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Opinion

Harnessing Big Data in Amyotrophic Lateral Sclerosis: Machine Learning Applications for Clinical Practice and Pharmaceutical Trials

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Abstract

The arrival of genotype-specific therapies in amyotrophic lateral sclerosis (ALS) signals the dawn of precision medicine in motor neuron diseases (MNDs). After decades of academic studies in ALS, we are now witnessing tangible clinical advances. An ever increasing number of well-designed descriptive studies have been published in recent years, characterizing typical disease-burden patterns *in vivo* and *post mortem*. Phenotype- and genotype-associated traits and "typical" propagation patterns have been described based on longitudinal clinical and biomarker data. The practical caveat of these studies is that they report "group-level", stereotyped trajectories representative of ALS as a whole. In the clinical setting, however, "group-level" biomarker signatures have limited practical relevance and what matters is the meaningful interpretation of data from a single individual. The increasing availability of large normative data sets, national registries, extant academic data, consortium repositories, and emerging data platforms now permit the meaningful interpretation of individual biomarker profiles and allow the categorization of single patients into relevant diagnostic, phenotypic, and prognostic categories. A variety of machine learning (ML) strategies have been recently explored in MND to demonstrate the feasibility of interpreting data from a single patient. Despite the considerable clinical prospects of classification models, a number of pragmatic challenges need to be overcome to unleash the full potential of ML in ALS. Cohort size limitations, administrative hurdles, data harmonization challenges, regulatory differences, methodological obstacles, and financial implications and are just some of the barriers to readily implement ML in routine clinical practice. Despite these challenges, machine-learning strategies are likely to be firmly integrated in clinical decision-making and pharmacological trials in the near future.

Keywords: machine-learning; artificial intelligence; amyotrophic lateral sclerosis; primary lateral sclerosis; motor neuron disease; neuroimaging; biomarkers

1. Introduction

Biomarker development is a key goal of amyotrophic lateral sclerosis (ALS) research and a vast array of promising biomarkers have been evaluated including molecular, transcriptomic, and metabolic markers; panels of serum, urine, and cerebrospinal fluid (CSF) "wet" biomarkers; and positron emission tomography (PET) and magnetic resonance imaging (MRI) biomarkers [1]. Neuroimaging in ALS has been remarkably successful in capturing the substrate of phenotype-defining pathological change *in vivo* along the entire neuro-axis. ALS-associated imaging alterations have been described in the brain, spinal cord, plexi, and muscles with remarkable anatomical consistency between various studies. The archetypal imaging signature of ALS includes bilateral precentral gyrus atrophy, degeneration of descending corticospinal and corticobulbar tracts, degeneration of the corpus callosum and brainstem, changes in the lateral columns and the anterior horns of the spinal cord, and fatty infiltration of denervated muscles [2]. Based on statistical observations in large cohorts, fairly consistent disease-associated, genotype-specific, and phenotype-associated disease-burden patterns have been described [3]. To account for observations captured in various disease stages, a series of robust longitudinal studies have also been published, describing anatomical propagation patterns and generating disease-spread models *in vivo* [4]. Imaging metrics are often correlated with clinical data and linked to pathological stages. Presymptomatic changes have been captured decades before projected symptom onset in asymptomatic carriers of genetic variants, paving the way for viable presymptomatic interventions [5,6]. While the description of "typical" disease burden patterns, "stereotyped" disease propagation trajectories, and "representative" presymptomatic signatures are important academic milestones and help to generate novel biological hypotheses, they have remarkably limited clinical relevance to the diagnosis, monitoring, and management of individual patients. From a purely clinical perspective, "average" survival and "typical" progression rates have limited importance in the assessment of specific individuals. In clinics, we face individual patients who enquire about their own specific phenotype, their own survival prospects, their expected progression rate, likely prognosis, and likely response to therapy as opposed to overall

