DukeHealth

Department of Neurology

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Dear Friends of the Duke ALS Program,

As 2025 ends, I wanted to write and personally thank you for helping us to raise the bar again. This was without a doubt our most productive year ever.

All our education, advocacy, and research programs are built on a foundation of great patient care. In 2025, our 20-person team welcomed more than 500 unique individuals living with ALS to our multi-disciplinary (https://alsclinic.duke.edu/our-team/ ) and telemedicine (https://alsclinic.duke.edu/telemedecine/ ) clinics. Our creative, and hope-centric approach to their care was featured in several high profile media articles (ex. https://www.wunc.org/health/2025-08-07/duke-als-clinic-doctor, https://www.theassemblync.com/health/als-duke-richard-bedlack-nc/ ).

We continue to believe that people living with ALS should be partners in everything we do. Along these lines, we led several more Clinical Research Learning Institutes, empowering them to thrive in this role. These included 2 international ones, and one specifically for military veterans (who are more likely to get ALS). There are now 1000 graduates from these programs, and they are helping to change laws, raise funds, design more patient-centric studies, educate regulators and pressure payors toward optimizing ALS care and research (https://www.tandfonline.com/doi/10.1080/21678421.2019.1690519?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed ).

Members of our team published 19 papers in peer-reviewed literature this year (https://pubmed.ncbi.nlm.nih.gov/?term=bedlack&sort=date). This is a new record for us and another testament to the power of having the Stewart, Hughes, and Wendt Endowed Professorship in ALS, which allows me to work full time on ending this disease. We also spoke through invited lectures to people living with ALS, as well as students, clinicians and scientists all over the world. Many of these talks are available online, and the recordings have already been viewed thousands of times (ex. https://www.youtube.com/watch?v=-J7YghkGGT4 )

Dr Li and I again managed the unique, award-winning ALSUntangled program (www.alsuntangled.org) , which scientifically reviews alternative and off label treatments to help people living with ALS to make more informed decisions about them. We now have 140 clinicians and scientists from 12 different countries working together on this. We reviewed 6 new products this year, as well as updating and recording podcasts (https://www.spreaker.com/podcast/create-podcast--2845933 ) about older ones. ALSUntangled articles are now being translated into multiple languages and collectively have over half a million downloads.

In addition to participating in the Combat ALS Phase 3 trial, the Healey Platform Trial, and expanded access programs for CNM-Au8, Pridopidine and Ibudilast, this year we also completed an unusual investigator-initiated trial called ROAR-DIGAP (https://clinicaltrials.gov/study/NCT06429059?cond=ALS&term=DIGAP&rank=1 ). Here we utilized a new technology from GenieUS called Deep Integrated Genomics Analysis Platform (https://www.genieus.co/digap ) to categorize each participant's ALS in terms of the molecular pathway most likely driving their progression. Each participant then received a personalized treatment that was previously associated with at least 1 ALS reversal. While the categorization was successful and the supplements all affected mechanistic biomarkers, unfortunately this approach did not appear to slow, stop or reverse ALS. On to the next idea!

We continued our innovative studies on "outliers"-people with ALS who are still doing extraordinarily well more than 10 years into their illness (ex. https://www.teamdrea.org/about/#about-andrea ). We have now discovered three things that these outliers have in common that might explain why they are beating the odds. First, they are more hopeful. We believe hope itself can be a treatment. Across every disease where hope has been studied, people with more of it do better medically. We have developed our own approach to boosting hope, and this is described in an editorial we wrote (https://www.tandfonline.com/doi/10.1080/21678421.2025.2454903?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed ) as well as a documentary short film called Stitching Strength (https://www.stitchingstrength.com ). This film has travelled the world over the past year, to community screenings and film festivals (where it won several awards) bringing with it an awareness of ALS and the power of hope. We understand that our approach to hope boosting is time-intensive and this will create challenges for other clinics who wish to adopt it. So we have partnered with a group called Hummingbird (https://hummingbirdfundva.com ) to study 2 hope boosting interventions that each take less than 5 minutes to conduct. If we can show that these boost hope scores and improve ALS outcomes, we will have a better chance of seeing other clinics focus on hope.

Second, outliers have a different gut microbiome compared to those with typically fast ALS progression (https://www.researchsquare.com/article/rs-6370840/v1 ). Transplanting stool from fast or slow progressing patients into a mouse model of ALS can dramatically change

the animal's progression rate (https://www.researchsquare.com/article/rs-6370840/v1 ). This suggests that our finding is more than an association; there is something in the gut microbiome that determines the rate of ALS progression. One theory is that organisms in the microbiome are driving the amount of neuroinflammation, itself a predictor of ALS progression (https://pmc.ncbi.nlm.nih.gov/articles/PMC12407898/ ) via a gut-brain axis. We are now just days away from enrolling our first patient into a trial of fecal transplants for ALS (https://www.clinicaltrials.gov/study/NCT07017946?cond=ALS&term=fecal%20transplants&rank=1 ) and we will be measuring markers of neuroinflammation (as well as ALS progression) in this trial. We expect this to enroll very quickly and to have an answer by the end of 2026.

Finally we come to the most extreme group of outliers-the patients who appear to recover from ALS. Last year we got our first clue about how these "ALS Reversals" might be happening when we discovered that several of them have a unusual mutation in a gene that reduces levels of a protein called IGFBP7 (https://www.neurology.org/doi/10.1212/WNL.0000000000209696?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed ). This year we further confirmed that IGFBP7 is a plausible target for ALS trials by showing in 4 different ways that IGFBP7 levels are higher in patients who get ALS compared to those who do not (https://www.tandfonline.com/doi/10.1080/21678421.2025.2559441?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed ). In the next few months we will launch the first trial attempting to knock down IGFBP7 in people with ALS by way of a nutritional supplement.

None of this would be possible without partners like you who support our work. Margaret Meade once said: "never doubt that a small group of committed citizens can work together to make a difference. In fact, that is the only thing that ever does." Thanks for being part of a small group that cares about creating more options, more hope, and eventually a cure for people living with ALS. Can't wait to see where we go together in 2026!

Sincerely,

Richard Bedlack MD PhD

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