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Foreword

Biomarkers for Alzheimer's disease

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The data that define the state of biological markers (biomarkers) for Alzheimer's disease (AD) are reviewed in the articles that follow along with a summary of clinical examination, the gold standard to which any successful biomarker will be compared. Some biomarkers focus on reflecting events specific to AD, such as amyloid β (Aβ)$_{42}$ and phospho-tau, while other biomarkers are directed at assessing pathogenic processes that occur in AD as well as other diseases of brain. As will be discussed in the coming articles, both have important roles to serve. AD-specific biomarkers clearly are needed for the differential diagnosis of cognitive impairment in the elderly. Process-specific biomarkers, like markers for inflammation of oxidative damage, although unlikely on their own to be sufficiently discriminating of AD vs. other diseases of brain, will be very useful in determining pharmacologic responses to therapeutics in patients already identified by clinical exam, neuroimaging, and disease-specific biomarkers to be in the early stages of AD. Here we wish to convey the critical need to discover and develop biomarkers for AD and the impact this will have on improving the diagnosis and management of dementia.

AD and related dementias are degenerative disorders, primarily of the aged. They are not dissimilar from many other age-related disorders for which clinicians diligently screen and monitor, often with expensive tests and procedures. Such clinical activities are done less with the expectation of reversing disease than with the goal of preventing further end-organ damage. However, what sets hypertension, hypercholesterolemia, and diabetes mellitus apart from AD is that each has biomarkers that can be followed easily and repeatedly, not simply to diagnose but also to monitor response and to optimize treatment. In contrast, the current role of clinical laboratory evaluation for dementia is exclusionary. The development of such biomarkers is critical to translating efficiently the new therapeutic approaches for AD under development by many research groups into treatments for the millions who suffer from AD.

Advances in neuroimaging also likely will lead to it serving an important role in understanding dementia and its prodrome. Indeed, the Alzheimer's Disease Neuroimaging Initiative, a large collaboration among the National Institute on Aging, several university-based research groups, and industry, evaluates the utility of both structural and functional brain imaging to follow the progression of early AD and its prodrome. Imaging probes for selected facets of AD also are being developed; for example, in vivo imaging of brain amyloid appears to show promise even in asymptomatic individuals [3]. However, neuroimaging has its own set of scientific, technical, and practical limitations that, in our opinion, limit this approach from becoming more than complementary to biochemical markers of AD. Put another way, the diagnosis and management of diabetes mellitus would be entirely different if it relied principally on structural and functional imaging of the pancreas rather than blood tests.

In terms of clinical laboratory evaluation, although it is self-evident that a blood or urine biomarker for AD would be most practical and acceptable to both clinicians and patients, current data point to cerebrospinal fluid (CSF) obtained by lumbar puncture (LP) as providing the most reliable approach, although not without its own limitations. Since the target organ of AD is the brain, the blood-brain barrier presents a substantial and unfortunately inconsistent obstacle to blood-based biomarkers. Interpreting concentrations of molecules in blood or urine as having derived from brain has several confounders that will be discussed in

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the coming chapters and include dilution, mixing with peripherally-derived pools, and transport processes, among others. Some of these can be controlled, but not without labeling or other such interventions. Moreover, the integrity of the blood-brain barrier is diminished by age, drugs, co-morbid conditions, and perhaps even AD itself, further confounding interpretation.

While CSF also has limitations, the major perceived limitation needs a fresh look. If we are to have practical CSF biomarkers, it is important for patients, families, and clinicians develop informed attitudes towards LP. In the hands of a trained clinician using proper techniques and equipment, LP is less unpleasant than many other procedures patients undergo on a yearly basis, including pelvic exams, digital rectal exams, and mammograms. It carries a very low risk of adverse events, even for patients with AD [2,4,5]. Indeed, the American Academy of Neurology, in recently published guidelines on post-LP headache [1], concluded that use of small gauge atraumatic spinal needles very substantially reduces risk of post-LP headache and calls for the development of standardized educational materials to train clinicians in these techniques. In this context, it is important to remember that structural and functional imaging are not without risk to patients, and even cognitive testing can be unpleasant for patients who may find being confronted by their deficits distressing.

Progress toward controlling if not eradicating AD is at a crossroads where clinical, pathological, and basic science studies have identified therapeutic targets that are now being tested. Critical to translating this knowledge to improved patient care will be developing panels of biomarkers that complement the clinical exam, cognitive testing, and neuroimaging. Here, experts provide reviews of the major biomarker candidates for AD and related neurodegenerative diseases.

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