

# Serial electrodiagnostic testing: Utility and indications in adult neurological disorders

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## Abstract

Although existing guidelines address electrodiagnostic (EDX) testing in identifying neuromuscular conditions, guidance regarding the uses and limitations of serial (or repeat) EDX testing is limited. By assessing neurophysiological change longitudinally across time, serial electrodiagnosis can clarify a diagnosis and potentially provide valuable prognostic information. This monograph presents four broad indications for serial electrodiagnosis in adult peripheral neurological disorders. First, where clinical change has raised suspicion for a new or ongoing lesion, EDX reassessment for spatial spread of abnormality, involvement of previously normal muscle or nerve, and/or evolving pathophysiology can clarify a diagnosis. Second, where diagnosis of a progressive neuromuscular condition is uncertain, electrophysiological data from a second time point can confirm or refute suspicion. Third, to establish prognosis after a static nerve injury, a repeat study can assess the presence and extent of reinnervation. Finally, faced with a limited initial study (as when complicated by patient or environmental factors), a repeat EDX study can supplement missing or limited data to provide needed clarity. Repeat EDX studies carry certain limitations, however, such as with prognostication in the setting of remote or chronic lesions, sensory

**Abbreviations:** AIDP, acute inflammatory demyelinating polyradiculoneuropathy; ALS, amyotrophic lateral sclerosis; AMAN, acute motor axonal neuropathy; AMSAN, acute motor and sensory axonal neuropathy; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CMAP, compound muscle action potential; CTR, carpal tunnel release; EDX, electrodiagnostic; EMC, electrodiagnostic medical consultant; EMG, electromyography; GBS, Guillain-Barré syndrome; IVIg, intravenous immunoglobulin; MAG, myelin-associated glycoprotein; MUAP, motor unit action potential; MUNE, motor unit number estimation; MUNIX, motor unit number index; NCS, nerve conduction study; PLS, primary lateral sclerosis; POEMS, polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes; SNAP, sensory nerve action potential; UNE, ulnar neuropathy at the elbow.

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The objectives of this activity are to (1) recognize the situations in which serial electrodiagnostic testing is indicated; (2) implement serial electrodiagnostic testing in the setting of suspicion for a new or ongoing lesion or diagnostic uncertainty regarding possible progressive disease; (3) implement serial electrodiagnostic testing when needed for prognosis in the setting of a clinically stable deficit with weakness and in settings in which the initial EDX data are incomplete.

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predominant fascicular injury, or mild axonal injury. Nevertheless, serial electrodiagnosis remains a valuable and underused tool in the diagnostic and prognostic evaluation of neuromuscular conditions.

#### KEYWORDS

electrodiagnosis, electromyography, repeat, serial

## 1 | BACKGROUND

Electrodiagnostic (EDX) medicine applies electrophysiological testing, as an extension of the history and physical examination, to assist with the diagnosis, prognosis, and management of peripheral neurological disorders. Typically, diagnostic and prognostic conclusions have been based upon data collected at a single point in time. However, serial EDX testing can offer a more precise and powerful understanding of a patient's neurophysiological function by assessing change over time. Judicious application of serial EDX testing entails a clear understanding of the diagnostic or prognostic question at hand and the potential or likelihood that electrophysiological information at a second point will enhance that understanding.

In repeating EDX studies, an electrodiagnostic medical consultant (EMC) typically seeks clarity around diagnosis and/or trajectory of evolving neurophysiology. If each study is a neurophysiological “snapshot” of the patient, serial studies add a temporal dimension, enhancing diagnostic power and/or offering a patient-specific neurophysiological trajectory of natural history or treatment response. The ideal time frame for a follow-up study is, accordingly, guided by expected evolution of physiological change. For example, gauging reinnervation by axonal regeneration may require many months, assessing for resolution

of neurapraxia may require about 3 months, whereas evaluating evolution of Guillain-Barré syndrome (GBS) may be meaningfully reassessed within weeks. The interval data help establish a prognosis, which, in turn, determines management options and shapes expectations of patients and their physicians, who adjust therapeutic interventions as needed and who help the patients adapt to changing functional needs. This monograph provides EMCs with a paradigm for considering the insight that serial EDX testing can provide and a framework of four broad clinical indications for considering serial EDX testing and deciding what clinically meaningful information to extract. It addresses limitations of serial studies and offers future directions.

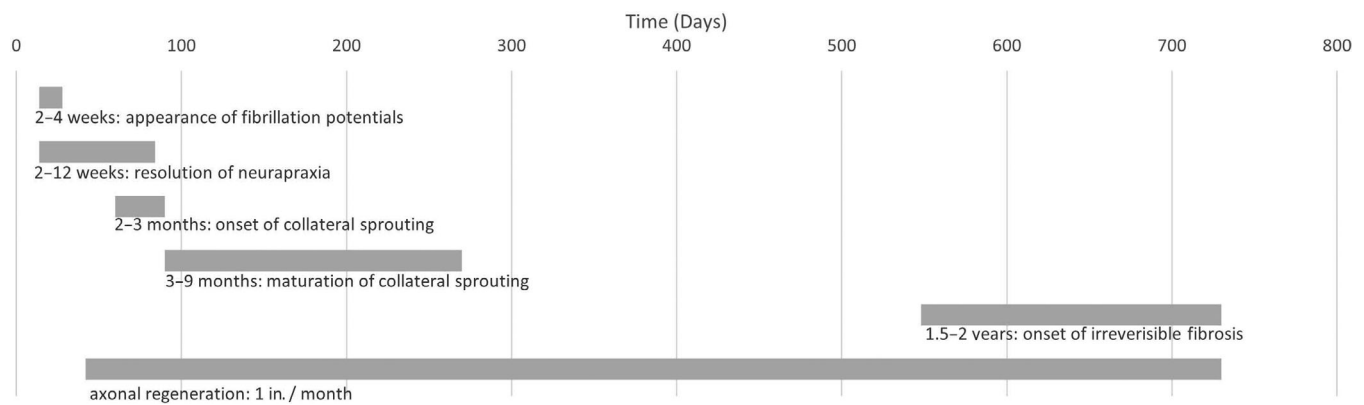
## 2 | ASSESSING ELECTROPHYSIOLOGICAL CHANGE: A PARADIGM OF PROCESS, SPACE, AND TIME