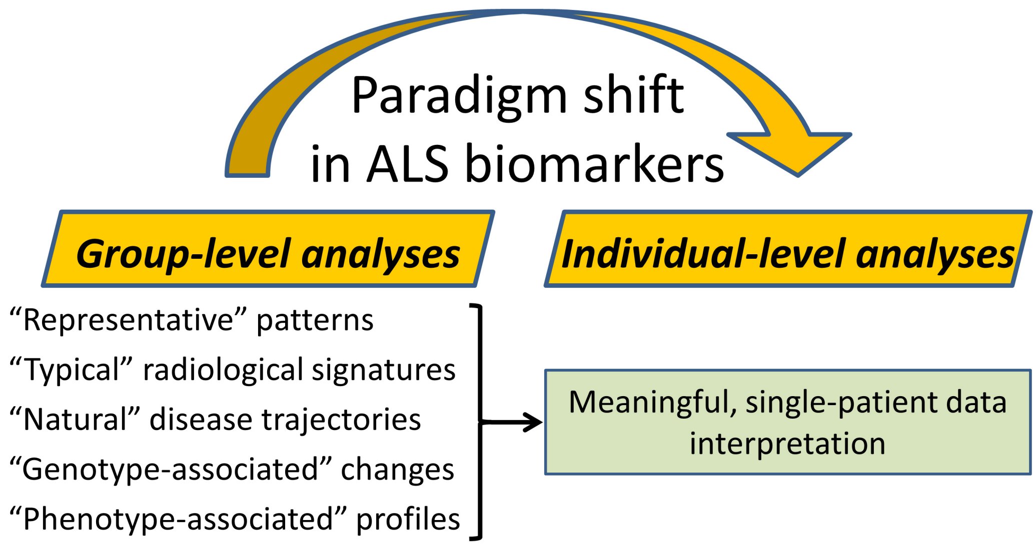

Fig. 1. The conceptual evolution of amyotrophic lateral sclerosis (ALS) research studies—the transition from group-level descriptive studies to single-patient data interpretation frameworks.

disease-, genotype-, or phenotype-associated averaged values. Accordingly, what is relevant in the clinic is the accurate and meaningful interpretation of single subject data profiles (Fig. 1). The quest, therefore, is the interpretation of the biomarker profile of a single patient when first met in clinic and the ambition is to accurately categorize that individual into a specific diagnostic group, phenotypic class, likely genotype for targeted testing, likely prognostic category, and likely response to specific therapies. There is a notion among ALS researchers that by the time a patient fulfils clinical criteria for ALS, a considerable disease burden has already been accrued, hindering effective pharmacological interventions. Longitudinal studies suggest that by the time a patient is formally diagnosed, the motor cortex, corticospinal, and corticobulbar tracts are already affected [7,8]; therefore, the expectation that a disease-modifying agent introduced at that point would result in perceptible functional gain may be naïve. The optimal therapeutic window, therefore, is likely to precede the point of meeting formal diagnostic criteria and we probably need to shift our attention to "suspected" patients not meeting diagnostic criteria and presymptomatic cohorts harboring ALS-associated genetic variants. From a biomarker perspective, the departure from large academic studies describing "group-level" observation to "single-patient" data interpretation frameworks is long-overdue.

2. Promising Machine Learning Initiatives across Biomarker Domains

2.1 Examples from Clinical Biomarker Data

Bulbar onset, comorbid cognitive, behavioral deficits, short symptom onset to diagnosis interval, early respiratory involvement, and low body mass index (BMI) have long been established as adverse prognostic indicators, but well-trained machine learning (ML) models promise accurate individual predictions [9–16]. ML has been successfully applied to data collected by wearable sensors generating functional insights that are superior to standard rating scales [17]. Gait features have been interpreted in a multiclass (Parkinson's disease (PD), Huntington's disease (HD), and ALS) environment combining Naïve Bayes and logistic regression approaches in an ensemble framework [18]. Concise panels of basic demographic and clinical variables have been repeatedly explored in ML models to predict functional disability [19], clinical subtypes [20], functional decline [21], rate of progression [13], caregiver quality of life [22], caregiver burden [23], and survival [16]. Other clinical features such as voice [24], facial movement [25], and electromyography (EMG) variables [26] have also been successfully integrated in ML models to distinguish subjects with ALS from controls. ML models are increasingly applied to rich epidemiology data sets, and interactions between clinical and environmental factors have also been investigated in a logistic regression model [27].

