Precision medicine: Clarity for the clinical and biological complexity of Alzheimer's and Parkinson's diseases

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The goal of precision medicine is to deliver optimally targeted and timed interventions tailored to an individual's molecular drivers of disease. This concept has wide currency in cancer care and in some diseases caused by monogenetic mutations, such as cystic fibrosis, and recently has been endorsed by the White House Office of Science and Technology for more widespread application in medicine. Here we describe our vision of how precision medicine can bring greater clarity to the clinical and biological complexity of the two most common neurodegenerative diseases, Alzheimer's disease and Parkinson's disease.

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Precision medicine is an approach to health care that employs new knowledge and emerging technologies to deliver optimally targeted and timed interventions that are tailored to an individual's molecular drivers of disease. This approach of tailored, mechanism-based care is gaining progressively greater impact as it is applied to the care of patients with cancer, but it is only beginning to be considered in chronic neurodegenerative diseases like Alzheimer's disease (AD) and Parkinson's disease (PD).

AD and PD are major and increasing challenges to older individuals, public health, health care systems, and national economies (Alzheimer's Association and Centers for Disease Control and Prevention, 2013). The Institute for Health Metrics and Evaluation recently determined that AD is the 4th leading cause of death in the US, and PD is the 24th; moreover, AD and PD were the two most rapidly increasing causes of death in the US between 1990 and 2010 (Murray et al., 2013). Even more concerning, as health care systems throughout the world continue to make advances in managing and treating acute diseases, chronic illnesses such as AD and PD are increasing as major contributors to the global burden of disease (Dorsey et al., 2007; Lim et al., 2012).

Dementia, a clinical diagnosis of severe cognitive impairment, is a syndrome that is uncommon in people younger than 65 yr of age but increases exponentially with age greater than 65 yr (Montine et al., 2014). Dementia in these older individuals is a complex convergent trait that derives most commonly from an idiosyncratic mix of AD, dementia with Lewy bodies (DLB), and vascular brain injury (VBI), with AD being the most common contributor (Hyman et al., 2012; Montine et al., 2014). PD is diagnosed as a movement disorder characterized by both restricted and excessive movement that also can be mimicked by other less common diseases. There are effective interventions for some forms of VBI; indeed, the burden of stroke in the US has decreased over the last 15 yr (Murray et al., 2013). However, there is no disease-modifying therapy for AD or PD yet. Indeed, interventions to prevent, stop, or slow the progression of these neurodegenerative diseases would relieve untold suffering and be very valuable contributions to the sustainability of health care systems.

We refer to pathophysiologic processes that underlie the clinical expression of disease that derives from a complex mix not only of the pathophysiologic processes of injury and response to injury but also consumption of reserve and compensation. AD and PD are chronic diseases and thereby are characterized by latency (when pathophysiologic processes are active but without signs or symptoms), prodrome (when some limited expression of disease is apparent clinically), and full clinical expression. For AD, prodrome most often

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is diagnosed according to consensus criteria for mild cognitive impairment (MCI), and full clinical expression is diagnosed as dementia (Albert et al., 2011; McKhann et al., 2011). Latency is detected only by laboratory testing because by definition it has no clinical expression and is often called preclinical or antecedent disease (Sperling et al., 2011); however, this can become confusing because latent pathophysiologic processes may never progress to clinical expression. For PD, there are a variety of prodromal signs and symptoms that vary among individuals but include altered olfaction, rapid eye movement sleep behavior disorder, autonomic dysfunction, behavioral changes, and cognitive impairment (Postuma et al., 2012). Indeed, this last feature of PD complicates the clinical situation because a diagnosis of PD (based on movement abnormalities) is accompanied by cognitive impairment or dementia in about one-third of patients and greatly increases the risk of developing MCI (PD-MCI) or dementia (PDD) over the ensuing decade in the remaining PD patients who did not present initially with cognitive impairment or dementia (Aarsland et al., 2003; Litvan et al., 2011). Further complexity is introduced with DLB, which has broad overlap with AD and PD. The group of clinical diagnoses characterized pathologically by Lewy body formation includes PD, PD-MCI, PDD, and DLB; collectively, they are referred to as Lewy body disease (LBD; Montine et al., 2014). Although there may be clinical utility in maintaining these diagnostic categories, the biological distinctiveness among each LBD and the extent to which they share mechanisms with AD are not at all clear. Indeed, several groups have reported that coincident pathological changes of AD and LBD occur more commonly than would be predicted by chance alone, raising the possibility that these two diseases somehow interact and may even promote each other (Gomperts et al., 2008; Dugger et al., 2012; Irwin et al., 2012). These findings have led others to test hypotheses concerning shared risk factors or common pathogenic mechanisms for AD and LBD (Clinton et al., 2010; Guo et al., 2013).

