News Release

Decoding Individual Differences in Disease Progression from Data
A new method captures differences in both how fast disease progresses and how it unfolds

Key Points

- Developed DiSPAH, a novel machine learning method that decomposes individual differences in disease progression into progression pathway (“how the disease unfolds”) and progression speed (“how fast it progresses”).
- Analysis of longitudinal data from patients with limb-onset amyotrophic lateral sclerosis (ALS) revealed multiple subgroups with distinct progression pathways, with substantial variation in progression speed even within each subgroup.
- The study shed light on genetic features and part of the molecular basis associated with progression speed.
- Information derived from DiSPAH may help assess the risk of ALS-related functional decline and may provide clues for anticipating future disease progression from early clinical and genetic information.

Summary

A research group led by Associate Professor Yuichiro Yada and Professor Naoki Honda at the Graduate School of Medicine, Nagoya University has developed DiSPAH, a new machine learning method that decomposes individual differences in disease progression into progression pathway (“how the disease unfolds”) and progression speed (“how fast it progresses”). In many chronic diseases, including neurodegenerative disorders, patients differ greatly in both symptom patterns and rates of progression, making prognosis, treatment planning, and clinical trial design challenging. Existing analytical methods, however, have had difficulty clearly distinguishing between these two aspects of progression heterogeneity.

In this study, the researchers appl

ied DiSPAH to ALS, a disease known for marked inter-individual variability in progression. Using longitudinal data from an ALS functional rating scale in 264 patients with limb-onset ALS, they found that ALS progression is not uniform, but instead consists of multiple subgroups with distinct progression pathways, with additional variation in progression speed even within the same subgroup. Similar progression patterns were reproduced in an analysis of a larger independent cohort of 2,565 individuals.

The study also suggested associations between progression speed and certain genetic features, as well as part of the molecular basis underlying progression. In addition, the results indicated that information obtained from DiSPAH may be useful for assessing the future risk of ALS-related functional decline. With further validation, DiSPAH is expected to deepen our understanding of disease progression and may eventually contribute to patient-specific prognosis and personalized me dicine.

These findings were published in the international journal npj Digital Medicine on May 19, 2026.

Research Background

In chronic diseases, including neurodegenerative disorders, disease progression varies greatly from one patient to another. Even among patients with the same diagnosis, some experience rapid progression, whereas others decline more slowly. In addition, the symptoms that appear first and the order in which they progress also differ across patients. Such marked inter-individual variability has made prognosis, treatment planning, and clinical trial design especially challenging.

In recent years, machine learning approaches have increasingly been used to analyze longitudinal clinical data collected by following the same patients over time. These approaches aim to infer the evolution of underlying disease progression states that cannot be directly observed, based on changes in symptoms and clinical measurements. However, existing methods have generally not clearly distinguished between progression pathway—which symptoms tend to appear first and in what order—and progression speed—how quickly symptoms worsen. As a result, the factors underlying these two types of variability have remained difficult to disentangle.

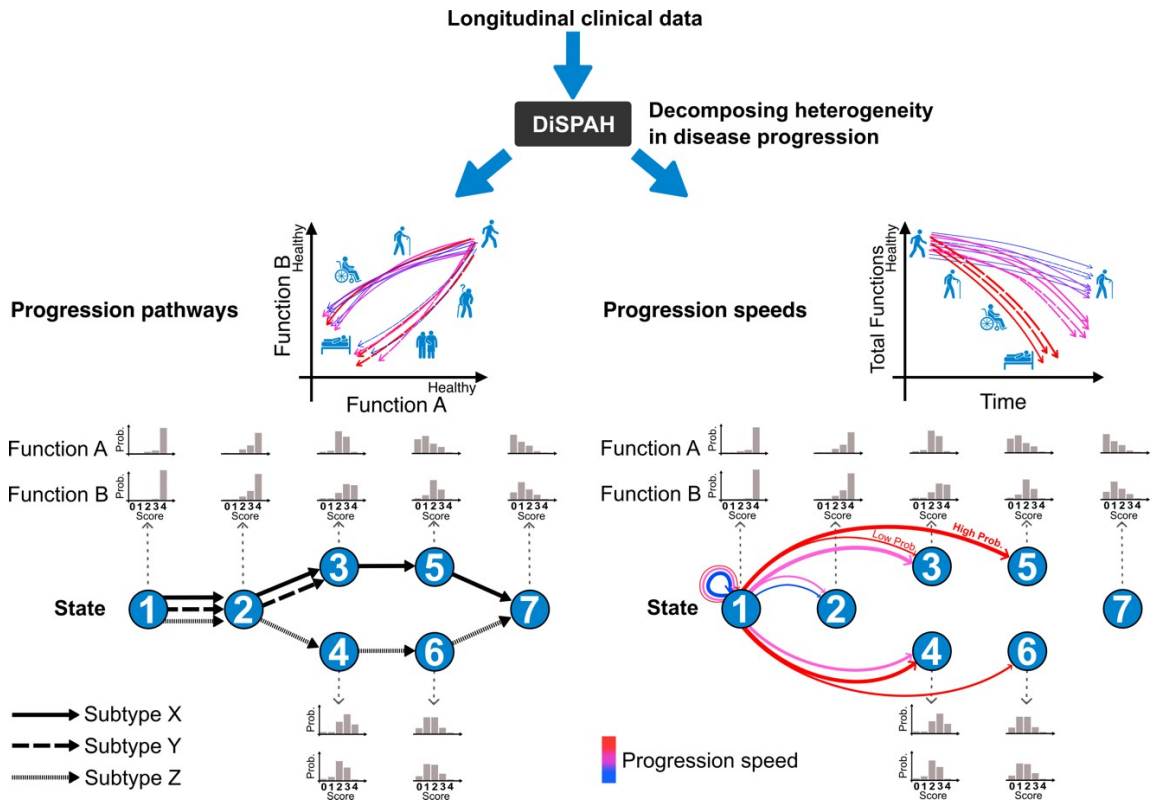

Figure 1. A machine learning model that decomposes individual differences in progression speed and progression pathway

Research Results

To simultaneously estimate patient-specific progression pathway and progression speed, the research group developed DiSPAH, a machine learning method based on a continuous-time hidden Markov model. By analyzing longitudinal clinical data, DiSPAH infers latent disease progression states that are not directly observable and, for each patient, estimates both the progression pathway represented by patterns of transitions between latent disease progression states and the progression speed representing how readily those transitions occur (Figure 1).