2.2 Examples form Imaging

The archetypal imaging features of ALS include primary motor cortex, corpus callosum, corticospinal tract, and brainstem degeneration [28–30], but selective basal ganglia, thalamic, hippocampal and cerebellar involvement [31–36] is increasingly accepted as part of the imaging signature of ALS. Despite initial focus on the primary motor cortex, the contribution of cerebellar and subcortical grey matter pathology to key clinical manifestations are increasingly recognized [37–39]. A wide range of imaging-derived metrics have been explored in single-patient classification models [40,41], including diffusion data [42,43], morphometric data, functional MRI data [44], network dynamics parameters [45], functional near-infrared spectroscopy (fNIRS) variables [46], and combined panels of structural and diffusivity metrics [47–50]. In line with multi-class categorization efforts, MRI data have been increasingly utilized to distinguish specific phenotypes [51,52]. MRI-derived indices have also been evaluated in survival prediction [53,54]. More recently, vision transformer architectures were tested to distinguish subjects with ALS from controls combining spatial and frequency domain information to enhance model performance [55]. It is noteworthy that promising single-patient data interpretation has also been achieved using z-score-based contrasting of MRI-derived metrics to pools of demographically-matched normative data [8,29,56]. In addition to cerebral MRI-derived metrics, the utility of muscle ultrasonography data [57], positron emission tomography (PET) [58], and spinal markers [59,60] have also been demonstrated in ML applications. ML has also been harnessed to enhance the development of effective brain-computer interface (BCI) protocols relying on electroencephalography (EEG) signal patterns [61]. Anatomical patterns of cerebral involvement in primary lateral sclerosis (PLS) are remarkably similar to ALS [62–65]; therefore, reliable discrimination based on brain metrics alone remains relatively challenging [51,52].

2.3 Examples from "Wet Biomarkers"

The challenge of categorizing into relevant pathological stages and subtyping TDP-43 proteinopathies has been successful met through a variety of approaches [66,67]. Metabolomic profiles have been evaluated in ML frameworks to differentiate controls from patient with ALS [68], predict clinical outcomes in a clinical trial setting [69], and identify potential future targets for pharmacological interventions [70]. Lipidomics data were successfully assessed in ML frameworks to distinguish ALS from PLS [71]. There is a presumed publication bias for models with moderate-to-high classification accuracy, but approaches yielding limited biomarker potential have also been reported, which are invaluable for the research community. One such study highlighted the practical biomarker limitations of multivariate models using patient-derived fibroblast morphometry features [72], while another innovative study evaluated metabolomic profiles years before the diagnosis attempting to separate controls from presymptomatic ALS cases [73].

2.4 Examples from Genetics and Transcriptomics

Innovative ML strategies have been developed integrating functional genomics with genome-wide association study (GWAS) summary statistics to aid gene discovery [74]. ML models have been used to predict the pathogenicity of *TARDBP* and *FUS* gene variants [75] and also successfully applied to transcriptomic [76] and microRNA profiles [77]. The polygenic underpinnings of cognitive dysfunction in ALS have been recently explored by an innovative ML approach [78]. Advanced clustering methods have been applied to genetic [79], clinical and imaging [80] data sets capturing unique subpopulations with distinctive genetic, clinical, or radiological features.

3. Discussion

3.1 Shortcomings of Recent Studies

As demonstrated by the examples above, several methodologically diverse and promising pilot studies have been published recently. While all of these indicate the potential clinical role of ML in motor neuron disease (MND) and signal tangible future opportunities, a number of practical caveats hinder the implementation of these models in routine clinical practice (Table 1). The vast majority of recent ML initiatives in ALS were either single-center studies or merely trained and validated on national data sets. From a diagnostic perspective, strikingly few multi-class classification models were tested. The vast majority of biomarker and imaging studies in MND focus on ALS, and cohorts of Kennedy's disease, PLS, post-polio syndrome, are spinal muscular atrophy patients are seldom included [81–83] despite overlapping clinical and imaging features [84]. Similarly, despite promising results, the accuracy of proposed models has not been convincingly tested on early-stage, suspected, or presymptomatic cohorts. Moreover, existing models rely either exclusively on clinical data, biomarker data, or imaging data and strikingly few studies have attempted to integrate inputs from a multitude of biomarker domains.

Similarly, procedures to account for missing data are often overlooked or inadequately addressed. Models developed for "real-life" clinical applications must accommodate for the fact that many patients do not have an entire array of comprehensive data sets encompassing clinical, CSF, serum, urine, and imaging inputs. Classification models to date have mostly categorized patients into diagnostic subgroups, phenotypic classes, survival prospect categories, and pathological stages, but unlike in other conditions, the potential of ML to predict response to therapy or likely genotypes have not been comprehensively explored to date. The acknowledgement and candid discussion of these limitations will likely help to shape future study designs and determine research priorities.

