Applying a clinical algorithm on real world EMR data for patient risk stratification of undiagnosed Amyotrophic Lateral Sclerosis (ALS)

Mitsubishi Tanabe Pharma Canada

AUTHORS AND AFFILIATIONS

Taha Bandukwala, MD, FRCPC: Chief Medical Officer, Ensho Health
Angela Genge, MD: Executive Director Clinical Research Unit, Montreal Neurological Institute-Hospital
Amer Ghavanini, MD, PhD, FRCPC: Division Head of Neurology, Trillium Health Partners
Pinay Kainth, PhD: Mitsubishi Tanabe Pharma Canada, Inc.

INTRODUCTION

- Amyotrophic lateral sclerosis ("ALS") is a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord
- It is characterized by progressive loss of upper and lower motor neurons
- Initial symptoms are often subtle and can cause delays in diagnosis or misdiagnosis
- Early diagnosis of ALS and referral to a specialized multidisciplinary centre has proven to improve quality of life and prolong survival while misdiagnosis can result in unnecessary interventions including surgery[1]
- We investigated the feasibility of developing a clinical algorithm to screen electronic medical record data for patients in which follow-up investigations for ALS was clinically appropriate (the "Algorithm")

METHODS

- An algorithm was developed by Ensho Health in consultation with ALS clinicians
- The Algorithm categorizes patients into four risk groupings based on evidence of upper motor neuron ("UMN") degeneration, lower motor neuron ("LMN") degeneration and spinal region involvement (**Figure 1**)

Figure 1. ALS Risk Straitifcation Algorithm

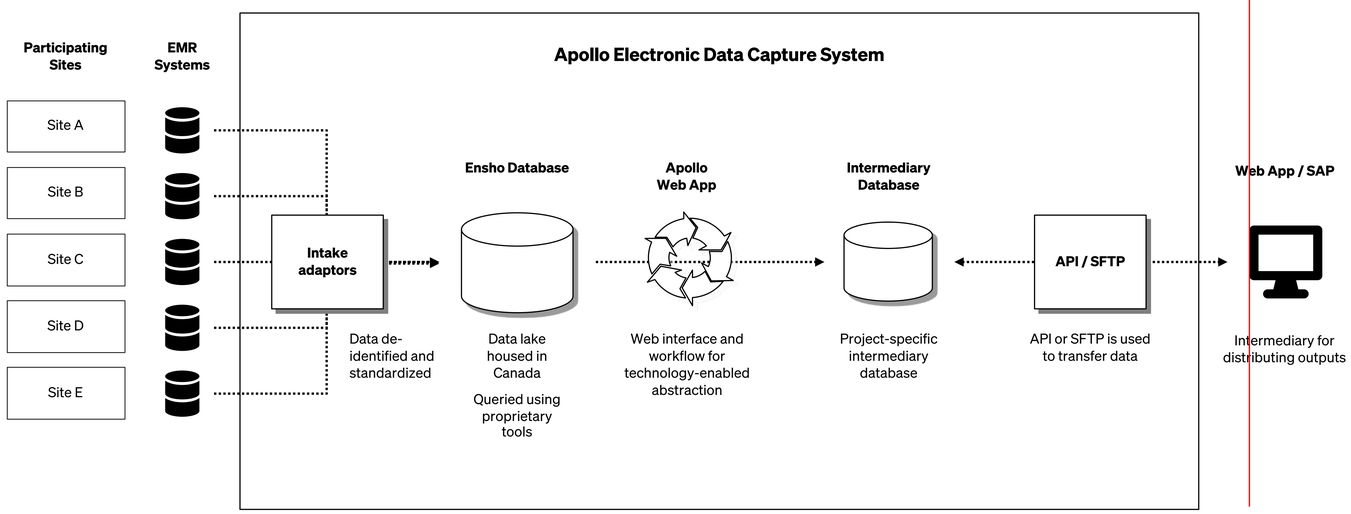
	UMN Degeneration	LMN Degeneration	Spinal Region Involvement
Very High Risk	Yes	Yes	≥2
High Risk	Yes	Yes	1
Moderate Risk	Yes	No	≥2
Low Risk	All other combinations		

- The Algorithm was encoded in software and applied to the electronic medical records of 3,372 patients of a single community neurology practice in Ontario, Canada using the Apollo Electronic Data Capture system ("Apollo") by Ensho Health
- Apollo is an integrated set of computing tools and systems designed to extract clinical features from structured and unstructured electronic health record data with high fidelity (**Figure 2**)
- Patients were risk-stratified based on the results of sequential queries for (1) clinical or electromyographic ("EMG") evidence of UMN and LMN degeneration and (2) involvement of the bulbar, cervical, thoracic or lumbosacral regions of the spine (**Figure 3**)
- Past investigations or clinical features inconsistent with ALS were subsequently queried to exclude patients whose symptoms had alternative explanations (**Figure 4**)

Figure 3. Clinical Features Queried

Clinical LMN Findings	• Weakness • Atrophy • Wasting • Fasciculations/twitching • Palsy • Hypotonia • Decreased reflexes (absent or 1+) • Muscle denervation • Declining mobility • MRC less than 5/5
EMG LMN Findings	• Reduced recruitment • Reduced interference pattern • Large motor unit action potentials • Voluntary motor unit potentials • Large amplitude • Long duration • Fibrillation potentials • Fasciculation(s) • Positive sharp waves • Combined muscle action potential
Clinical UMN Findings	• Spasticity • Pathologic reflex(es) (e.g., Hoffman) • Increased deep tendon reflexes (3+ or 4+) • Extensor plantar response (e.g., Babinski) • Pyramidal weakness • Pronator drift • Contracture
Spinal Region Involvement	• Bulbar, including bulbar related symptoms (swallowing/drooling, speaking/speech abnormalities, chewing, facial weakness, dyspnea, dysphagia, vision abnormality) • Cervical • Thoracic • Lumbosacral

