# Will imaging biomarkers transform spinal cord injury trials?

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The gold standard for diagnosis and classification of traumatic spinal cord injury is the American Spinal Injury Association (ASIA)'s impairment scale (AIS), consisting of motor and sensory testing by a qualified clinician that classifies patients into five grades—A to E—in which grade A is the most severely damaged spinal cord and grade E is a full neurological recovery.[1] Despite the somewhat subjective nature of this scale, it is easy to use and easy to communicate information between treating physicians. Unfortunately, the ASIA classification system does not incorporate advances in our understanding of spinal cord injury and it does not recognise its heterogeneity. Both primary and secondary injury mechanisms result in heterogeneity within an AIS class and this heterogeneity, in turn, can be shown by an apparent spontaneous recovery within an AIS class. For example, up to 20% of patients with an AIS grade of A will convert to AIS grade B or C.[2] The consequence of use of this classification scheme is that large clinical trials are needed to distinguish a treatment effect from natural history. An alternative strategy for assessment of patients is to use a surrogate endpoint that shows changes in the intended target of new therapeutic agents. The work[3] presented by Patrick Freund and colleagues in this issue of *The Lancet Neurology* provides a clever example of an imaging biomarker that could be used as a surrogate for clinical examination. Use of such a technique in the context of a therapeutic intervention would reduce the reliance on broad classification schemes and offer the prospect of less expensive and more efficient clinical trials than we have at present.

Attempts at development of non-invasive imaging techniques to help guide the diagnosis and prognosis of spinal cord injury are not new. After widespread adoption of MRI into clinical practice in around 1990, the notion of imaging biomarkers to aid in the clinical management of spinal cord injury was developed, whereby T1-weighted and T2-weighted signal characteristics were used to classify patients.[4] This idea was largely abandoned because of a low sensitivity of signal characteristics to establish either the severity of injury or prognosis. After all, imaging biomarkers are intended to serve as surrogate endpoints in assessment of the efficacy of new therapeutics. Some success was achieved in prognostication of outcomes after acute cervical spinal cord injury through undertaking of measurements of spinal cord compression and spinal canal compromise on standard T1-weighted and T2-weighted images.[5] More recently, standard imaging metrics have been incorporated into a clinical prediction rule as a means to amalgamate clinical factors with a structural imaging assessment to predict functional motor recovery.[6,7] In the future, the marriage of advanced imaging techniques with clinical assessment is probably going to be the best means of assessment of recovery after spinal cord injury. In the past decade, substantial progress has been made in the specialty of neuroimaging as applied to patients with spinal cord injury.[8] Interdisciplinary collaborations have resulted in striking progress towards characterisation of residual structure and function after traumatic spinal cord injury, and early studies have documented changes at the cortical, subcortical, and spinal cord levels.[9–11]

Freund and colleagues[3] have set a benchmark for future work in this area. The investigators undertook an elegant study with careful attention to neuroanatomical structure and function. Through the use of a prospective longitudinal design and follow-up of 13 patients and 18 controls, they showed how the spinal cord, the cerebral white matter tracts, and the cortical grey matter change in response to injury, and also show how these changes relate to clinical function. By targeting of the corticospinal tract—through measurements of cortical grey matter volume change, white matter volume along the corticospinal tract, myelin sensitive measurement including both magnetisation transfer and longitudinal relaxation rate, and spinal cord area—the investigators have rightfully selected the neuroanatomical substrate whose change has the potential to affect patients' quality of life most through gain of motor control. Most importantly, these methods show a high degree of sensitivity to change—an essential component of an imaging biomarker. The main limitation of this work is its generalisability for use in high-volume clinical centres that treat patients with spinal cord injury. The data acquisition and post-processing techniques described by Freund and colleagues[3] are probably beyond the reach of most neurosurgery and neuroradiology experts. Nonetheless, efforts should be made to bridge this

knowledge gap through exchanges at neuroimaging meetings and specialised work groups such as the recent spinal cord imaging meeting sponsored by the International Spinal Research Trust and the Wings for Life Foundation.[12]

Imaging biomarkers can potentially be used at any stage of spinal cord injury, from acute to subacute to chronic dependent on the intended target of the therapeutic intervention. Furthermore, they are capable of targeting a multitude of substrates within the CNS, from motor to sensory to autonomic pathways. Such surrogate markers could serve as the endpoint for stratified block randomisation trials, reported as a percentage change from baseline. When the interpretation of any specific biomarker is called into question, the use of animals through a reverse-translation approach will be useful. If this strategy is to be successful, investigators need to establish whether or not an imaging biomarker is capable of detecting subclinical changes to the CNS and ultimately whether or not such subclinical changes provide a favourable conduit to improved clinical function. As discussed by many leading authors in the specialty, an individual therapeutic strategy is unlikely to serve as the magic bullet for restoration of function after injury. Rather, a combination of strategies at different timepoints is probably needed[13]—for example, the use of neuroprotective strategies during the acute phase followed by neuroregenerative therapies in later stages of recovery, after hostile, secondary injury mechanisms have subsided. Through a combination of treatment strategies and adoption of imaging biomarkers, the next generation of clinical trials will have the potential to personalise the care of patients with spinal cord injury.

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