We as health care leaders of the 21st century now face a major task when and how are we going to redefine and reclassify all previous neurological disorders that were merely a clinical diagnosis?

Pushed by ever-rising health care costs, changes in health care systems, and modern technology, there is even a stronger need for finding blood-based biomarkers for diagnosis, disease progression and assessing response to therapy for all medical conditions that are clinically diagnosed. The days of relying solely on patient history, subjective scales/measures, and human interpretation of studies are slowing coming to an end. Such conditions include Alzheimer’s Disease (AD) (DSM V criteria), Parkinson’s disease (the 4 cardinal signs), epilepsy, migraine (IHS classification), and multiple sclerosis (Barkhof or McDonald criteria, etc.), which affect millions across the globe, are to this date still clinically diagnosed disorders [1].

Although it seems easy, finding a biomarker for diagnosis is not. It should be: A. commercially available and not limited to certain regions or countries B. Cost-effective. C. Acceptable in terms of sensitivity and specificity. D. A small, if any, range of overlap between normal and abnormal. E. Reproducible and valid [2].

In AD, short of obtaining post-mortem cerebral tissue, currently the most accurate biomarkers for diagnosis are CSF analysis [3] and amyloid PET studies [4], however, there are several limitations: A. There are few patients who are willing to have a lumbar puncture. B. Lumbar punctures are in general performed by either neurologists or radiologists, which limits their access. C. Amyloid PET studies are performed at large tertiary academic centers and read by trained faculty, further limiting their access. D. Amyloid PET studies, although FDA approved, are not always reimbursed nor approved by insurance companies or medical groups.

To date there is a plethora of biomarkers (serum, plasma, CSF or imaging) published for AD. However, one must realize that: A. The most accurate biomarker might not be the most easily accessible one; hence one might have to sacrifice sensitivity to achieve cost-effectiveness (e.g., CSF beta-amyloid and tau for blood-based biomarkers). B. Certain ones are more downstream along the disease process than others, decreasing their specificity (e.g., phospholipids, inflammatory markers). C. Concurrent medical conditions are also common in patients with Alzheimer’s disease, such as infection, inflammation, cardiac disorders, diabetes, or even age itself, further affecting its specificity (e.g., pro-inflammatory markers, BNP, IGF-I levels). D. The cutoff between normal and ‘abnormal’ might be unclear with overlap, and this would require even further scrutiny [5-17].

Last but not least, all studies are biased [18]; once we draw the human outlines of a study and separate this from nature it includes results that need to be interpreted with caution.

Recently there have been more evidence supporting N-terminal-pro-brain natriuretic peptide (NT-proBNP) as a potential blood biomarker for AD.

B-type Natriuretic Peptide (BNP) is a neurohormone synthesized in the cardiac ventricles. It is first released as preproBNP, then enzymatically cleaved into NT-proBNP and BNP upon ventricular myocyte stretch [19].

Both BNP and NT-proBNP initially made their mark as biomarkers for heart failure, but NT-proBNP plasma concentration is 2-10 times higher than BNP in patients with heart failure [20], with a half-life 3-6 times longer than BNP [21], hence making NT-proBNP a more attractive biomarker for AD.

The relationship between BNP and cognitive function was first described by Gunstad J et al [22]. BNP was then found to be associated with a decline in MMSE scores and the incidence of new onset dementia in an elderly general population [23]. Both Hu et al. [24] and Llano et al. [25] found that BNP levels are elevated in AD. Interestingly, BNP levels decreased after administration of donepezil (116.39 ± 76.58 pg/mL at baseline to 82.24 ± 46.64 pg/mL at first evaluation; P = 0.011), the prototypical drug for treatment of Alzheimer’s disease [26].

Nilsson et al. then described NT-proBNP as a vascular risk marker in the elderly with mental illness [27].

Initially these were thought to be elevated due to the relationship between cardiovascular risk factors and dementia, but Daniels et al. [28] demonstrated that elevated NT-proBNP levels in aged 60 or older without any history of dementia were independently associated with poor cognitive performance on MMSE and Trails B, whether adjusting for history of cardiovascular disease or excluding those with a previous history of stroke.
The recent article by Marksteiner et al. is a fascinating one. They found that 8 (namely, alpha2-macroglobulin, apolipoprotein A1, NT-proBNP, PAI, RAGE, SAA, TIMP-1 and TSP-2) out of 27 candidate vascular-related proteins were significantly increased in AD as opposed to healthy controls, however, only NT-proBNP levels were increased in both mild cognitive impairment (MCI) and AD [29]. Limitations of the study include the following:

A. The study size was relatively small (23 controls, 24 MCI patients and 33 AD patients). B. Although stated that there was no currently clinically significant cardiovascular disease, there were no echocardiogram results to provide objective evidence of normal left ventricular ejection fraction. C. The controls were significantly younger than the AD patients by 10 years.

We now know that Insulin Degrading Enzyme (IDE) is involved in the clearance of Aβ (beta-amyloid) 1-40 as well as other natriuretic peptides [30]. Internalization of Aβ1-40 into cultured mouse brain capillary endothelial cells (TM-BBB4) competes with insulin and other natriuretic peptides, which could explain why NT-proBNP levels are high in patients with Alzheimer’s disease [31].

Ultimately, NT-proBNP will have to stand up to the final test of comparing with the gold standard of the diagnosis of AD, which are the amyloid plaques and neurofibrillary tangles. Would this be comparable to the 97.9% sensitive and 88.9% specific florbetaben (Neuraceq) PET scans [32]? Only time will tell.

REFERENCES
29. Marksteiner J, Imarhiagbe D, Defrancesco M, Deisenhammer EA.


Sabbagh M, et al. A negative florbetaben PET scan reliably excludes amyloid pathology as confirmed by histopathology in a large Phase 3 trial. AAN. 2014; Abstract 004.