A repeat EDX study can be designed to assess for changes in three key areas: pathophysiology (“process”), localization within the peripheral nervous system (“space”), and evolution of the lesion within its established territory (“degree over time”), as shown in Table 1. Accordingly, a repeat study should be planned with appropriate nerve

**TABLE 1** How serial electrodiagnosis of process, space, and time aids clinical understanding.

Element	Assessed by	Considerations in clinical context
Pathophysiology (process)	Evaluation of extent and relative contributions of the following: <ul style="list-style-type: none"> <li>demyelination</li> <li>reversible conduction failure<sup>1</sup></li> <li>axonal loss</li> </ul>	Diagnosis and prognosis informed by the following: <ul style="list-style-type: none"> <li>conduction slowing</li> <li>conduction block</li> <li>reversal of conduction failure</li> <li>reinnervation by collateral sprouting</li> <li>reinnervation by proximodistal axonal regrowth</li> </ul> Trajectory informs capacity for recovery. Alternative diagnosis is considered if findings are unexpected relative to disease trajectory.
Localization (space)	Serial evaluation near borders of the abnormal territory, which illustrates the following: <ul style="list-style-type: none"> <li>stability</li> <li>improvement or worsening</li> <li>rate of change</li> </ul>	New subclinical EDX findings can inform the following: <ul style="list-style-type: none"> <li>pattern of progression or recovery</li> <li>expected functional changes</li> <li>possible disease trajectory</li> <li>diagnostic clarity</li> <li>role of additional evaluation</li> </ul>
Evolution (degree over time)	Reevaluation over time, which elucidates the following: <ul style="list-style-type: none"> <li>rate of physiological change</li> <li>progressive denervation</li> <li>ongoing reinnervation</li> <li>expected time course</li> </ul>	Degree of change within a nerve or muscle over time can inform the following: <ul style="list-style-type: none"> <li>expected disease time course</li> <li>timing/need for interventions</li> </ul>

Abbreviation: EDX, electrodiagnostic.



**FIGURE 1** Expected chronology of electrophysiological processes observed following a peripheral neurological lesion.

and muscle selection to assess the parameters that would reveal relevant interval change. The EMC interprets these findings relative to the historical and expected clinical trajectories to refine (or, at times, correct) the understanding of the diagnosis and prognosis. As a review, the expected trajectory of electrophysiological changes following a static lesion is depicted in Figure 1. The principles summarized in Table 2 define how serial EDX testing provides prognostic information following a peripheral nerve lesion.

### 3 | INDICATIONS FOR SERIAL ELECTRODIAGNOSTIC TESTING

Based on how serial studies provide diagnostic guidance, consider the following four broad indications for which serial EDX testing may add value: (1) when clinical change raises suspicion for a new or ongoing lesion, (2) when there is diagnostic uncertainty regarding possible progressive disease, (3) when needing to determine prognosis for a clinically stable deficit with significant weakness, and (4) when initial EDX data are incomplete.

#### 3.1 | Suspicion for new or ongoing lesion based on clinical change

When a patient with a previously established peripheral neurological disorder develops new and unforeseen symptoms, a repeat EDX examination is often indicated. The purpose may be evaluation for a recurrent or persistent process after a presumably successful intervention, or reconsideration of an initial diagnosis in light of unexpected progression or spread of abnormality. The repeat study should be interpreted in the context of the prior study, with close attention to changes in pathophysiology, localization, and evolution (Table 1) of the electrophysiological pattern of abnormality. In addition to evaluation of clinically affected nerves and muscles, evaluation of muscles at or beyond the spatial borders of the previously established disease process can apprise of any interval change.

The application and interpretation of repeat EDX studies when clinical symptoms suggest a new or ongoing disease process is depicted below through several examples.

#### 3.1.1 | Example 1: Recurrent or persistent paresthesias after carpal tunnel release or intervention for ulnar neuropathy at the elbow

This entails evaluation for ongoing demyelination (considering degree of slowing relative to previous studies), extent of residual axon loss, and evidence of new or ongoing axonal loss. Notably, mild-to-moderate persistent slowing can be expected after successful carpal tunnel release (CTR) or ulnar nerve decompressive interventions,<sup>7-10</sup> due to (A) the nature of remyelination<sup>2</sup> and (B) loss of fastest fibers in cases of secondary axonal loss. Findings suggestive of interval progression can include relative decrease of compound muscle action potential (CMAP) amplitude, new fibrillation potentials, interval slowing of conduction velocity across the lesion, or decreased motor unit action potential (MUAP) recruitment when compared with preoperative study. The possibility of an unrelated lesion causing new or changing symptoms should also be considered.

