REVIEW

Precision Medicine

Clarity for the Complexity of Dementia

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Three key elements to precision medicine are stratification by risk, detection of pathophysiological processes as early as possible (even before clinical presentation), and alignment of mechanism of action of intervention(s) with an individual's molecular driver(s) of disease. Used for decades in the management of some rare diseases and now gaining broad currency in cancer care, a precision medicine approach is beginning to be adapted to cognitive impairment and dementia. This review focuses on the application of precision medicine to address the clinical and biological complexity of two common neurodegenerative causes of dementia: Alzheimer disease and Parkinson disease. (*Am J Pathol* 2016, 186: 500–506; <http://dx.doi.org/10.1016/j.ajpath.2015.12.001>)

The goal of precision medicine is to harness new knowledge and technology to optimize the timing and targeting of interventions for maximal therapeutic benefit. There are three key elements to precision medicine: stratification by risk, detection of pathophysiological processes as early as possible and preferably before clinical presentation, and alignment of mechanism of action of intervention(s) with an individual's molecular driver(s) of disease.¹ Ideally, precision medicine contrasts with the traditional approach in graded surveillance on the basis of level of risk, and intervention to suppress pathophysiologic processes while still latent (Figure 1). The approach of precision medicine, applied for decades to rare diseases like phenylketonuria and, more recently, to cystic fibrosis,² now has broad currency in cancer care and is the focus of a recent White House initiative to transform medical practice (Precision Medicine Cohort Program, <https://www.nih.gov/research-training/precision-medicine-initiative>, last accessed December 3, 2015). Herein, we review how the key elements of precision medicine are beginning to bring clarity to the clinical and biological complexity of dementia.

Clinical Complexity

Dementia is a major public health threat that causes untold suffering to patients and caregivers, and is poised to overwhelm health care systems in the coming decades.^{3,4} Population- or community-based studies of brain aging and incident dementia from around the world have repeatedly identified three common pathological correlates of dementia. These include Alzheimer disease (AD) neuropathologic changes, including senile plaques (SPs) and neurofibrillary tangles (NFTs); vascular brain injury (VBI), especially caused by small-vessel disease; and Lewy body disease (LBD; *vide infra*), with recognition that other neuropathologic changes, including cerebral

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	<i>Traditional Approach</i>			<i>Precision Medicine Approach</i>		
Population of Individuals
Classify by Risk
Surveillance for Preclinical Disease
Signs or Symptoms
Treat with
Strategy	"One Size Fits All" Leads to Overall Mixed Results			Focus Existing	Repurpose FDA Approval	Invent New

Outcome
				Benefit	Benefit	Benefit

Figure 1 Schematic of traditional and precision medicine approaches. Key elements of precision medicine are classification by risk, surveillance for preclinical disease, and alignment of an expanding repertoire of treatments with the molecular drivers of disease.

amyloid angiopathy and hippocampal sclerosis, are found in older adults and associated with cognitive impairment.^{5–12} In the Seattle-based Adult Changes in Thought study, a population-based study of brain aging and incident dementia in individuals 65 years or older, the population attributable risk for dementia from these diseases is 45% for AD, 33% for VBI, and 10% for LBD.¹³

In a collaborative study that pooled data from 1672 brain autopsies from multiple population- and community-based studies, the most common neuropathologic finding was some combination of these diseases, leaving open the extent to which each disease may have contributed to cognitive decline.⁵ More important, 424 cognitively nonimpaired individuals in the same research studies, who died proximate to extensive neuropsychological evaluation, also showed neuropathologic evidence for the same diseases but at generally lower levels, although some individuals died with advanced neuropathologic changes despite relatively preserved function. **Figure 2** presents updated results from 405 brain autopsies from the Adult Changes in Thought study as of December 2014, following exactly the same approach as our earlier publication.⁵ Results are separated by cognitive status into high cognitive performers (**Figure 2A**), low cognitive performers (**Figure 2B**), early dementia (**Figure 2C**), and late dementia (**Figure 2D**). **Figure 2E** shows average values for each group. The proportion of individuals with any pathological evidence of the two neurodegenerative diseases did not change substantially across the four groups; AD pathological change was present in 97% to 100%, and LBD was present in 12% to 20%. The proportion of individuals with VBI ranged from 32% in high cognitive performers to 64% in late dementia. These results from a typical US urban and suburban population demonstrate that the aging brain is a complex environment in which AD, VBI, and LBD each have a latent phase, are variably mixed in older patients with and without dementia, and the overall burden of disease(s) increases in severity with increasing cognitive impairment.