The clinical complexity of AD and PD is compounded by biological complexity. Indeed, numerous genetic association studies have discovered and validated about two to three dozen genetic risk factors each for AD and PD (Lambert et al., 2013; Nalls et al., 2014). Broadly summarizing, prevalence of these genetic variants spans from common to rare, with risk spanning from low to causative in adults. One example is the *APOE* ε4 allele that is present in ∼5% to 35% of populations and imparts a gene dosage–dependent increase in risk for AD (Corder et al., 1993; Mahley and Rall, 2000). *TREM2* is a comparably strong risk factor for AD but is much less prevalent than *APOE* ε4 (Guerreiro et al., 2013; Jonsson et al., 2013). Examples of uncommon causative mutations for AD include mutations in *APP*, *PSEN1*, and *PSEN2* (Schellenberg and Montine, 2012). The most common causative genetic mutations for PD occur in *LRRK2*, whereas the most common risk mutations for PD occur in *GBA* (Paisán-Ruíz et al., 2004; Sidransky et al., 2009; Verstraeten et al., 2015). Because of the complexity of the clinical trait, several large consortia have attempted to link genetic risk with neuropathologic features of AD or PD (Tsuang et al., 2012, 2013; Beecham et al., 2014, 2015; Nuytemans et al., 2014). The situation with PD is more complicated because the genetic variants linked to the classic motor phenotype only partially overlap with genetic variants linked to cognitive impairment and dementia. For example, *GBA* mutations are associated with increased risk of cognitive impairment and dementia in PD (Alcalay et al., 2012), but *LRRK2* mutations are not; in fact, PD patients with *LRRK2* mutations appear to have reduced risk of dementia (Srivatsal et al., 2015). Also, *APOE* ε4 is not reproducibly associated with risk for PD motor phenotype, but in the context of PD, *APOE* ε4 is associated with increased risk of dementia (Mata et al., 2014).

With limited exceptions, this heterogeneity underlying AD and PD risk has been a barrier to widespread genetic screening, although this may improve as technology advances and more comprehensive genetic assessments become common in clinical settings. Perhaps more importantly, each verified genetic risk locus focuses attention on the encoded protein or regulatory sequence as somehow important to the initiation, progression, or penetrance of disease. From this perspective, genetic association studies have greatly advanced our knowledge of molecules relevant to AD and PD. The extent to which these relevant molecules highlight distinct or shared mechanisms of disease, and thereby therapeutic targets, remains largely unknown but is the focus in many functional genomic and mechanistic studies.

Precision medicine

How best to approach the clinical and biological complexity of these two common neurodegenerative illnesses? We and others have proposed "precision medicine," meaning optimally targeted and timed interventions that prevent, stop, or slow progression based on an individual's molecular driver(s) (Sieber et al., 2014). In 2011, the National Academy of Sciences said the following in *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease*: "As used in this report 'Precision Medicine' refers to the tailoring of medical treatment to the individual characteristics of each patient. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not. Although the term 'Personalized Medicine' is also used to convey this meaning, that term is sometimes misinterpreted. For this reason, the Committee thinks the term 'Precision Medicine' is preferable" (National Research Council of the National Academies, 2011). Indeed, this approach is being widely adopted in cancer care and in new mechanism-based therapies for cystic fibrosis as highlighted by the Precision Medicine Initiative put forth by the White House Office of Science and Technology in early 2015 (http://www.whitehouse.gov/blog/2015/01/30/precision-medicine-initiative-data-driven-treatments-unique-your-own-body). We envision three key elements of precision medicine for AD and PD: comprehensive risk assessment, tools for preclinical detection of pathophysiologic

processes, and interventions tailored to an individual's molecular drivers of disease (Fig. 1).

Comprehensive risk assessment. Currently, the major goal of risk assessment is to illuminate relevant mechanisms and thereby effective therapeutic interventions. Several examples of genetic risk for AD and PD are provided above. It is important to recognize that much effort currently is focused on understanding genetic risk, but presumably environmental factors also will be key to comprehensive risk assessment. As we learn more about environmental influences associated with disease, we will gain additional insights into gene–environment interactions and relevant mechanisms. Two examples of known environmental factors that increase risk are traumatic brain injury for AD (Plassman and Grafman, 2015) and toxicant exposure for PD (Goldman, 2014). Ultimately, comprehensive risk assessment will serve two additional goals: allow individual counseling on the likelihood of future disease and define an individual's drivers of disease. Again, current cancer care provides illustrative examples where patient management, frequency of surveillance for preclinical disease, and treatment options can vary with underlying genetic risk.

Tools for detection of latent pathophysiologic processes. It is important to recognize that risk, whether genetic or environmental, is an estimate of the future likelihood of disease but not an actual measurement of ongoing pathophysiologic processes or disease. Consider that someone homozygous for *APOE* ε4 is conceived with that genetic risk but will not express AD for many decades, if ever (Strittmatter et al., 1993). Even someone who inherits a causative mutation, such as an autosomal-dominant mutation in *LRRK2* or *SNCA*, will not clinically express PD for decades (Polymeropoulos et al., 1997; Paisán-Ruíz et al., 2004). Rarely is treatment initiated based on risk alone; however, treatment commonly is initiated based on the detection of latent pathophysiologic processes. Indeed, all medical disciplines seek to develop tools to detect latent pathophysiologic processes in the expectation that earliest detection provides greatest opportunity for effective intervention. Examples from cancer care with varying levels of success include Pap staining for cervical dysplasia, mammography, colonoscopy, and measurement of plasma prostate–specific antigen concentration. Examples from metabolic diseases include measurement of plasma lipid profile, fasting glucose concentration, urinalysis, and brachial blood pressure. Much of health care management and recommendations for treatment decisions hinge on the outcomes of these tests.

