2026 ALS Disrupt: Community Report

Key insights from the ALS Disrupt meeting, translated for the ALS community.

The 2026 edition of ALS Disrupt brought together researchers, clinicians, and key research voices to examine some of the biggest questions in ALS research. While many of the challenges discussed are not new, there is growing momentum to rethink long-standing approaches, and push the field to think more openly about what is and is not working.

Across all four sessions, participants spoke candidly about the limits of current disease models, the difficulty of translating promising biology into successful clinical trials, and the need to learn more systematically from both positive and negative results.

At the end of the day, the discussions were grounded in a shared goal: to build a stronger foundation for better therapies. This report highlights the main ideas from each session in clear, lay language while keeping important research details that were central to the conversation.

KEY INSIGHTS FROM THE DAY

- Many believe that ALS is likely not one disease with one answer. Heterogeneity (differences between people, cell types, and disease stages) was a recurring theme across all sessions.
- Researchers repeatedly emphasized the need for stronger evidence, better biomarkers, and more realistic ways of studying ALS biology before moving potential therapies forward. There can be an overreliance on imperfect ALS lab models, leading to repeated cycles of negative trials and limited new insight.
- ALS is a systems-level disease. Beyond motor neurons, factors like glial cells, stress, aging, and the broader cellular environment all play a role.
- Stronger decision-making is needed before moving to clinical trials, and especially, Phase 3 trials. Attendees emphasized looking at the full body of evidence, biology, target engagement, models, biomarkers, and trial data, rather than relying on one or a few promising signal(s). Not considering the full dataset as evidence has misled the field into negative Phase 3 trials on multiple occasions.
- There are missed learning opportunities. Sharing negative and inconclusive findings can be critical to avoid repeating mistakes.
- Challenging assumptions is essential. Unexpected “black swan” findings can reveal gaps in current thinking and point to new directions. They are telling us something important, even when they do not align with what we expect or believe is happening.
- Systemic barriers are holding progress back. Challenges often stem from research culture and incentives, not just scientific gaps. The field favors speed, simplicity, and familiar approaches.
- Mismatch between questions and tools. Preclinical models and clinical trials are often asked to answer questions they aren’t designed for, contributing to unclear or misleading results.
- Disruption as an important starting point: meaningful change will require coordinated shifts across the research community. These discussions help surface shared challenges and lay the groundwork for deeper, more action-oriented conversations moving forward.

Session 1 | What evidence is needed before moving a drug toward clinical development?

Moderator: Michael Benatar, University of Miami
Pietro Fratta, University College London
Cat Lutz, JAX Rare Disease Translational Center
Piera Pasinelli, Thomas Jefferson University
Ludo Van Den Bosch, KU Leuven

The first session explored what level of preclinical evidence, in research labs, is needed before advancing a potential therapy into clinical trials.

In ALS, this question carries particular weight. The field has seen a long history of promising therapies that showed encouraging results in preclinical models but ultimately failed to demonstrate meaningful benefit in clinical trials. At the same time, limited funding and a relatively small patient population mean that every decision to move a therapy forward carries significant opportunity cost. Prioritizing one approach can mean delaying, or overlooking, another. As a result, determining the right threshold for preclinical evidence in the lab, with animal and cellular models, is not just a scientific question, but a strategic and ethical one. It forces the field to reflect on how to balance urgency with rigor, how to learn from past setbacks, and how to make the most of constrained resources to ensure that the most promising ideas have the best chance of reaching the clinic.

The panel's answer was clear: there is no single checklist. Instead, the right decision depends on how well biology, the model, the mechanism, and the clinical question all fit together.

Speakers emphasized that ALS doesn't show up as one single disease. It is complex and varies from person to person, shaped by multiple biological factors, and by the time symptoms appear, the disease is often already quite advanced at a biological level. That makes drug development especially difficult. Several participants pointed out that current models are useful tools, but they are often asked to do more than they can reasonably tell us. Mouse models, for example, can help explore how drugs work or target engagement, but they do not fully reproduce human ALS, aging, or the full range of cell interactions that shape disease. As a researcher argued, "a person living with ALS is the only perfect model".

