Diagnosis of genetic cause in motor neuron disease patients could be missed due to age limits on genetic testing

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Based on the findings of a new study published in *Brain*, researchers from the Institute of Psychiatry, Psychology & Neuroscience (IoPPN) at

King's College London are calling for a complete rethink of the national guidelines surrounding who can access genetic testing for amyotrophic lateral sclerosis (ALS), also called motor neuron disease. The research suggests that there are hundreds of people with ALS in the UK for whom a genetic basis of their ALS is being missed, as they do not fit the narrow requirements for genetic testing. As guidelines are similar in many countries, this situation will likely be the same internationally, meaning potentially thousands of people being unaware of a genetic link to their ALS.

The research estimates that although nearly a quarter of people with ALS who do not have family members with the illness do have a genetic link to their ALS, this link goes undetected in 98% of cases because of current guidelines. As a result, they are not offered proper genetic advice and counseling, and would not be able to access gene-based therapies likely to be available soon or in trials. The researchers say that genetic testing should be open to all patients with ALS, regardless of whether or not other family members are affected, and for all ages.

ALS is a progressive nervous system disease that affects nerve cells in the brain and spinal cord, causing paralysis of muscles. Around 1 in 300 people will be diagnosed with ALS at some point in their lives, with the average person surviving for between two and five years after their symptoms begin. There is currently no cure for ALS.

In some cases, there is an identifiable genetic cause. Given the current restrictive testing guidelines, the researchers wanted to establish the probability of a positive genetic test result in various scenarios to provide evidence for how and when genetic testing should be used. They performed two analyses on global data sets, analyzing the four most common ALS genes and a larger panel of 26 ALS genes.

Their analysis revealed that by limiting testing in those without a family

history to people with symptom onset below 40 years, as per current UK guidelines, 115 of 117 positive test results were missed. Extrapolating this data to other health systems across the world, they found that potentially thousands of people with ALS will not know they have a genetic cause of their ALS due to the inaccessibility of testing.

Professor Ammar Al-Chalabi, Professor of Neurology and Complex Disease Genetics at King's IoPPN, and the study's lead author, said, "ALS is a condition that destroys lives. Genetic testing means that people and their families can be given correct advice and access to genetic counseling and be supported with family planning. Our study found that there are large numbers of people who are unable to access this care and support because of the arbitrary age limits and rules currently in place."

While the researchers recognize that expanding the guidelines to include more people will be resource-intensive, they argue that where possible, countries should aim to offer genetic testing to ALS patients of all ages.

Dr. Puja Mehta, the study's first author, said, "Our study shows the importance of being able to offer people with ALS of all ages a blood test to identify a possible genetic cause. In addition to accessing appropriate genetic counseling and support, with the exciting prospect of specific gene-based therapies on the horizon, and with clinical trials underway, it will become all the more important for people with ALS to know if they have an identifiable genetic cause."

Dr. Nicholas Cole, Head of Research at the MND Association, said, "This research, supported by the MND Association, adds weight to the suggestion that routine genetic testing should be offered to MND patients, regardless of their age at onset or family history of the disease. Genetic testing could provide opportunity for more people with MND to be involved in tailored clinical trials. However, it is imperative that testing is supported by a robust genetic counseling infrastructure to

provide tailored support to all those who choose to embark upon this process."

More information: Puja Mehta et al, The impact of age on genetic testing decisions in amyotrophic lateral sclerosis, *Brain* (2022). DOI: 10.1093/brain/awac279

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