3.2 Future Directions

Model validation schemes in the future should include suspected cases, subjects with short disease duration, and presymptomatic gene carriers to compellingly demonstrate the discriminatory potential of a proposed model between patients with ALS and ALS mimics. While the majority of recent studies have implemented supervised ML models, the potential of robust unsupervised models needs to be

Table 1. Prospects and challenges of implementing effective machine-learning strategies in amyotrophic lateral sclerosis and other motor neuron diseases.

Opportunities	Challenges
Early diagnosis of suspected cases	Data harmonization: scanners, immune assays etc.
Prognostic categorization	Data storage challenges: expense, maintenance, access, screening
Predicting response to specific therapies	Data regulations and regional regulatory differences: GDPR, European Union (EU), United States (USA), Australia etc.
Phenotypic classification	Cloud storage: expense, regulations
Identification of likely genotype for targeted testing	Computational demands: real-time versus post hoc analyses
Rate of functional decline predictions	Validation platforms and model adjustments
Classification into clinical and pathological disease stages	Financial implications: funding applications, industry collaborations, annual reports
Pre-enrolment patient stratification for clinical trials	Maintenance and curation of data repositories
Ascertainment of slow progressors and limited phenotypes	Inclusion bias in training data sets: cognitive, bulbar, NIV-dependent phenotypes may be underrepresented
Disability profile prediction	Defining access: only raw data contributors versus open-access platforms
Extra-motor expansion prediction (cognitive, behavioral, cerebellar features)	Weighted/balanced integration of multimodal data: wet biomarkers, clinical data, imaging etc.
Informing resource allocation (finances, PT, OT, modifications, adaptive strategies)	Legal framework and acknowledging the limitations of ML predictions and classification
Informing timing of interventions (PEG, NIV)	Data ownership questions
Phenoconversion prediction in asymptomatic/presymptomatic mutation carriers	Consenting for participation, right of withdrawing from training data sets
Discrimination of ALS from mimic syndromes and low-incidence phenotypes e.g., PLS, SBMA	Anonymization procedures and pseudonymization for cross-platform, multi-domain data
Identification of early ALS in FTD and cohorts with psychiatric conditions	Regulation of industry–academia collaborations
Clustering to identify subsets of patients with unique clinical, radiological, or biomarker profiles potentially harboring rare genetic variants	Intellectual property (IP) issues, IP ownership, commercialization issues: open-access versus subscription based access
Establishing the comparative diagnostic/monitoring/discriminatory sensitivity (hierarchy) of multiple markers across several domains; some of which may be cheaper yet superior	Imaging logistics: limited availability of PET, high-field MRI platforms and high scanning fees
Precision, objective tracking of disease burden over time in clinical trials instead relying on functional rating scales and indirect clinical measures	Wet biomarker logistics: LP, storage, transfer, freezing and cold-chain etc.

Abbreviations: ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; GDPR, General Data Protection Regulation; LP, lumbar puncture; MRI, Magnetic resonance imaging; NIV, non-invasive ventilation; OT, Occupational therapy; PEG, percutaneous endoscopic gastrostomy; PET, Positron emission tomography; PLS, primary lateral sclerosis; PT, physiotherapy; SBMA, spinal bulbar muscular atrophy; ML, machine learning.

explored in forthcoming studies. To avoid model overfitting to local data, it seems imperative to build, test, and validate models on multi-site international data sets. Instead of relying on single-domain data, such as clinical metrics, serum markers, or imaging indices in isolation, future models should attempt to integrate features from a multitude of modalities and biomarker platforms. Instead of defining features *a priori* and restricting analyses to predefined regions of interest in advance, formal variable importance analyses and ranking is important for streamlining models for the evaluation of the most relevant variables only. Binary classification initiatives have to be superseded by robust multi-class classification models to account for disease heterogeneity and common disease mimics to mirror real-life clinical dilemmas. Data harmonization efforts need to be doubled internationally and data transfer legislation needs to be simplified.