There was strong agreement on the importance of target engagement, which is evidence that a drug actually reaches and affects the biological process it is designed to change. For example, if a drug is designed to reduce harmful TDP-43 buildup in ALS, researchers would look for clear signs that TDP-43 levels or activity are reduced after treatment. Target engagement was framed as necessary, but not enough on its own if there is no reason to believe that hitting the target is reasonably likely to change the course of disease.

Researchers also called for stronger and more transparent research practices, including:

- Independent replication of positive results across different labs to confirm findings are reliable;
- Using multiple models rather than relying on a single system, to better reflect the complexity of ALS;
- A greater willingness to share negative findings, so the field can learn from them and avoid repeating the same mistakes.

The session also returned several times to a broader concern: the field often values speed and simplicity, even when ALS biology clearly demands more nuance.

KEY INSIGHTS: PRECLINICAL EVIDENCE

- Researchers argued that the field needs a stronger, more agreed-upon way to judge whether a therapy is ready to move forward.
- Models should be chosen based on the question being asked, not simply because they are convenient, familiar, or fast. When models cannot accurately reflect the disease, they can create false confidence in potential therapies and contribute to repeated cycles of failure.
- Scientific plausibility (ie. does the science make sense for ALS?), target engagement, and independent confirmation were all described as critical pieces of a more credible evidence package.

Session 2 | TDP-43: pathological cornerstone or tombstone?

Moderator: Martin Turner, Oxford University
Richard Robitaille, Université de Montréal
Chantelle Sephton, Université Laval
Michael Strong, Western University
Christine Vande Velde, Université de Montréal

The second session focused on the TDP-43 protein, one of the most important, and debated, topics in ALS research.

In most cases of ALS, even when there isn't a known genetic cause, something seems to go wrong with this protein. It is found primarily within the nucleus of a cell, where it helps to regulate essential cell processes, but in ALS, it becomes trapped outside in the cytoplasm forming clumps or aggregates. These clumps are theorized to contribute to motor neuron damage and death, as is the loss of its critical function in the nucleus.

The real question researchers debated was *how* TDP-43 contributes to the disease. Some speakers asked whether TDP-43 disruption is the main driver of the disease or whether it is better understood as a sign of processes that have already gone wrong. In simple terms, is TDP-43 dysfunction a *cause* or a *consequence* of the disease? Some suggested the answer may not be either-or.

TDP-43 is dynamic: it normally moves in and out of the nucleus, responds to stress, and may play adaptive roles before becoming part of a damaging process. In that framing, the problem may not be TDP-43 alone, but a failure of resilience and recovery over time. The discussion also encouraged the audience to think about TDP-43 in a broader, more nuanced way:

- How the protein might be chemically changed after it's made, and how those changes could affect what it does in the body.
- TDP-43 may also act differently in different types of cells. Most research focuses on motor neurons, but support cells like glia could play an important, and still underexplored role.
- There is growing recognition that people with *TARDBP* gene variants do not appear to have a clearly distinct clinical presentation compared to others with ALS. While it might be expected that these individuals would develop disease earlier, a key point is that the presence of the variant leads to ALS itself. This also highlights an important consideration in the field. Even though abnormal TDP-43 is seen across many neurological conditions, families with *TARDBP* variants overwhelmingly develop ALS, reinforcing its central role in the disease.
- Researchers also think that TDP-43 isn't just one thing, and different forms or states of the protein may behave differently depending on the context.
- A key open question is where to intervene: should therapies focus on what causes TDP-43 to go wrong in the first place, or on the downstream effects caused when it stops working properly inside cells?

- Finally, to fully understand TDP-43, we may need to look beyond the usual focus areas like clumping (aggregation) and changes in RNA processing (cryptic splicing) and consider a broader range of its roles in the cell.
- Genes and targets discussed in relation to TDP-43 included STMN2 and UNC13A, both of which are relevant to neuron health and function and are currently being targeted in clinical trial.
- While TDP-43 remains the most studied and targeted biology in ALS research and clinical trials as of 2026, there are still many people who don't believe it is an ideal, or even important, treatment target.

In simple terms, the message was that TDP-43 isn't just one single problem, as it affects many processes in the cell, and understanding that complexity will be key to moving the field forward.