Post-CTR, persistent unequivocal focal demyelination of the median nerve implies a new or ongoing lesion; rarely is the distal motor latency in the demyelinating range ( $\geq 130\%$  of the upper limit of normal) after successful CTR.<sup>11-14</sup>

Postsurgical intervention for UNE, the specific surgery performed may indicate the underlying reasons for failure/recurrence.<sup>15-17</sup> Although motor nerve conduction across the elbow rarely normalizes postoperatively, worsening slowing of conduction velocity (compared with a preoperative study) raises concern for a persistent or recurrent lesion. Studies nearly unanimously report postoperative mean conduction velocity improvement (30% when successful and 15% when unsuccessful), without normalization, regardless of preoperative clinical severity or type of surgery.<sup>7-10</sup>

**TABLE 2** Guiding principles for electrophysiological prognostication in peripheral nerve lesions.

Principle	Implications for interpretation
Neurapraxia = good prognosis	<ul style="list-style-type: none"> <li>• Neurapraxia resolves by 3 months.</li> <li>• Demyelination &gt;3 months implies a new or ongoing lesion.</li> </ul>
Lesions with <70% axonal loss generally have a favorable prognosis	<p>Axonal loss best quantified by distal CMAP amplitude:</p> <ul style="list-style-type: none"> <li>• after Wallerian degeneration.</li> <li>• before substantial collateral sprouting.</li> <li>• using side-to-side comparisons as needed.</li> </ul> <p>Surviving axons have a “reserve capacity” to extend their motor unit territory up to 5-fold via collateral sprouting.<sup>2,3</sup></p>
Any axonal continuity carries a more favorable prognosis than none	<ul style="list-style-type: none"> <li>• Presence of axonal continuity early after a lesion establishes capacity for collateral sprouting.</li> <li>• It also increases likelihood that supportive tissue scaffolding around the lesioned axons can support proximodistal regrowth.</li> </ul>
Very small amplitude fibrillation potentials are seen in chronic (>10 months) denervation	<p>Progressive decline in amplitudes of fibrillation potentials from onset of injury until leveling off at approximately 10–15 months.</p> <p>Denervated fibers progressively atrophy, degenerate, and may undergo substitution by connective tissue.<sup>4</sup></p> <p>Denervated fibers fibrillate indefinitely with adequate vascular supply and retention of the membrane characteristics required for action potential generation.</p>
Increasing motor unit recruitment over time	<ul style="list-style-type: none"> <li>• Several voluntary MUAPs early after injury carry a more favorable prognosis than “discrete recruitment” of a single unit.<sup>5</sup></li> <li>• Increasing MUAPs over time in a single muscle or the wave of reinnervation moving distally suggests successful reinnervation and carries favorable prognosis.</li> </ul>
Muscle reinnervation will plateau by 18–24 months, prior to irreversible muscle degeneration. <sup>2,6</sup>	<ul style="list-style-type: none"> <li>• Beyond 18–24 months, significant motor recovery unlikely.</li> <li>• Sensory recovery may proceed for a longer period.</li> </ul>
Assessment of MUAP recruitment enables only crude estimation of axonal quantification	<ul style="list-style-type: none"> <li>• Distal CMAP amplitude more quantitative to assess extent of muscle innervation.</li> <li>• Mild axon loss may not be perceived.</li> <li>• When countable numbers of MUAPs are present, test/retest comparison may be useful.</li> <li>• Recruitment analysis is largely limited to early firing type 1 motor units.</li> </ul>

Abbreviations: CMAP, compound muscle action potential; MUAP, motor unit action potential.

### 3.1.2 | Example 2: Recurrent or persistent limb pain after decompressive spinal surgery

This evaluation involves comparison to preoperative EDX studies to assess for interval and ongoing motor axonal loss and for other potential new lesions. Because fibrillation potentials and positive sharp waves can persist for months or years, their presence alone—without comparison to a preoperative study and especially if scant or within the first year postoperatively—cannot imply a new lesion. Evaluation of sensory nerve conduction or focal demyelination plays an important role in searching for alternative lesions, but it cannot determine severity or persistence of root lesions. Muscles with progressive weakness or supplied by the same root level as dermatomes with persistent or worsening pain should be compared with prior studies (by needle electromyography [EMG] and by nerve conduction studies [NCSs], where applicable). Unequivocal changes in (A) MUAP recruitment, (B) degree and extent of active denervation, (C) myotomal CMAP amplitude changes (with growth suggesting reinnervation and reduction raising question of a new or ongoing lesion), and (D) evidence of ongoing reinnervation (increased MUAP polyphasia) versus mature reinnervation (increased MUAP amplitude without or with minimal polyphasia) can, in clinical context, provide support for a persistent or recurrent lesion.

### 3.1.3 | Example 3: Evaluation of a monophasic versus progressive inflammatory neuropathy

This entails evaluation for progressive versus resolving demyelinating features (conduction block, temporal dispersion, distal latency prolongation, conduction velocity slowing, distal CMAP dispersion) and progressive versus stable axonal changes. The presence of persistent CMAP amplitude reduction (beyond acute phase) coupled with dense fibrillation potentials suggests ongoing axonal injury rather than reversible conduction failure. New sites of conduction block, temporal dispersion, or distal latency prolongation better suggest a progressive acquired inflammatory polyneuropathy (e.g., chronic inflammatory demyelinating polyradiculoneuropathy [CIDP]), rather than a monophasic process (e.g., GBS), although one study showed that evolving demyelinating changes can also be seen in GBS for weeks to months after symptom onset.<sup>18</sup> Progressive CMAP amplitude reduction of commonly affected motor nerves (e.g., radial, ulnar, fibular) across serial EDX studies suggests progressive axonal injury. Progression of a motor CMAP from normal through “pseudo-conduction block” to reduced amplitude could be seen in the setting of a vasculitic ischemic multiple mononeuropathy.

