instance, most of the 90 variants identified by Nalls and colleagues[2] are either in introns or intergenic regions.

Thus, a meta-analysis of GWAS is just the starting point, requiring further functional analyses; Nalls and colleagues[2] went to great efforts to gain insight into the functionality of the identified variants by using tissue-specific expression, methylation, rare variants, and non-genetic risk factors. Importantly, use of additional data and statistical tests raises the probability of false positive results. Because the statistical tests are not independent from one another, adequate adjustment for multiple testing is not straightforward. Caution is thus needed when interpreting findings considered to be significant. Particular caution is required for results from Mendelian randomisation studies, which contribute substantially to the work by Nalls and colleagues.[2] In general, accounting for the number of tests requires knowledge of how many hypotheses are being tested, but this number can be established only if the non-genetic risk factors that are investigated are defined a priori. However, when selective reporting of findings occurs, the denominator of tested hypotheses is unknown, thus making it impossible to evaluate the significance of a finding.

Nalls and colleagues provide the most complete picture of the genetic background of Parkinson's disease to date. Although direct practical consequences cannot be drawn from their findings yet, they have provided the groundwork for future studies, which is likely to yield exciting results soon. Tackling the general challenges, as described above, will be a task for the broader scientific community.

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Serum neurofilament light chain as a preclinical marker of neurodegeneration


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To date, most clinical trials of disease-modifying drugs for neurodegenerative diseases, namely Alzheimer's disease, have been unsuccessful, mainly due to the inclusion of patients with too advanced disease.[1] One explanation is that, once the pathophysiological process overcomes the clinical threshold, the excessive neuronal loss could make the therapeutic intervention ineffective. Besides the overarching need for a timely diagnosis, the possibility of detecting neurodegeneration before the appearance of clinical symptoms is captivating.

Genetic forms of neurodegenerative diseases represent a unique model for studying the presymptomatic phases of these disorders, since they allow for a better understanding of biomarker dynamics at the stages before clinical manifestations. In *The Lancet Neurology*, Emma L van der Ende and colleagues[2] report their investigation of the longitudinal trajectories of serum neurofilament light chain (NfL), a sensitive and reliable biomarker of neuronal damage,[3] in a large international multicentre cohort of individuals carrying different genetic mutations for frontotemporal dementia (namely mutations in GRN, C9orf72, or MAPT) and their healthy first-degree relatives who were followed up for about 2 years. The authors looked at the differences in serum NfL concentration over time between presymptomatic carriers who did not develop frontotemporal dementia during follow-up (n=140), presymptomatic carriers who developed the disease during follow-up (ie, converters; n=9), symptomatic carriers (n=59), and healthy non-carriers (n=127). Changes in NfL were correlated with longitudinal imaging and clinical parameters, after adjustment for age, sex, and study site.

At baseline, healthy participants had the lowest serum NfL concentration, followed by presymptomatic mutation carriers, converters, and symptomatic carriers, which highlights NfL as a marker of disease intensity. During

follow-up, the greatest increase of NfL was in converters, with less evident changes in participants who were already symptomatic. Thus, in genetic frontotemporal dementia, serum concentration of NfL might start to increase 2 years before the appearance of symptoms. These findings are similar to those of a MRI study[4] done on a similar cohort, wherein extensive involvement of white matter and a decrease of grey matter volumes in prefrontal, temporal, cingulate, and insular cortices were seen 2 years before clinical onset. Similar to frontotemporal dementia, in presymptomatic amyotrophic lateral sclerosis mutation carriers, elevated concentrations of serum NfL have been found about 1 year before clinical onset.[5] The relatively short presymptomatic phase of the frontotemporal lobar degeneration spectrum is substantially different from that of familial forms of Alzheimer's disease, wherein presymptomatic carriers of mutations in presenilin-1 and amyloid precursor protein genes show high serum NfL concentrations up to 10 years before the estimated onset of disease.[6] Thus, it seems that the window for early detection of the risk of conversion from the asymptomatic phase to clinical phase of frontotemporal dementia might be particularly short and should be closely monitored. Notably, research interest in the presymptomatic phase has extended to other neurological diseases, such as multiple sclerosis, where serum concentrations of NfL increase as early as 6 years before clinical onset.[7]

These research efforts will hopefully lead to the use of serum NfL as a biomarker to monitor asymptomatic individuals who are either carrying causal mutations of different neurodegenerative diseases or have a strong familiar history for neurological disorders, thus giving them the chance to undergo timely and effective disease-modifying treatments.

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Is a four-limb exoskeleton a step in the wrong direction?

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Before the Second World War, life expectancy for people with spinal cord injury was low, with most people dying within 3 years of injury. The arrival of antibiotics, improved bladder care, and the introduction of new treatments meant that life expectancy greatly increased, and with this increase came greater interest in rehabilitation.[1] Walking was central to this rehabilitation project, with a belief that full independence and productivity can only come through ambulation. A life in a wheelchair was seen as in some way lacking. This view is perhaps best represented by neurosurgeon and founder of modern spinal cord injury rehabilitation Professsor Donald Munro's lengthy diatribe to the Paralyzed Veterans of America,[2] in which he criticised the adoption of a wheel as the symbol of their organisation. Munro stated that, were he paralysed, he would be "ashamed to be photographed in a wheelchair". "Why be represented by an admission of failure?" he argued; "why not have the courage to live greatly and make the symbol what it ought to be—calliper braces or crossed crutches inside a laurel wreath?"

From the 1950s onwards, the promotion of crutch-walking or orthosis-assisted walking has remained the goal of spinal cord injury rehabilitation. In a meta-analysis of orthosis for people with spinal cord injury, Karimi and Esrafilian[3] found little evidence to suggest that there was any improvement in function and that the performance in mechanical and power-assisted orthosis was low. Despite this finding, bioengineers and rehabilitation engineers continue to search for a new solution. Walking, as Mike Oliver[4] has pointed out, is more than a means of