Additionally, a major theme of this session was that ALS should be understood as a systems-level disease. Several speakers cautioned against a motor-neuron-only view and called for more attention to glial cells (support cells in the nervous system), stress responses, aging, metabolism, and the wider environment around vulnerable neurons. The conversation suggested that ALS may be less like a single switch that breaks, and more like a system under ongoing stress, where several protective processes start to falter over time.

KEY INSIGHTS: UNDERSTANDING TDP-43

- Researchers agree that TDP-43 is important, but there is no consensus that it is always the first event or the only event that matters in disease.
- TDP-43 biology is more complex than a single mechanism. ALS likely cannot be explained by one simple model of TDP-43 dysfunction.
- The group repeatedly returned to questions of stress, aging, adaptation, and resilience, suggesting that timing and context may be just as important as the protein itself.

Session 3 | What should guide decisions about moving drugs from Phase 2 to Phase 3?

Moderator: Michael Benatar, University of Miami
Lucie Brujin, Novartis
Stephanie Fradette, Biogen
Keith Mayl, argenx
Ruben Van Eijk, University Medical Center Utrecht

The third session focused on a key translational challenge: how we decide whether a therapy has enough promise to advance from Phase 2 to Phase 3 testing in clinical trials. Here, too, the panel emphasized that the field often tries to get more certainty from trials than those trials are actually designed to deliver. Small, short Phase 2 studies may be able to show whether a drug hits a target or changes a biomarker, but they are almost always too underpowered to make confident claims about clinical benefit.

Throughout the session, speakers emphasized the need to be more careful and thorough when making decisions. Rather than relying on a single encouraging signal, they said it's important to look at the full picture: whether the science makes sense, whether the treatment is actually hitting its intended target, and whether all the different pieces of evidence line up in a consistent, believable way. Several warned against cherry-picking results or overstating meaning in press releases when the totality of the data does not support a strong conclusion. This cherry-picking approach has misled the field many times, resulting in negative Phase 3 clinical trials.

One of the central biomarkers discussed was neurofilament light chain (NfL). NfL is a protein released when neurons are damaged and can be detected in the cerebrospinal fluid and blood. In clinical trials, NfL is evolving as a biomarker to help researchers understand whether a treatment may be reducing underlying motor neuron damage. The hope is that if NfL levels go down, it could be a sign that the treatment is helping protect neurons.

Panelists described NfL as a helpful but imperfect tool. Much of the discussion focused on how to interpret changes, what level of change really matters, whether small shifts can be trusted, and how to look at NfL alongside other results. NfL levels typically stabilize early in the disease but fluctuate over time, which makes small changes impossible to differentiate between treatment effect and natural variability. The test for NfL also has some level of uncertainty so these factors combined makes a larger drop, considered as 30% or more, necessary to feel confidence that a treatment is doing something meaningful.

The session also highlighted broader challenges in how trials are designed. Speakers stressed the importance of accounting for differences between people with ALS (heterogeneity), since not everyone's disease progresses the same way. They also talked about the need to adjust for baseline risk, which means understanding how quickly someone's disease is expected to progress from the start. NfL once again serves as an important tool because baseline NfL levels (how high their NfL is at the beginning of a study) can be used to adjust results for greater accuracy. Taking this into account helps ensure that any changes seen in a trial are more likely due to the treatment, and not just differences between how participants would have progressed regardless of treatment.

The overall message was not simply that Phase 2 studies have to be larger or longer, although that came up often. It was that the field needs more rigorous and approach limited data with more honesty if it wants fewer weak bets and more credible therapies moving into late-stage development. As a panelist shared, "we need more good drugs in Phase 3, as opposed to more drugs in Phase 3."

KEY INSIGHTS: TRIAL DECISIONS

- Target engagement was described as essential, but most speakers argued it is only one step, not the whole answer.
- Neurofilament (NfL) was discussed as an important biomarker of nerve cell injury, but participants repeatedly stressed that it should be interpreted alongside other evidence.
- The group called for more thoughtful Phase 2 studies, with designs strong enough to reduce uncertainty before moving into Phase 3.

Session 4 | What areas of dogma in ALS research should we be discussing more constructively?