### 3.1.4 | Example 4: Spread of weakness to other body regions after decompressive surgery

Spread of weakness after spine or peripheral nerve surgery calls the original diagnosis into question and invites EDX studies to provide clarity. Clinical and electrophysiological spread of the disease process over time may indicate a more diffuse lesion, such as a generalized neuropathy or motor neuron disease. The repeat study should assess electrophysiological progression versus stability in previously abnormal muscles (degree over time) as well as in previously normal innervation territories (space). The study should be designed to include potential subclinical regions that may confirm the presence of a more widespread disorder. Conversely, electrophysiological stability or improvement in the face of spreading weakness suggests a cause beyond the peripheral nervous system, pointing toward central nervous system etiologies of weakness, or functional decline in the setting of chronic pain, arthritis, psychological comorbidity, or other disorders that affect function.

### 3.1.5 | A note on amplitudes of fibrillation potentials

Caution should be exercised in the use of fibrillation potential amplitudes to identify a new or superimposed lesion. Multiple factors mediate these amplitudes, including recording electrode distance from the muscle fiber, intervening tissues (connective, vascular, muscle), and muscle fiber size. Progressive decline in fibrillation potential amplitudes is observed from onset of denervation<sup>19,20</sup> until a relative leveling off at approximately 10–15 months, due to both decreasing muscle fiber cross-sectional area and filtering effects of the increasing proliferation of surrounding interstitial connective tissue.<sup>19–22</sup> Although denervated fibers are known to progressively atrophy, degenerate and undergo eventual substitution by connective tissue,<sup>4</sup> they can fibrillate indefinitely if there is adequate vascular supply and retention of the membrane characteristics required for action potential generation,<sup>22,23</sup> sometimes producing low amplitude fibrillation potentials long after lesion resolution. In the clinical context of new or changing symptoms, large amplitude fibrillation potentials superimposed over very small ones on serial testing may indicate a new lesion. However, once reinnervation has occurred, large amplitude fibrillation potentials can also arise for other reasons. First, asymptomatic collateral sprout failure can occur. Second, motor units at or approaching their maximum capacity for collateral sprouting may achieve a dynamic equilibrium with ongoing denervation and reinnervation,<sup>21,23–27</sup> manifesting some large fibrillation potentials, as evidenced after neuronal loss in poliomyelitis.<sup>28</sup> Third, new fibrillation potentials, unrelated to prior injury, can arise from physiological age-related dropout of motor units,<sup>29</sup> resulting in a disproportionate quantity of new fibrillation potentials, given the relatively high innervation ratio of collaterally sprouted units. For these reasons, the authors recommend caution in theoretically identifying neurogenic lesions with different time courses when reporting the

observation of larger fibrillation potentials superimposed on smaller ones on serial testing. Clinical context should be closely considered.

## 3.2 | Diagnostic uncertainty in possible progressive disease

In contrast to the situation of new or changing symptoms that prompt a repeat study, there are cases in which the initial study carries diagnostic uncertainty that can be clarified with data from a second point in time. For example, due to the wide spectrum of normal electrophysiology of the distal lower limbs (modified by body morphologies and other attributes),<sup>30</sup> electrophysiology at or around the margins of normative data limits may represent stable and normal findings for a given patient or may reflect a subtle disease process. A study performed later can provide diagnostic clarity by quantifying interval change. Examples follow.

### 3.2.1 | Example 1: Distal symmetric polyneuropathy

Distal symmetric polyneuropathy (axonal) entails gradual distal neuromuscular decline along a continuum, with clinically relevant proprioceptive deficits and increased fall risk occurring well before distal CMAP amplitudes fall below the lower reference values, and often preceding a clinical diagnosis of neuropathy.<sup>31</sup> Distal proprioceptive and motor function may become suboptimal once fibular motor amplitudes fall below about 4.0 mV,<sup>32</sup> although reference values in most laboratories are substantially lower. Estimates of the sensitivity of the sural sensory amplitude for detecting neuropathy range from 29% to 62%,<sup>33</sup> suggesting electrodiagnosis as a whole may be insensitive to early neuropathy and clinically relevant distal neuromuscular decline.<sup>31</sup> In a clinical context concerning for peripheral polyneuropathy, a patient with sensory nerve action potential (SNAP) and CMAP amplitudes in the low-to-normal range may benefit from a follow-up study in 6–18 months to assess for interval change. Progressive decline would suggest neuropathy, whereas stable electrophysiology (especially in the context of progressive symptoms) implies a different underlying etiology of the clinical presentation.

### 3.2.2 | Example 2: Amyotrophic lateral sclerosis

Until the establishment of the Gold Coast diagnostic criteria in 2020,<sup>34</sup> EDX sensitivity for detection of early amyotrophic lateral sclerosis (ALS) and related motor neuron diseases had been limited, with average diagnostic delay ranging 10–16 months from onset of symptoms<sup>35</sup> and with up to 29% patients failing to reach a diagnostic certainty of “definite ALS” at time of death.<sup>36</sup> As a result, serial EDX testing has had an important and practical role in confirming or refuting a diagnosis and in monitoring for relevant disease progression.

### Confirming a diagnosis

Spread of electrophysiological abnormalities over time can support an ALS diagnosis where the initial study findings are uncertain. Careful muscle selection to increase EDX sensitivity as well as evaluation of muscles not characteristically involved in compressive nerve or nerve root lesions (bulbar, thoracic paraspinals) can improve the diagnostic yield.<sup>37</sup> Misdiagnosis of ALS as a different entity is unfortunately common, estimated as ranging from 13.0% to 68.4% of cases.<sup>35</sup> Establishment of a clear ALS diagnosis, supported by electrodiagnosis, has important implications for treatment planning and for personal planning by patients and families. In addition, a clear diagnosis with EDX confirmation may facilitate initiation of pharmacological therapies (most effective in early stages of disease), referral to interdisciplinary specialty ALS clinics (associated with improved survival and quality of life), access to clinical trials, and qualification for disability benefits.

