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COMPETING FINANCIAL INTERESTS

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Learning from genetic forms of neurodegeneration

To the Editor:

Many important questions remain to be answered about translational research in neurodegenerative diseases^{1–7}. However, I feel that not enough emphasis has been put on the extent of the knowledge that could be gained from studying genetic forms of these disorders.

Monogenic forms of adult-onset disorders that show autosomal dominant inheritance offer a unique opportunity to investigate the presymptomatic phase of the disease before clinical onset. This can be done in relatives of individuals with disease-causing mutations before the occurrence of signs or symptoms that correspond to the most recent criteria for early clinical diagnosis. Prospective follow-up of individuals who are at risk of a monogenic neurodegenerative disorder with clinical, imaging and biological investigations will allow researchers to identify markers of the presymptomatic phase. In turn, determining the natural history of the presymptomatic phase will lead to the development of markers of early neuronal dysfunction (before overt degeneration and clinical signs). This is crucial for defining when to start disease-modifying treatments as well as for monitoring their effects.

However, there are several limitations to these studies and their clinical application. The first is that knowledge regarding the presymptomatic phase of neurodegenerative disorders will be fully useful only when true disease-modifying (neuroprotective) treatments become available. The second is that, partly because of the absence of such treatments, only a small proportion of at-risk individuals in families with monogenic neurodegenerative disorders request presymptomatic genetic testing.

Accordingly, a limited number of asymptomatic gene carriers are available for these studies. Another challenge, therefore, is to design these studies in such a way that at-risk individuals who are unaware of their genetic status (carriers or noncarriers) can participate in these studies without the risk of a breach of confidentiality concerning their genetic status. Nevertheless, several such studies are already ongoing and should generate many more useful preclinical biomarkers. This will also pave the way for trials of potential disease-modifying treatments that could be initiated at the preclinical stage of the disease before the occurrence of irreversible dysfunction or neurodegeneration.

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Searching for biomarkers in neurodegeneration

To the Editor:

In addition to imaging and cerebrospinal fluid (CSF) markers¹, blood-based protein biomarkers, gene-based markers and metabolomics are other potentially interesting approaches for biomarker discovery in neurodegenerative disease.

In terms of blood markers, why would they be altered in Alzheimer's disease? The source of proteins in the blood is often assumed to be peripheral—from the liver in particular—and nonspecific and therefore of possibly less interest. Putting aside the observation that some of the most widely used biomarkers in medicine are entirely nonspecific (erythrocyte sedimentation rate, a marker of inflammation and disease activity in a number of disorders, being just one example), there are many possible reasons for nonspecific changes in Alzheimer's disease. People with Alzheimer's disease are frequently elderly, infirm and with multiple other illnesses, and, indeed, medications and any of these illnesses might reasonably affect gene or protein expression peripherally. Another possible explanation for peripheral changes is that Alzheimer's disease is to some extent a systemic illness with pathol-

ogy being expressed most notably in, but not limited to, the brain. A third possible reason is that some proteins might cross the blood-brain barrier to reach the periphery.

What would a blood-based marker look like, and how might it be used in practice? It remains to be seen, but nothing yet published points toward a single marker—a prostate-specific antigen equivalent. Instead, some findings point to a panel of markers², and possibly markers of different modalities: proteins and imaging, for example. Blennow¹ makes a compelling case for biomarkers to be used to identify prodromal states for trial inclusion including, but not limited to, mild cognitive impairment (MCI). The problem is that MCI encountered in memory clinics seems to be different from the same condition in the community³. Apparently, people with MCI at memory clinics convert to dementia substantially more often than do otherwise similar community-dwelling cognitively impaired individuals. As memory clinics move to earlier identification, one would predict that the conversion rates would decline as patients in memory clinics come to match the pool that is in the community. The proportion with true prodromal disease, including altered