3.3 Cause for Optimism

Funding agencies, charities, and academic centers have long recognized the imperative of multi-site, cross-border collaborations, which are indispensable for effective model development and validation. Clinical trials sometimes make some of their raw data available after the con-

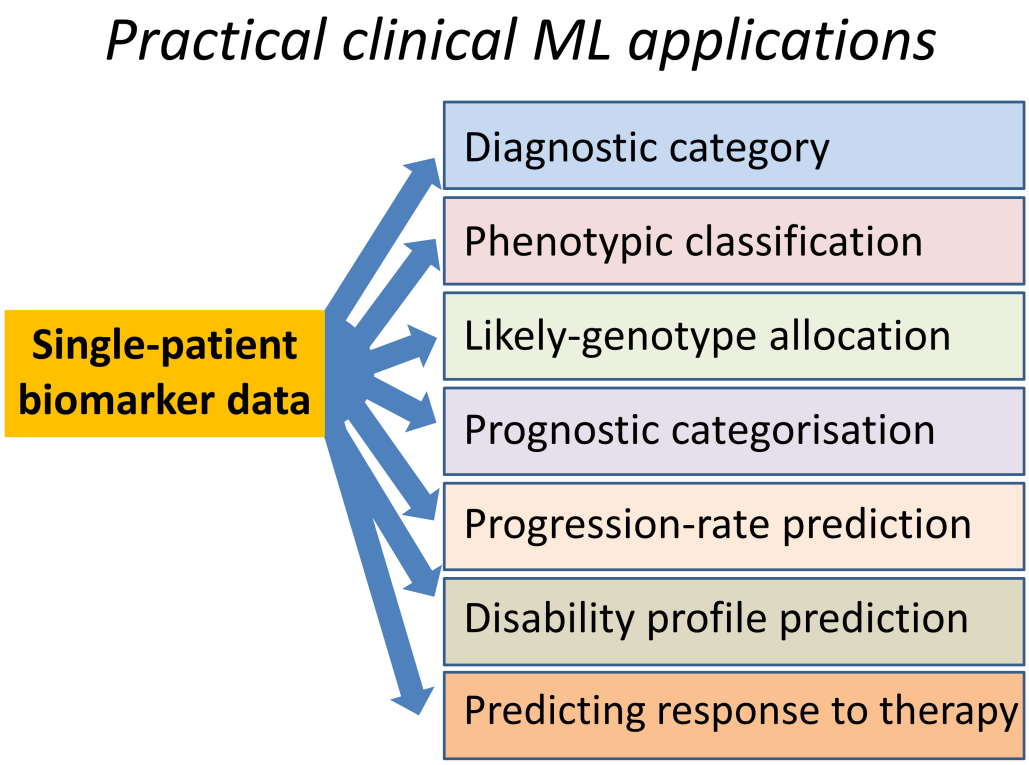

Fig. 2. The practical relevance of machine learning initiatives—potential clinical deliverables.

clusion of a pharmaceutical trial. Data form initiatives such as the "Pooled Resource Open-Access ALS Clinical Trials" (PRO-ACT) and "Project MinE ALS Sequencing Consortium" have been instrumental for the development, optimization, and validation of ML models. Large biomarker repositories have been successfully set up for a variety of neurodegenerative conditions such as Alzheimer's Disease (AD), frontotemporal dementia (FTD), and HD and a number of promising multi-site initiatives also exist in ALS [85,86], paving the way for model optimization and translation into viable clinical applications [87]. The Neuroimaging Society of ALS (NiSALS) has undertaken a number of successful collaborative projects and demonstrated the feasibility of cross-platform data interpretation [88]. In addition to analogous efforts in other neurodegenerative conditions such as AD, HD, and FTD [89], promising artificial intelligence (AI) frameworks have been trialed in clinical oncology, radiology, ophthalmology, and histopathology, demonstrating the prospect of viable computer-aided screening and diagnostic tools. In recognition of the urgency of prospective, harmonized, multisite data acquisition, a number of robust data collection and analysis platforms have been recently developed in ALS [90–95], several of them proposing innovative novel clinical trial designs [96,97]. Project MinE, Precision ALS (PALS), PRO-ACT, NiSALS, Northeast ALS (NEALS) and the Western ALS (WALS) consortia, and the Canadian ALS Neuroimaging Consortium (CALSNIC) are just some examples of successful multi-site data platforms. In parallel with increased international collaborations, a number of technological advances are also aiding data collection and real-time data interpretation such as the drop in the price of cloud solutions, the availability of high-performance computational facilities at academic centers, and wearable devices with wireless connection, etc. Despite current sample size limitations, data harmonization difficulties, and legislative challenges, ML methods will no doubt be firmly integrated in individualized diagnostic pipelines, clinical predictions, and assessment of treatment response in the near future (Fig. 2). Academic ML initiatives are likely to filter down to routine clinical practice and develop into viable clinical applications.

Author Contributions

ELT, JL and PB contributed equally to the conceptualisation and drafting of this manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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