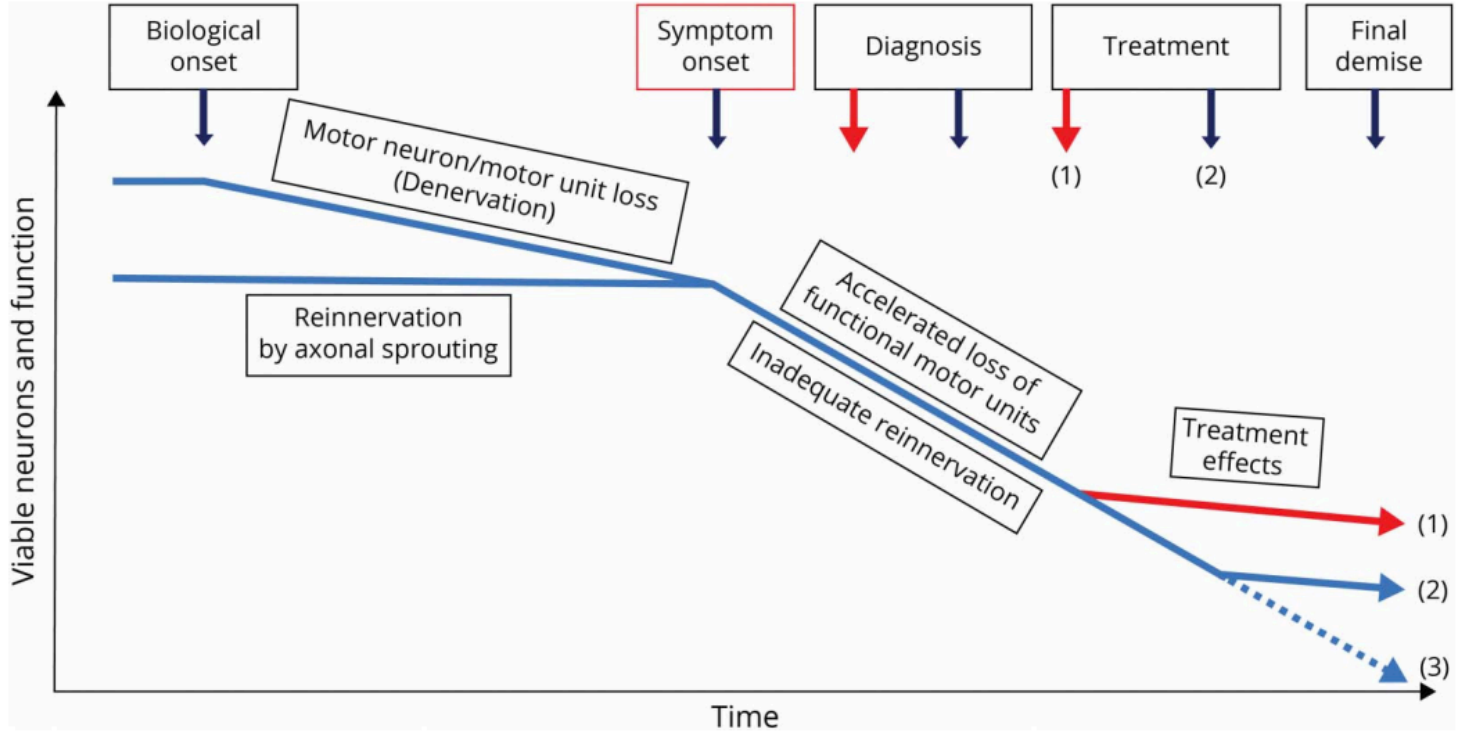
Figure 1: Hypothetical Illustration of ALS Disease Progression and Intervention



The biological process in ALS (loss of motor neurons) precedes symptom onset.[3] When intrinsic compensatory muscle reinnervation by axonal sprouting is no longer possible because of relentless motor neuron loss, symptoms begin to appear and loss of functional motor units may be accelerated. Currently, it takes approximately 11–12 months after symptom onset to reach a diagnosis of ALS, at which time appropriate disease-modifying drug therapy can be initiated to slow disease progression. Three possible trajectories are indicated: (1) The greatest slowing of disease progression is achieved with early diagnosis after symptom onset and early initiation of treatment, as indicated by the red arrows. (2) More modest slowing of disease progression results from the conventional timeframe for diagnosis and treatment, indicated by the dark blue arrows. (3) Disease trajectory is most rapid in the absence of any disease-modifying therapy, indicated by the blue dotted arrow. Blue arrows demonstrate several critical time points. ALS = amyotrophic lateral sclerosis.