### Refuting a diagnosis

Conversely, an estimated 8% to 10% of persons initially diagnosed with ALS are later found to have an alternative diagnosis.<sup>38</sup> Therefore, atypical clinical features, such as very rapid progression of weakness (over days), lack of progression of weakness (over months), new or progressive sensory symptoms, prominent bowel or bladder dysfunction, or other uncharacteristic signs or symptoms, should prompt consideration of a repeat EDX study to refute a diagnosis. In these circumstances, repeat study may reveal a condition with more effective treatments available (e.g., multifocal motor neuropathy) or with a more benign prognosis (e.g., inclusion body myositis). The repeat study should be guided by the clinical presentation but may include NCSs to assess for evidence of cranial nerve involvement, demyelination of motor nerves, sensory nerve abnormalities, and neuromuscular junction dysfunction (via repetitive stimulation studies).<sup>38</sup> Needle EMG can assess for abnormal spontaneous activity usually associated with other diagnoses (such as myotonia or myokymia).

The Gold Coast diagnostic criteria lowered the threshold of required EDX and clinical findings to meet diagnosis, in order to improve sensitivity and hasten diagnosis. Preliminary studies have confirmed their improved diagnostic sensitivity<sup>39</sup> and likelihood of meeting eligibility for clinical trials when applied.<sup>40</sup> In this context, the role of serial electrodiagnosis in establishing an initial diagnosis is evolving and may lessen over time. However, electrodiagnosis will likely retain an important role in refuting or reexamining a diagnosis when expected clinical progression does not occur.

### 3.2.3 | Example 3: Primary lateral sclerosis

EDX studies have also been used to monitor persons with primary lateral sclerosis (PLS) for evidence of progression to lower motor neuron involvement and evolution to classic or typical ALS, which carries a less favorable prognosis. In one retrospective natural history study of PLS, EDX evidence of lower motor neuron involvement preceded clinical signs by an average of 6 months.<sup>41</sup>

### 3.2.4 | Example 4: Sensory neuropathy versus neuronopathy

Distinguishing sensory neuropathy (axonopathy) from neuronopathy can be challenging early in the disease course, especially when the initial pattern manifests in a length-dependent fashion. A repeat EDX study can elucidate a non-length-dependent pattern suggestive of neuronopathy. Criteria developed by Camdessanché et al.<sup>42</sup> helped standardize the EDX evaluation for sensory neuronopathy and assign likelihood based on upper and lower limb SNAP abnormalities. Of note, up to one third of sensory neuronopathy cases can have a distal sensory polyneuropathy phenotype at time of symptom onset. Thus, in cases of diagnostic ambiguity, a repeat EDX study at 6 months should be considered to screen for length independence.<sup>43</sup> In acute and subacute dysimmune sensory neuronopathy, SNAP amplitude typically declines most rapidly within the first 2 months of evolution and begins to slow down by 7 months. Through serial study, electrodiagnosis can serve as a marker of disease progression.<sup>44</sup>

### 3.2.5 | Example 5: Lumbar spinal stenosis

Lumbar spinal stenosis, which presents as neurogenic claudication, has a heterogeneous electrophysiological presentation, ranging from normal electrophysiology with no axonal loss, to chronic and active polyradiculopathies of varying severity. Given the potential for waxing and waning symptoms across many years, serial electrophysiology can assess degree and activity of axonal loss and guide treatment decisions. A pilot study of 11 patients with lumbar spinal stenosis found that a positive needle EMG predicted lower pain and disability scores following epidural steroid injection.<sup>45</sup> Considering radiculopathy more broadly, electrophysiological abnormalities portend a more favorable response to conservative therapy,<sup>46,47</sup> transforaminal epidural steroid injections,<sup>48–50</sup> and surgical interventions<sup>51,52</sup> compared with patients with a needle EMG that does not meet criteria for radiculopathy. A study of 21 patients with electrophysiological follow-up 5–12 months after conservative care revealed clinical and electromyographic improvement (resolution of fibrillation potentials and evolution of neuropathic MUAPs) in most.<sup>47</sup> These findings support a natural history of clinical and electrophysiological improvement in radiculopathy and support the notion that persistent active denervation in the clinical context of decreasing corresponding neurological function holds clinical relevance. Nonetheless, other studies have shown that electrophysiological abnormalities can occasionally persist up to 1 year postoperatively, even in patients with symptom resolution.<sup>51</sup> Thus, although the persistence of mild postoperative electrophysiological abnormalities cannot establish an ongoing process, interval electrophysiological change—interpreted in conjunction with a patient's interval history and neurological examination—may hold diagnostic value. This value may be especially relevant considering the limited ability of the structural measure of spinal canal diameter (as determined by magnetic resonance imaging) to align with clinical symptoms.<sup>53</sup>

### 3.2.6 | Example 6: Confirming a diagnosis of acute GBS

Electrophysiological studies in GBS are often normal early in the disease course, especially when weakness is mild or proximal, and in the setting of variants.<sup>54</sup> Thus, the greatest value of serial electrodiagnosis in GBS lies in either securing or refuting the diagnosis, with repeat EDX testing in 2–3 weeks being a reasonable approach in those instances.<sup>54</sup>

The role for serial EDX in subclassifying GBS into subtypes (such as acute inflammatory demyelinating polyradiculoneuropathy, acute motor axonal neuropathy, and acute motor and sensory axonal neuropathy), however, remains less certain. Some have suggested performing a baseline study in the first 2 weeks followed by a repeat study between 3 and 8 weeks,<sup>55,56</sup> whereas others challenge the added value of a repeat study in subtyping. One prospective study that performed baseline and subsequent studies at 5 and 33 days, respectively, found no classification shifts between demyelinating and axonal subtypes following the second study.<sup>57</sup> Electrodiagnosis often fails to distinguish between such pathophysiological processes as demyelinating conduction block, reversible conduction failure, and length-dependent axonal loss.<sup>58</sup> Early reversible distal conduction failure, which often leads to a misclassification of GBS as an axonal neuropathy, may actually represent nodal or paranodal dysfunction.<sup>58</sup> Thus, from a practical standpoint, serial EDX studies may be more useful in establishing a confirmatory diagnosis of GBS, rather than in subtyping a confirmed case of GBS.

