichon, C. E., & Dominguez, S. L. (2017). Epidermal growth factor receptor: A potential therapeutic target for amyotrophic lateral sclerosis. Neurotherapeutics, 14(2), 351–356.
[24] Valle, C., (2017). Cysteine modifications in the pathogenesis of ALS. Frontiers in Molecular Neuroscience, 10, 5.
[25] For people who have sporadic (sALS), a major barrier to drug development has been the lack of a predictive preclinical human model for sALS. The Answer ALS program generates iPSC lines to understand the heterogeneity of sporadic AL .

(3) therapies like NurOwn that work on "some" must be rushed to market as its unprecedented results in a large proportion of patients can be a bridge to help people live longer and live better while scientists figure out how to develop drugs personalized for the vast heterogeneity of this heinous disease.

These scientific graphics also illustrate why Dr. Ajay Sampat, a young neurologist with ALS, submitted a Public Comment and reminded the FDA:

> *"The teaching I learned in residency is that **'if you have met one ALS patient, you have met one ALS patient.'** As a result of this, we cannot expect a drug to impact every individual the same way. And we should not deny an opportunity for treatment based on this flawed notion that a drug can and will help the majority of patients in this diverse condition."*

Some must be enough.

B. ALS Lifespan and Dying Motor Neurons

Every year, approximately 6,000 people are diagnosed with ALS and 6,000 die. The ALS community refers to this as the "turnstile of death." According to the most recent data from the CDC's ALS Registry, the incidence of ALS is 1.6 per 100,000. But because ALS is so rapidly lethal, the prevalence is approximately 32,000 instead of 1 million like MS. Thus, ALS meets the statutory definition as a "rare disease" and investigational therapies for ALS qualify for all benefits conferred with orphan drug status. But as Petitioner Patty Manhardt often shared: ***"it's only rare because we die so quickly."***

Early in ALS, as motor neurons are dying, people experience no symptoms because of the redundancies in the central nervous system. Surviving motor neurons can compensate by sprouting new connections to denervated muscle fibers, delaying symptom onset. Symptoms emerge only after this compensatory capacity is overwhelmed. By the time someone is diagnosed, researchers estimate that approximately 50% to 80% of motor neurons in affected regions are damaged or dead, with the higher end (70%–80%) more common in bulbar-onset cases or rapidly progressing disease.[26]

According to the NIH and CDC's ALS Registry, the average lifespan for people with ALS is 3-5 years.[27] But that survival statistic can be misleading as it encompasses a diverse population, including those who rely on life-support measures and opt for a tracheostomy to maintain breathing, which can significantly extend survival beyond the average. The inclusion of this "trached" population skews the overall figure, masking the variability in disease progression and the impact of advanced interventions. Thus, the more accurate assessment of a therapy's impact on survival outcomes in clinical trials is to consider "tracheostomy -free" ("trach-free") survival.

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[26] Swash, M. (2013). Why are upper motor neuron signs difficult to elicit in amyotrophic lateral sclerosis? Journal of Neurology, Neurosurgery & Psychiatry, 84(6), 711–712.

[27] "Priorities of the NIH Amyotrophic Lateral Sclerosis (ALS) Strategic Planning Working Group" https://www.ninds.nih.gov/sites/default/files/documents/ALS%20Strategic%20Plan_11_20_23_508C.pdf