The team applied this method to longitudinal ALSFRS-R data from ALS, a disease known to show large inter-individual differences not only in progression pathway but also in progression speed. First, they analyzed longitudinal data from 264 patients with limb-onset ALS in the US-based Answer ALS cohort who met the study criteria. Using DiSPAH, they estimated patient-specific progression speeds and progression pathways. The results showed that ALS progression is not uniform, but instead includes six subgroups

with characteristic progression pathways, with noticeable variation in progression speed even within each subgroup (Figure 2). Furthermore,

when the researchers applied the same approach to data from the larger PRO-ACT cohort of 2,565 individuals, using disease progression states identified from the Answer ALS cohort as a reference, they reproduced trends similar to the progression patterns observed in the Answer ALS cohort.

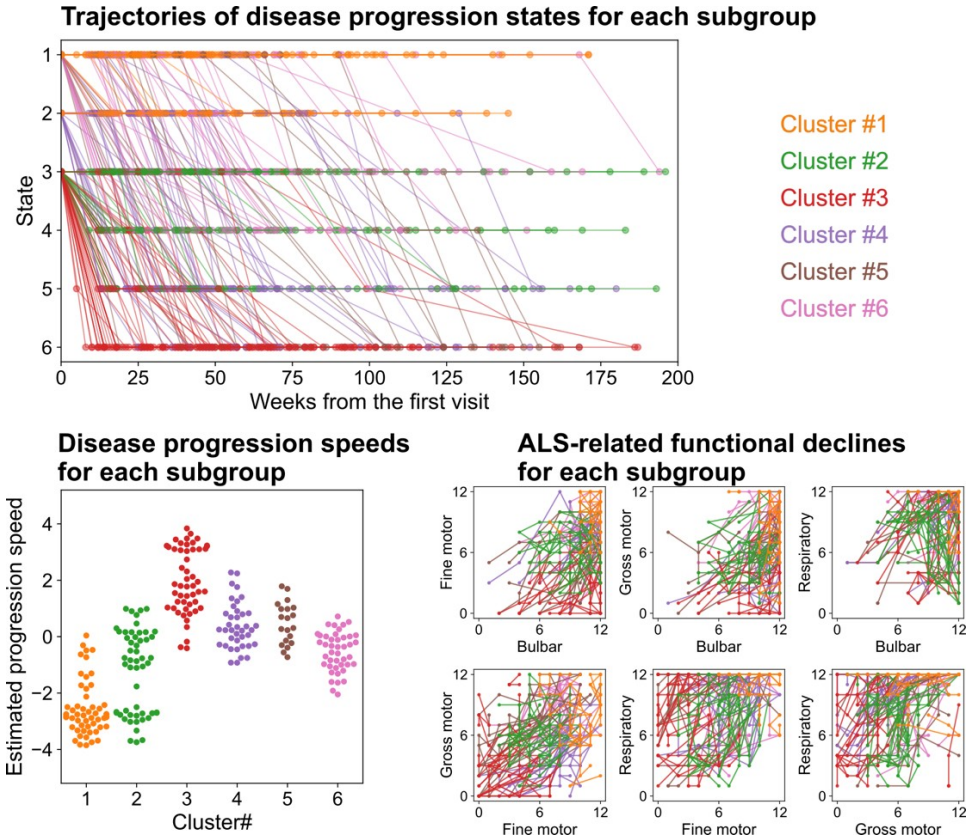

Figure 2. Progression pathway subgroups and progression speeds identified by DiSPAH

The researchers then examined the relationship between estimated progression speed and genetic characteristics. They found that patients carrying C9orf72 mutations tended to show faster progression. In addition, analysis of comprehensive gene expression and protein expression data from motor neurons derived from patient iPS cells suggested that disrupted protein translational homeostasis and oxidative stress may be involved in progression speed.

From a clinical perspective, the progression speeds and pathways estimated by DiSPAH from the full follow-up period of longitudinal clinical data were associated with survival and with the risk of ALS-related functional decline. The researchers also found that progression speed and progression pathway could be predicted to some extent from clinical and genetic information available at the start of

follow-up. Evaluation of predictive performance for ALS-related functional decline further suggested that DiSPAH may complement information that is difficult to capture using conventional indicators alone.

Research Summary and Future Perspective

DiSPAH provides a new framework for understanding disease progression in greater detail by separating inter-individual variability into progression pathway and progression speed. Further validation in more diverse ALS subtypes, as well as in other chronic diseases including additional neurodegenerative disorders, and across multiple centers and cohorts, is expected to improve the robustness and generalizability of the method.

In the future, if disease progression can be anticipated from information obtained near the initial clinical visit, DiSPAH may help support patient-specific explanations, treatment planning, and selection of participants for clinical trials. Moreover, a deeper understanding of the genetic and molecular factors associated with different patterns of progression may contribute to new insights into disease mechanisms and to the identification of potential therapeutic targets.

Publication

Yuichiro Yada[1,2] and Honda Naoki[1,3,4], Decomposing heterogeneity in disease progression speeds and pathways, npj Digital Medicine

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