Perhaps the role of serial EDX testing in establishing a correct diagnosis plays out most evidently in the case of nodopathies and paranodopathies, which are immunoglobulin G4 antibody-mediated conditions characterized by disruption of the node of Ranvier and adjacent paranodal integrity.<sup>59</sup> Such disease presentations may be mistaken for GBS, given the rapid nature of presentation. The presence of evolving findings of acquired demyelination on serial EDX testing (e.g., conduction block or reversible conduction failure), in the proper clinical context, would favor nodopathies/paranodopathies over GBS. Nevertheless, the distinction between GBS and nodopathies or CIDP can, at times, be particularly challenging, as GBS can also present with evolving demyelinating changes on electrodiagnosis that continue to worsen several weeks to even months after symptom onset.<sup>18</sup> Thus, a cogent history in the setting of targeted laboratory testing, when appropriate, is paramount to properly interpreting EDX findings. In addition, nodopathies/paranodopathies tend to have more axonal involvement and more pronounced demyelinating changes than typical CIDP.<sup>60</sup>

### 3.2.7 | Example 7: Evaluation of chronic inflammatory polyneuropathies

#### *Confirming a diagnosis*

CIDP exemplifies a progressive inflammatory polyneuropathy with a well-established and validated set of EDX criteria, summarized in the

European Academy of Neurology/Peripheral Nerve Society 2021 guideline, that are both sensitive and specific.<sup>61</sup> There are instances, however, when diagnostic criteria are not fulfilled and serial EDX testing is advised to establish greater diagnostic certainty.<sup>61</sup> In addition, misdiagnosis and overdiagnosis of CIDP based on EDX findings are both significant problems,<sup>62</sup> and serial testing is worthwhile in cases of diagnostic uncertainty, especially when the first study is of questionable technical and interpretive quality. EDX findings that may favor disease mimickers over CIDP include disproportionate distal latency prolongation with reduced terminal latency index (anti-myelin-associated glycoprotein neuropathy),<sup>63</sup> uniform velocity slowing with lack of conduction block or temporal dispersion (Charcot-Marie-Tooth disease type 1),<sup>64</sup> more uniform slowing with advanced axonal involvement and/or relatively preserved distal latencies (POEMS [polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes] syndrome),<sup>65</sup> and  $\geq 50\%$  asymmetry of median or ulnar motor amplitudes (vasculitic multiple mononeuropathy).<sup>66</sup>

#### *Predicting likelihood of relapse*

Serial EDX testing (baseline and post-intravenous immunoglobulin [IVIg]) can be useful in predicting CIDP relapse. Using data from the landmark IGIV-C CIDP Efficacy (ICE) study, investigators found that new demyelinating features, such as increased CMAP duration or F-wave prolongation, suggested an increased likelihood of relapse after IVIg discontinuation (especially if the number of demyelinating findings was  $>4$ ).<sup>67</sup> The first EDX study was performed at baseline (prior to IVIg treatment), whereas the second (serial) study was performed after the 24-week IVIg treatment phase and immediately before randomization to the placebo arm of the extension phase.

### 3.3 | Prognosis for static lesions with significant weakness

In a severe, static lesion resulting in clinical weakness, such as traumatic nerve injury, serial electrodiagnosis can help establish a prognosis, provide positive reinforcement and hope for patients where applicable, and guide consideration of surgical management, such as nerve grafting and nerve transfers. Serial electrodiagnosis adds value in cases of severe peripheral nerve injury with neurological weakness. Where an initial study shows no axonal continuity to key muscles and where there has been no clinical gain, electrodiagnosis can assess for early axonal regeneration by proximodistal regrowth by observing for low amplitude, polyphasic “nascent” MUAPs. This finding is a key prognostic indicator, in that it (A) affirms capacity for maturation of the reinnervation territory by the MUAPs observed, and (B) establishes that the supportive tissue structures surrounding the damaged axons are sufficiently intact (without extensive scarring, fibrosis, or neuroma formation)<sup>2</sup> to sustain regrowth, which is likely to continue. Contextually, appearance of nascent MUAPs often precedes clinically detectable muscle movement, rendering it an important herald of recovery. In contrast, absence of axonal regeneration to key muscles despite passage of adequate time for length-dependent

regeneration may guide a clinical team toward surgical intervention to restore nerve function. Because irreversible atrophy of muscle and endoneurial scaffolding occurs about 18–24 months postlesion, restorative surgical procedures need to be performed at a point early enough to allow subsequent axonal regeneration to take effect, estimated around 6 months.<sup>68</sup> Although these principles apply broadly across traumatic peripheral nerve lesions, there are nerve-specific data to guide prognostication for several common nerve lesions (especially the facial, radial, and fibular nerves).<sup>2</sup> Evaluation of key muscles for return of function optimizes functional relevance (e.g., anterior tibialis plays an important role in normal gait).