A similar approach for detection of latent pathophysiologic processes is now a major research focus in AD and PD, again with the reasonable assumption that detection of latent pathophysiologic processes provides optimal timing for effective intervention and prevention of clinical expression of disease. Similar to previous efforts in other types of diseases, these approaches include imaging, measurement of molecules in biofluids, and even assessment of tissue in the case of peripheral biopsies for evaluation of Lewy body formation

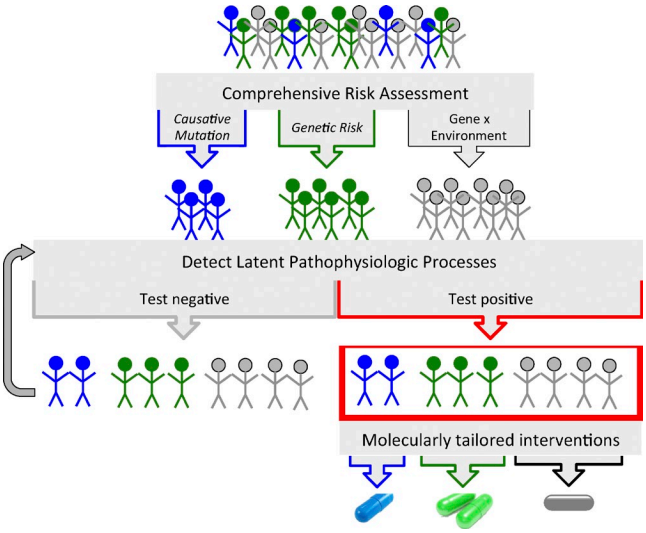

Figure 1. Three key elements of precision medicine for AD and PD. We envision an approach that begins with (1) comprehensive risk assessment to identify underlying factors, (2) utilizes tools for preclinical detection of pathophysiologic processes, and leads to (3) molecularly tailored interventions. Blue, green, and gray represent different risk groups.

(Del Tredici et al., 2010; Beach et al., 2013). Neuroimaging efforts show unusual promise because of their growing ability to measure brain function at increasingly higher levels of organization. Evaluation of specific molecules, whether by PET or biochemical assay of cerebrospinal fluid, has been comparably successful in the research arena (Roe et al., 2013), and both are being considered for more widespread application. Quantification of molecules singly or in large groups in other biofluids such as serum, plasma, or even urine has been investigated many times, although none has yet revealed a reproducible biomarker or ensemble of biomarkers.

Interventions tailored to an individual's molecular drivers. After comprehensive risk assessment and accurate surveillance for latent pathophysiologic processes, the promise of precision medicine culminates in interventions that prevent, stop, or slow progression based on an individual's molecular drivers. Currently, there is a limited repertoire of interventions for AD or PD, largely focused on the replenishment or replacement of the neurotransmitters acetylcholine or dopamine, suppression of ionotropic glutamatergic signaling by memantine, or modulation of neural systems with deep brain stimulation (Faulkner, 2014; Strauss et al., 2014; Zemek et al., 2014). Each carries some risk of untoward effects and is not undertaken until there is clinical expression. Although each represents an outcome of brilliant research and has brought relief to millions, none is thought to actually prevent, stop, or slow progression of pathophysiologic processes or disease expression.

Based on the most compelling data on molecular mechanisms from genetic studies and outcomes from experimental models, multiple clinical trials to test proposed disease-altering interventions have been attempted and failed in both AD and

PD. However, virtually all have neglected to consider the underlying clinical and biological complexity of these diseases, and until very recently, a precision medicine approach largely has been ignored. That is being rectified through the ongoing Dominantly Inherited Alzheimer Network (DIAN; Moulder et al., 2013), Alzheimer's Prevention Initiative (Reiman et al., 2011), and A4 trial (Sperling et al., 2014), which represent the initial attempts to align a priori the mechanism of action of an experimental therapeutic with a specific molecular driver. Along with expanding knowledge of molecular drivers and improved tools to detect latent pathophysiologic processes, we believe there is great promise in learning phase clinical trials of previously "failed" and novel interventions specifically designed to target a particular biological mechanism. Such interventions likely will be evaluated first by their ability to suppress or reverse latent pathophysiologic processes in subsets of individuals with shared molecular driver(s) (Sieber et al., 2014). Interventions successful in these initial evaluations subsequently will advance to trials powered to determine therapeutic effectiveness and potential for extension to individuals with different molecular drivers but perhaps shared mechanisms.

Together, the three key elements of comprehensive risk assessment, detection of latent pathophysiologic processes, and molecularly tailored interventions embody a precision medicine approach and provide a strategy for optimal targeting and timing of efforts to prevent, stop, or slow progression of AD and PD.

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