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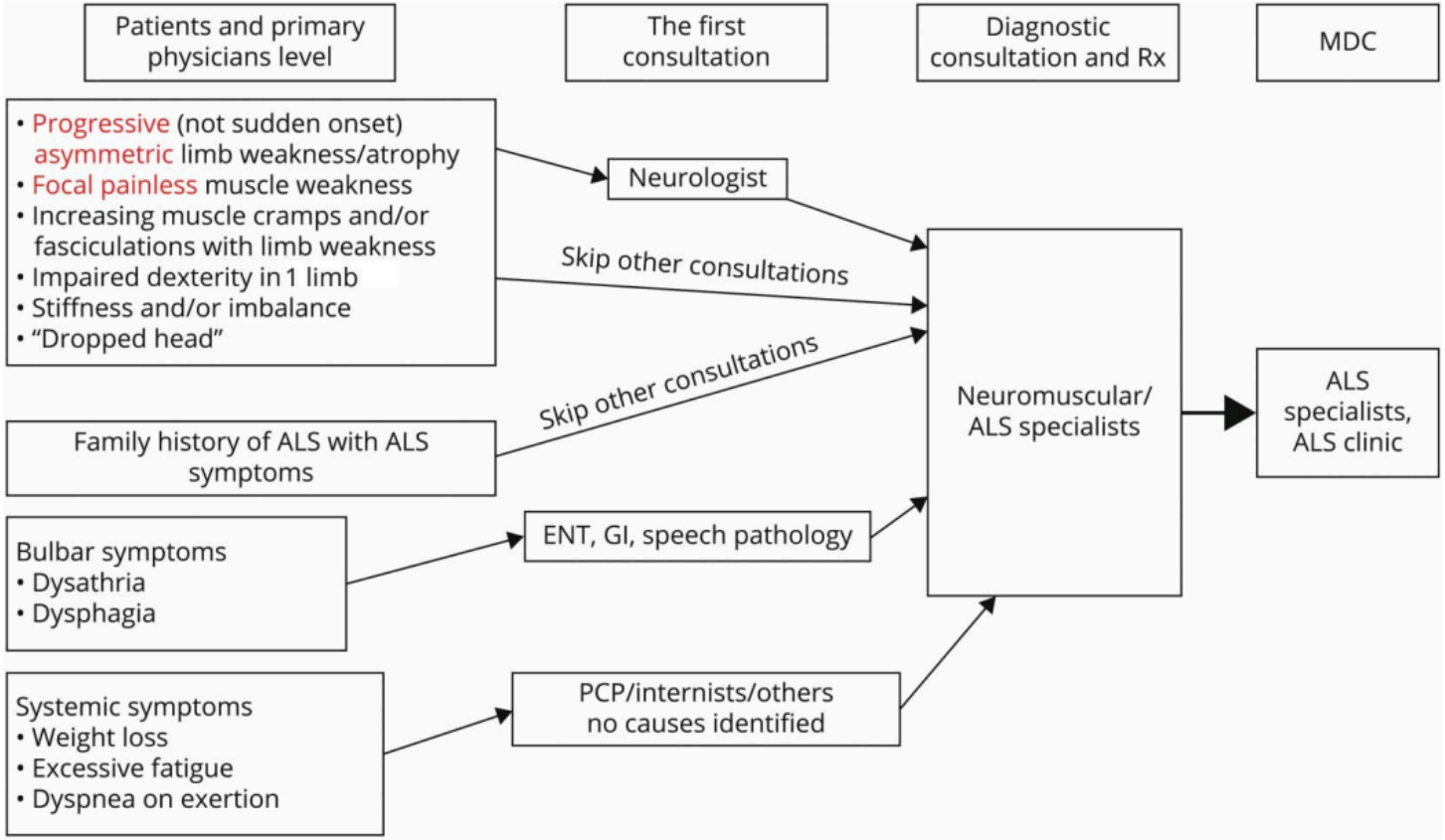
Figure 4: Idealized and Simplified Process to Hasten the Diagnostic Process of ALS



The reality often is more complex because ALS symptoms may be less clear-cut and judgements by patients and primary physicians often reflect more complex considerations than shown in the figure. "Dropped head" is caused by focal neck extensor muscle weakness. Painless, progressive, asymmetric limb weakness or painless, progressively worsening bulbar function should alert primary care physicians, nonneurologist specialists, and the lay public to the possibility of ALS. The aim of the diagnostic process should be referral to a neuromuscular specialist or ALS center in the shortest possible interval after symptom onset. ALS = amyotrophic lateral sclerosis; ENT = ear-nose-throat specialists; GI = gastroenterologists; MDC = multidisciplinary clinic; PCP = primary care physicians.

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Topics of Discussion

- NFL and pNFL are promising[2, 3] but who would order these tests? When is the right time to test? Would this overburden consulting neuromuscular neurologists and potentially lengthen the diagnostic timeline?

- Are the authors over-selling the benefit of early treatment intervention for currently available therapies[4-7]? Are the authors under-selling the benefit of multidisciplinary care[8,9]?

- Maybe SMA isn't the best comparison. The authors reference MS–the delay in diagnosis being about 6-8 months[10]—is this a better disease with which we should be comparing ALS and learning lessons from interventional therapies?

- What are the downsides to increasing sensitivity at the expense of specificity of diagnosis[11,12]?

- Are there other barriers to diagnosis that the authors aren't addressing? Distance to specialty neurology care[13]? Race[14]? Other factors?

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