When employing serial EDX studies to evaluate reinnervation potential in a lesion severe enough to rely on axonal regeneration (as opposed to collateral sprouting), one must account for two ongoing, time-based processes with opposing effects on prognosis: axonal regeneration and end-organ fibrosis. Under optimal conditions, an estimated axonal regeneration rate of about 1 inch per month enables estimation of time to early reinnervation based on the distance between the site of injury and each relevant functional muscle. However, irreversible fibrosis of muscle and distal endoneurial tubes precludes potential for reinnervation by about 18–24 months postdenervation. Awareness of these factors and the time elapsed since injury confer a crude estimate of capacity for reinnervation, further refined by electrophysiological assessment of the following:

- A. degree of muscle fiber viability, based on degree of insertional activity. Decreased or absent insertional activity<sup>68</sup> suggests a poor prognosis due to limited viability of muscle tissue.
- B. whether reinnervation is ongoing or mature, based on the following:
  1. degree of polyphasia and instability of the MUAPs observed,
  2. whether more MUAPs are observed in a single muscle over time (degree by time),<sup>68</sup> and
  3. whether successively distal muscles evidence signs of reinnervation (spatial progression).<sup>68</sup>

A repeat EDX study posttraumatic nerve injury can also help select the muscles and nerves to be incorporated in restorative nerve surgery, by evaluating viable donor nerves for a surgical plan. Guidance for EDX study planning has been published.<sup>68</sup>

Furthermore, serial electrodiagnosis can monitor reinnervation status following nerve repair or nerve transfer by evaluating for target muscle atrophy postoperatively. Since successful reinnervation postintervention depends partially on target muscle viability, degree of fiber atrophy can help indicate treatment strategies and prognosis. Sequential measurement of fibrillation potential amplitude may have an advantage over performing needle biopsies to assess degree of muscle atrophy, particularly when atrophy of multiple muscles must be evaluated repeatedly.<sup>20</sup> Findings of progressive muscle atrophy, in spite of nerve repair or nerve transfer, may signal need for a different intervention, such as a muscle or tendon transfer, to restore function.

### 3.3.1 | Special situations: Follow-up of EDX study performed early after nerve lesion

#### *Example 1: Hyperacute axonal loss*

EDX studies performed early after an axonal lesion, prior to completion of Wallerian degeneration (about 11 days postinjury), represents a specific situation in which a later EDX study clarifies pathophysiology. Studies in this hyperacute phase (0 to about 11 days postinjury) reveal decreased MUAP recruitment and low CMAP/SNAP amplitude of conduction performed across the lesion site (when the injury is distal enough to allow both proximal and distal stimulation). Albeit too early to fully characterize a lesion, these early studies can serve to (A) verify presence of a peripheral neurological lesion, (B) localize the lesion, (C) establish if a lesion is incomplete, (D) provide preinjury (distal) CMAP/SNAP responses prior to Wallerian degeneration, and (E) establish pre-morbid, coexisting pathology. Repeat EDX studies after Wallerian degeneration can distinguish neurapraxia from axonotmesis and, in some cases, more precisely localize the lesion through needle EMG.

#### *Example 2: Evolution of positive sharp waves to fibrillation potentials early after axon loss*

On serial EDX testing performed early (weeks) after an axon loss lesion, newly observed fibrillation potentials, where only positive sharp waves had been previously documented, confirms an evolving pathological process. Positive sharp waves develop sooner after denervation than fibrillation potentials. This change is relevant where initial positive waves may have been interpreted as nonspecific muscle membrane instability, possibly reflecting a localized response to EMG needle trauma or within normal limits in a distal muscle.

### 3.4 | Initial data incomplete

Although having incomplete data does not arise as a prospectively planned indication for serial EDX testing, this situation arises practically and often calls for a repeat study to provide key information. Myriad situations can give rise to incomplete data on initial study, including limited patient tolerance (resulting in limited voluntary motor unit activation or early termination of the study), anatomic factors limiting complete study (e.g., open wound or edema), technical factors (e.g., intensive care unit setting with environmental artifact), or a sub-optimal study plan. Upon performing the repeat EDX study, careful attention to interval clinical change can help tailor the study to confirm key electrophysiological findings and add additional components. Designing the follow-up study to define the borders of the neurological lesion, by including muscles/nerves with normal electrophysiological function, can help collect the data needed for accurate interpretation.

## 4 | LIMITATIONS OF SERIAL EDX TESTING

Despite serving as a powerful diagnostic and prognostic tool, electrodiagnosis has limitations. There are several situations in which serial

or repeat EDX testing has limited value. Awareness of these situations can help guide patients and referring providers while clearly acknowledging uncertainty.

#### 4.1 | Remote lesions with minimal residual weakness

Repeat study of a remote lesion incurred over 2 years ago will rarely localize a lesion better than a high-quality study performed in the 1–6 month time window. As reinnervation matures and denervation resolves, normal and abnormal blend into an indeterminate zone. In a patient with stable or improving function after a static nerve lesion, enlisting electrodiagnosis to establish and confirm the presence of a remote lesion (years ago) adds little value. In contradistinction, in the setting of substantial clinical weakness, electrodiagnosis can often confirm occurrence of a remote peripheral lesion, albeit with limited insight into precise etiology. For example, a patient with a remote history of childhood poliomyelitis and subsequent weakness will show remote and mature neurogenic changes in affected muscles.