LBD is especially complex because this pathological change is associated with clinical diagnoses of dementia

with Lewy bodies (DLB) or Parkinson disease (PD) with or without mild cognitive impairment (PD-MCI) or dementia (PDD).^{14–16} DLB most commonly is associated with a combination of the pathological features of AD and LBD, and less commonly with widespread LBD in the absence of AD neuropathologic changes.^{17,18} Although recognized as a disorder of motor control and characterized by brainstem Lewy bodies (LBs), PD also is accompanied by cognitive impairment or dementia in a large fraction of patients, approximately one-quarter even at the time of initial diagnosis.^{19–25} Results from the Pacific Northwest Udall Center widely replicate the experience of research cohorts from around the globe showing that MCI and dementia are common in PD.²⁶ Indeed, approximately 80% of the initial 603 research volunteers to the Pacific Northwest Udall Center with PD also were diagnosed with MCI or dementia on intake evaluation, although, admittedly, this estimate from a research cohort may be higher than in community settings. **Figure 3** shows basic characteristics of these 491 individuals with PD-MCI or PDD. MCI and dementia occurred much more commonly with shorter duration of PD in older individuals, and more commonly with longer disease duration in younger individuals (Fischer's exact test, $P < 0.0001$).²⁶ The pathological bases of PDD, and its distinction from DLB, remain unclear. Hence, the extent to which the pathophysiologic processes that lead to brain regional SP, NFT, or LB formation contribute to cognitive impairment and dementia in an individual with DLB, PD-MCI, or PDD remains impossible to determine. Increased knowledge of molecular drivers and accurate biomarkers of pathophysiologic processes from advances in precision medicine will help bring greater clarity to this complex clinical situation.

Biological Complexity

On the basis of abundant genetic, experimental, pathologic, and biomarker data, two key molecular drivers of AD

Figure 2 Results from 408 brain autopsies in the Adult Changes in Thought (ACT) study as of December 2014. Three cases of dementia were excluded that had neuropathologic diagnosis of frontotemporal lobar degeneration, traumatic brain injury, or extensive laminar necrosis. Summary neuropathology scores for Alzheimer disease (AD; blue bars), vascular brain injury (VBI; red bars), and Lewy body disease (LBD; green bars) for the remaining 405 cases were determined using consensus neuropathologic evaluations, as described previously,⁵ and then plotted for each individual stratified by cognitive performance (A–D) or summarized for each cognitive performance group (E). Cognitive performance was determined using the Cognitive Assessment Screening Instrument (CASI), and dementia was diagnosed according to Diagnostic Statistical Manual-IVR criteria. CASI scores ≥ 91 are in the upper four quintiles of the ACT cohort. The individuals (means $\pm$ SD age, M:F ratio) with i) CASI ≥ 91 at last evaluation within 2 years of death are the High Cognitive Performance group (85 ± 7 years, 73:85; A and E); ii) CASI < 91 but not diagnosed with dementia at last evaluation within 2 years of death are the Low Cognitive Performance group (87 ± 6 years, 46:44; B and E); iii) dementia at last evaluation within 2 years of death are the Early Dementia group (89 ± 6 years, 26:34; C and E), and iv) dementia at last evaluation > 2 years before death are the Late Dementia group (91 ± 6 years, 37:61; D and E). One-way analysis of variance for the data presented in E has $P < 0.0001$ and Bonferroni-corrected $P < 0.05$ for all possible paired comparisons.