Moderator: Martin Turner, Oxford University
Sami Barmada, University of Michigan Medical School
Jenna Gregory, University of Aberdeen
Evangelos Kiskinis, Northwestern University Feinberg School of Medicine
Rita Sattler, Barrow Neurological Institute

The final session turned toward dogma: ideas that become so established in a field that they start shaping what questions get asked, what data gets prioritized, and what possibilities get overlooked.

One speaker highlighted the idea that ALS might spread through the body in a way similar to prion diseases, where certain proteins trigger others to misfold. While there is some research that supports this idea, other findings don't fit as well with this explanation. As a result, there is not full agreement across the field. At the same time, this remains an area where assumptions are not often challenged openly, with supporters rarely questioned and those who are less certain not frequently pushing back in public discussions.

Another theme that surfaced was how we think about the key biological features of ALS, particularly through the lens of what the panel described as "black swan" observations. Black swans refer to unexpected findings that challenge what the field assumes to be true, much like the discovery of a single black swan was sufficient to overturn the long-held belief that all swans were white. One example raised in this discussion relates to TDP-43 aggregation, often described as a hallmark of the majority of ALS cases, though not typically seen as part of SOD1 and FUS-ALS. However, TDP-43-related changes *have* been observed in some cases linked to the *SOD1* and *FUS* genes. This overlap should challenge the usual view that these forms are distinct, and whether there may be more shared biology than we have typically assumed for over a decade.

This idea of looking more closely at outliers extended beyond TDP-43. Panelists emphasized that unexpected or contradictory findings, whether in pathology, disease progression, or model systems, are often set aside because they don't fit current thinking. Instead, they argued that these black swan observations can be particularly informative, helping reveal gaps in our understanding and pointing toward new directions for research.

The discussion also highlighted the continued dominance of neuron-centric thinking. Several participants argued that ALS cannot be fully understood by focusing only on motor neurons. Glial cells, including astrocytes, microglia, and oligodendrocytes, were repeatedly raised as important contributors to disease progression, stress responses, and the broader microenvironment in which neurons either cope or fail. This reinforced the idea, echoed earlier in the meeting, that ALS is a systems disease rather than a single-cell problem.

The session also revisited the strengths and weaknesses of current model systems. Many of the conclusions in ALS biology still come from overexpression models, where a protein is forced to appear at very high levels in cells or animals, potentially throwing off the normal balance of biology. Participants warned that these systems may be generating false signals that are not reflective of what is happening in people. That does not mean these models lack value, but it does highlight limitations in how well findings from these models translate to people.

Importantly, the discussion expanded beyond biology alone. Representation in research and clinical trials was raised as a real concern, with comments about the need to build trust, improve outreach, and create research participation that better reflects the diversity of the ALS community. Taken together, this session underscored that moving the field forward will require better science, but also better habits: more openness to alternate explanations and more willingness to challenge consensus.

KEY INSIGHTS: CHALLENGING DOGMA

- Participants encouraged the field to question long-standing assumptions, including how strongly it leans on overexpression models and single-protein explanations.
- Glial cells were repeatedly highlighted as important, with calls for more attention in both basic and translational research.
- The conversation also recognized that better ALS research includes better representation and stronger relationships with communities historically underrepresented in research.

How does this matter to the ALS community?

ALS Disrupt did not produce a single roadmap or a set of simple answers, and that was part of its value. The meeting created space for researchers to be honest about uncertainty, to challenge familiar assumptions, and to ask whether the field's current habits are how we are going to get to a cure. As a field, we are walking toward a path for stronger collaboration, more rigorous evidence, and a commitment to learning from both successes and failures.

For people affected by ALS, one message came through clearly: there is a growing recognition that this disease cannot be understood, or treated, through oversimplified thinking. Across the global research community, there is a deep, shared commitment to better understanding the full complexity of ALS, even when the path forward is not easy.

What stands out most is the dedication of researchers who live and breathe this work—continually questioning and pushing beyond what we know today.

There is real reason for hope. As the field continues to evolve, more thoughtful models, clearer decision-making, and a broader understanding of the biology are beginning to take shape. Together, these efforts to collectively disrupt our thinking and approach will bring us closer to treatments that can make a meaningful difference for the ALS community.