#### 4.2 | Prognosis of sensory lesions

Although serial studies of motor nerves and muscles are especially instructive regarding prognosis following a nerve lesion (as detailed above), serial studies of the sensory peripheral nervous system are less so. In the author group's experience, serial studies of sensory branches of a peripheral nerve rarely aid prognosis for a static lesion. SNAPs rendered unobtainable due to peripheral nerve injury often do not return to the detectable range even with significant clinical improvement, given that many more axons are needed to produce a detectable SNAP than for detection of voluntary MUAPs—namely, the SNAP can be unrecordable with as little as 50% axonal loss.<sup>30</sup> In addition, sensory axonal regeneration is not constrained by the same time limits as motor reinnervation,<sup>2,69</sup> as end plate and muscle fiber degradation plays no role. For these reasons, serial EDX studies of sensory fascicles rarely guide surgical management of restorative nerve procedures and are unlikely to assess the probability of sensory recovery. The authors recommend treating neuropathic pain based on symptoms and impairment rather than serial electrophysiology, once the lesion has been accurately localized.

#### 4.3 | Prognosis of mild-to-moderate axonal lesions that are recovering

If a patient is moving a muscle quite well early after an axonal lesion (e.g., around 3/5 strength or greater) and gradually gaining strength, prognosis for further functional recovery is good, assuming a static lesion. If pursued, serial EDX studies will show varying degrees of denervation and reinnervation over time, confirming the ongoing physiological course of reinnervation clinically observed. However,

this process carries little prognostic value, in that it cannot precisely predict how much additional strength is likely to return; it cannot quantify to what degree additional collateral sprouting or proximodistal axonal regeneration are likely to succeed. As described above, in lesions that are initially severe, evaluation for ongoing reinnervation (MUAP polyphasia and instability), as well as viability of remaining denervated muscle tissue (amplitude of fibrillation potentials), can provide diagnostic clues. However, in milder lesions in which MUAP recruitment is relatively well preserved, diagnostic utility of these findings is much less certain.

### 5 | FUTURE DIRECTIONS

While this monograph presents several broad indications for serial EDX testing as well as situations where it holds less value, future research should continue to define and evolve the role of serial electrodiagnosis. Research goals include:

#### 5.1 | Expansion of nerve- and condition-specific data regarding prognosis, especially relating to functional recovery

Obtaining a deeper understanding of the nerve lesions and circumstances around which prognosis is uncertain could instruct when selective use of serial EDX testing is warranted. For static nerve lesions, prognostication from noninitial points in time, when collateral sprouting has begun or is fairly mature, deserves more attention. An understanding of how the extent of reinnervation at a noninitial point relates to anticipated neurological recovery (extent of reinnervation expected) and functional recovery (e.g., ability to reach overhead or to walk unassisted) will enable serial EDX testing at specific points to help refine prognosis and treatment planning.

#### 5.2 | Establishment of reference values for repeated testing

Sometimes, when comparing latencies, amplitudes, or velocities between two points in time, there may not be a clear understanding of what represents a clinically important change versus natural variability between two examinations. These limitations in our knowledge are particularly salient when comparing studies preintervention and postintervention to assess intervention effectiveness.

#### 5.3 | Assessment of incremental diagnostic accuracy

Assessment of the incremental diagnostic accuracy (sensitivity and specificity) of combining and interpreting data from two studies from different points in time for specific medical conditions will establish if

there is a role for prospectively planned serial electrodiagnostic studies in improving diagnostic accuracy or prognostic precision.

## 5.4 | Further evolution of quantitative techniques

Although presently employed for research purposes only, some serial EDX techniques (including motor unit number estimation, CMAP amplitude, and motor unit number index) have been explored as more sensitive biomarkers for quantifying rate of progression and monitoring responses to treatment in clinical trials in ALS.<sup>70-73</sup> In the future, access to more precise, quantitative indicators of treatment response through these techniques could drive individualized treatment regimens and expand applicability across neurological conditions.

## 6 | CONCLUSIONS

When appropriately applied, serial EDX studies can deepen our understanding of diagnosis, prognosis, or treatment options in peripheral neurological disorders by enabling us to assess interval change in electrophysiology. When additional clarity around lesion pathophysiology, temporal evolution, or spatial progression may guide diagnostic impression, and where current EDX techniques can adequately assess these parameters, serial electrodiagnosis should be considered and tailored accordingly. As illustrated in Table 3, serial electrodiagnosis may be indicated in peripheral neurological disease when there is (A) clinical change leading to suspicion for new or ongoing lesion, (B) diagnostic uncertainty in possible progressive disease, (C) a question of prognosis for static lesions with significant weakness, or (D) incomplete EDX data from an initial study. Nonetheless, serial EDX testing has several limitations and does not answer all questions regarding prognosis and function. The clinical situations detailed in this monograph offer examples of how to judiciously apply, approach, and interpret serial EDX studies in the diagnosis and management of adult peripheral neurological disorders.

**TABLE 3** Summary of uses of serial electrodiagnosis.

Clinical condition	Need/timing of serial EDX studies
Stable clinical presentation	Not needed
Recovery as expected	
Progression as expected	
Sensory-only traumatic nerve lesion	
Unexpected clinical progression	Soon after progression
Diagnostic uncertainty	Often 3–6 months after initial studies
Prognosis after static injury	Often after 3 months to allow for remyelination and/or axonal sprouting or regrowth
Incomplete data	Soon as feasible

Abbreviation: EDX, electrodiagnostic.

## AUTHOR CONTRIBUTIONS

**Sandra L. Hearn:** Conceptualization; supervision; writing – original draft; writing – review and editing. **Amro Maher Stino:** Writing – original draft; writing – review and editing. **Ileana M. Howard:** Writing – original draft; writing – review and editing. **Gautam Malhotra:** Writing – original draft; writing – review and editing. **Lawrence Robinson:** Review and editing.

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## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

## ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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