appear to be $A\beta_{42}$ and pathological forms of tau.²⁷ We quantified $A\beta_{42}$ and paired helical filament (PHF)-tau in the cerebral cortex from 325 consecutive Adult Changes in Thought participants and observed a generally positive, but complex, relationship.²⁸ Given the comprehensiveness of brain autopsy, herein, we reanalyzed these published data²⁸ to test whether isolating AD from common comorbid conditions might bring greater clarity to the quantitative relationship between cerebral cortical $A\beta_{42}$ and PHF-tau among individuals without dementia who were last evaluated within 2 years of death (Figure 4). Indeed, exclusion of cases with LBD or VBI and focusing on those whose *APOE* genotype varied by only one allele revealed a strong positive correlation between cerebral cortical concentrations of $A\beta_{42}$ and PHF-tau in temporal lobe that approximated a line ($P < 0.0001$). In contrast, cerebral cortical concentrations of $A\beta_{42}$ and PHF-tau were weakly correlated in the frontal lobe ($P < 0.05$). The concentration of $A\beta_{42}$ was strongly related to *APOE* genotype regardless of cerebral cortical region, whereas the concentration of PHF-tau was significantly related to *APOE* genotype only in the temporal, and not in the frontal, lobe. These novel results provide insight into

the molecular underpinnings of AD, and will help guide molecular neuroimagers as they now are beginning to compare results of imaging ligands for cerebral amyloid and pathological tau.

Figure 3 Stratification by age of Parkinson disease (PD) onset and duration of PD for the 491 individuals who volunteered to join the Pacific Northwest Udall Center (PANUC). Data are the number of PANUC participants diagnosed as PD with mild cognitive impairment (PD-MCI) or PD with dementia (PDD) at their initial evaluation of a total cohort of 619 individuals with PD.

Figure 4 Quantification of $A\beta_{42}$ and paired helical filament (PHF)-tau in superior and middle temporal gyri (SMTG) or middle frontal gyrus (MFG) from Adult Changes in Thought study brain autopsies.²⁸ All participants were last evaluated within 2 years of death when they were diagnosed as not meeting criteria for dementia. Cases with neuropathologic changes other than Alzheimer disease were excluded, and we limited our analysis to only those with genotypes *APOE* $\epsilon 2/\epsilon 3$, *APOE* $\epsilon 3/\epsilon 3$, or *APOE* $\epsilon 3/\epsilon 4$. Molecular concentrations were obtained using a method called Histelde (histology and ELISA on a glass slide)²⁹ and expressed in units of absorbance (Abs) at 405 nm normalized to gray matter (GM) area. Concentrations of $A\beta_{42}$ did not vary significantly across the two regions (C) and were averaged into a single value for cerebral cortex in correlation analyses. A and B plot average cerebral cortical $A\beta_{42}$ versus PHF-tau concentrations in SMTG or MFG. There is a highly statistically significant correlation between $A\beta_{42}$ and PHF-tau concentrations in SMTG ($P < 0.0001$), and a much weaker correlation in MFG ($P < 0.05$). C and D plot average concentration of $A\beta_{42}$ or PHF-tau concentration in SMTG and MFG stratified by *APOE* genotype. Two-way analysis of variance for $A\beta_{42}$ concentration had $P < 0.0001$ for *APOE* genotype, but was not significant for region or interaction. Two-way analysis of variance for PHF-tau concentration in SMTG had $P < 0.01$ for *APOE* genotype, $P < 0.0001$ for region, and $P < 0.01$ for interaction. Tukey's multiple comparisons test for PHF-tau concentration showed $P < 0.01$ for all pair-wise comparisons of *APOE* genotypes in SMTG but no significant difference among *APOE* genotypes in MFG. $n = 105$ (A and B, SMTG); $n = 77$ (A and B, MFG).