Figure 2. Overview of Ensho Health's Apollo Electronic Data Capture System



- The medical records of patients in the Very High Risk group were reviewed to determine whether ALS was likely and/or referral to a specialized multidisciplinary team was appropriate

Figure 4. Clinical Features Inconsistent with ALS

Findings Inconsistent with ALS	• Sensory dysfunction (pain) • Abnormal quantitative sensory testing (QST) • Abnormal skin biopsy • Muscle biopsy of fatty replacement • Sphincter abnormalities • Autonomic nervous system dysfunction - orthostatic hypotension, abnormal tilt table test • Anterior visual pathway abnormalities • Movement abnormalities consistent with Parkinson's disease • Other common explanatory diagnoses such as stroke, myasthenia gravis, MVA and TBI, multiple sclerosis, radiculopathy, functional disorder, seizure disorder, spinocerebellar ataxia, CIDP, essential tremor, Parkinson's and other neurodegenerative disorders)

RESULTS

- 1,332 patients (39%) had evidence of UMN degeneration, LMN degeneration and/or spinal region involvement of which 12% were categorized as Very High Risk, 3% were categorized as High Risk, <1% were categorized as Moderate Risk and 84% were categorized as Low Risk before exclusionary findings were queried (**Figure 5**)
- 129 of the 160 patients (81%) in the Very High Risk group had alternative explanations for UMN and/or LMN degeneration
- Of the 31 remaing patients (19%), 3 (10%) had a diagnosis of ALS (100% sensitivity), 7 (23%) had a pending workup for ALS and 9 (29%) had ALS ruled out in prior clinical investigations leaving 12 patients in which ALS was not previously considered for clinical review (**Figure 6**)
- Clinical review of the remaining 12 patients identified one (8%) in which ALS was high likely and rejected the potential diagnosis in 11 (92%)

Figure 5. Outcomes of Application of Algorithm

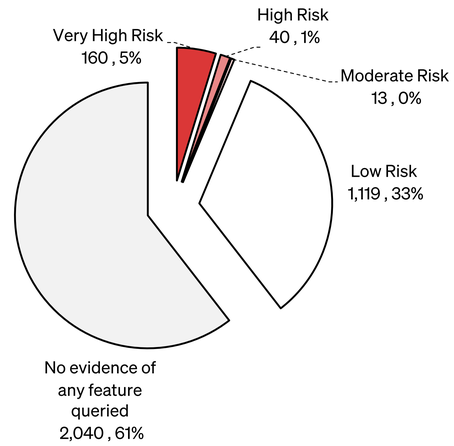
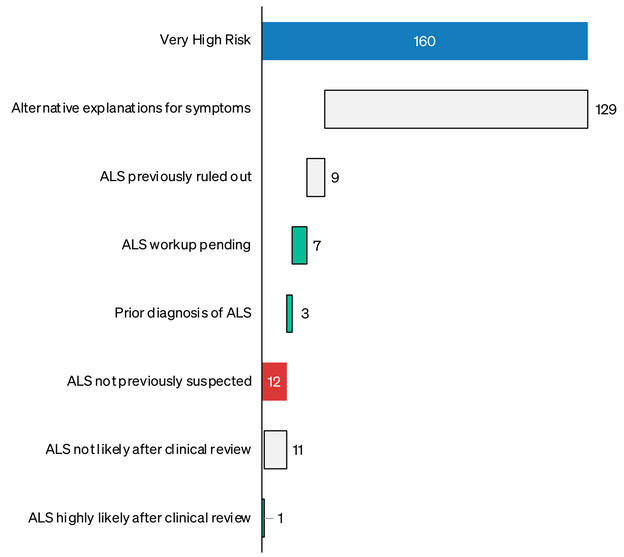


Figure 6. Results of Clinical Review of Very High Risk Patients



DISCUSSION

- We demonstrated that clinical algorithms can practically screen electronic medical record data for patients with ALS when deployed through software capable of analyzing structured and unstructured data
- The Algorithm correctly identified all three patients diagnosed with ALS prior to the study but its sensitivity and specificity could not be calculated without comprehensive workups in all 3,372 patients whose records were analyzed
- The positive predictive value of being categorized as Very High Risk was 17% and could likely be improved on by deriving optimal weights for the features of the Algorithm from a larger data set and emphasizing objective (EMG) over subjective (symptom-related) findings
- A limitation of the practice setting was that complex neurological patients were being referred to a tertiary neurological centre for management, potentially limiting the number of undiagnosed Very-High risk patients for subsequent investigation
- Further refinements to the Algorithm are planned as is a more comprehensive prospective validation at additional community neurology practices in Canada

Reference

1. Williams, J.R., Fitzhenry, D., Grant, L. *et al.* Diagnosis pathway for patients with amyotrophic lateral sclerosis: retrospective analysis of the US Medicare longitudinal claims database. *BMC Neurol* 13, 160 (2013). https://doi.org/10.1186/1471-2377-13-160

Acknowledgements

This work was funded by Mitsubishi Tanabe Pharma Canada, Inc.