One approach to identification of additional molecular drivers of disease is determining disease risk. Comprehensive risk assessment requires evaluation of environment, lifestyle, and inherited risk; herein, we focus on recent advances in understanding inherited risk. Recent genome-wide association studies have linked genetic variants across the human genome with a clinical diagnosis of AD dementia. In 2013, the International Genomics of Alzheimer's Project reported results from >74,000 individuals that brought to 21 the total number of genetic susceptibility loci for a clinical diagnosis of AD dementia,³⁰ and more have been discovered since.^{31,32} It is important to recognize that these genomic studies have linked genetic variants with the clinical diagnosis of AD dementia. Recognizing that the clinical expression of AD dementia is the culmination of stress and injury, response to injury, consumption of reserve, and compensation, we sought to clarify the mechanisms underlying genetic susceptibility for AD dementia by determining their association with SPs and NFTs. As part

of a large multisite collaboration, we assembled neuropathologic data from 4914 brain autopsies, largely from research cohorts, and performed a genome-wide association study as well as analysis of the then known 21 International Genomics of Alzheimer's Project genetic risk loci for AD dementia.³⁰ Genome-wide significance was observed for the following: i) neuritic plaques (a subset of SPs that had been assessed in all cases), NFTs, cerebral amyloid angiopathy, and LBD, with several variants in and around the apolipoprotein E gene (*APOE*); ii) neuritic plaques with GalNAc transferase 7 gene (*GALNT7*), ATP-binding cassette, subfamily G, member 1 gene (*ABCG1*), and an intergenic region on chromosome 9; and iii) hippocampal sclerosis with potassium large conductance calcium-activated channel, subfamily M, β member 2 (*KCNMB2*). Of the 21 International Genomics of Alzheimer's Project genetic risk loci for clinically defined AD dementia, 12 were confirmed in our smaller clinicopathologic sample: *CRI1*, *BIN1*, *CLU*, *MS4A6A*, *PICALM*, *ABCA7*, *CD33*, *PTK2B*, *SORL1*, *MEF2C*, *ZCWPW1*, and *CASS4*. Of these 12 loci, 9 showed a larger odds ratio in the clinicopathologic sample than in the clinical sample. As anticipated, comparison of effect sizes for risk of AD dementia (function) with effect size for NFTs or neuritic plaques (structure) showed a significant positive correlation. Although limited by relatively low sample size and design characteristics, such that only data from people with late-onset AD dementia and cognitively normal elderly controls were considered, the same approach showed no association with comorbid LBD and perhaps ominously showed a moderate negative correlation with comorbid VBI.

Like AD dementia, large consortia have pursued genetic variants associated with PD (defined by motor symptoms) using genomic approaches and have identified a similar number of risk loci.^{33,34} Furthermore, autopsy-based genome-wide association studies for PD also have contributed to novel insights into the genetic risk architecture for PD.³⁵ The Pacific Northwest Udall Center has organized the PD Cognitive Genetics Consortium to investigate the genetic risk for dementia in the context of PD. Initially using a candidate gene approach, this multisite collaborative effort has built on knowledge gained from prior case-control studies and identified genetic variants that increase risk for

Table 1 Risk from Candidate Genes for PD When Compared with Unaffected Individuals, or for PDD When Compared with Nondemented Individuals with PD

Candidate gene	PD risk	PDD risk
<i>SNCA</i>	↑	—
<i>MATP</i>	↑	—
<i>APOE</i> $\epsilon 4$	—	↑
<i>GBA</i>	↑	↑
<i>LRRK2</i>	↑	↓

—, no significant association; ↑, statistically increased risk; ↓, statistically decreased risk; PD, Parkinson disease; PDD, PD with dementia.

PD motor symptoms and PDD together, PD motor symptoms alone, and PDD alone (Table 1).^{36–38} Current efforts by the PD Cognitive Genetics Consortium are using genomic approaches to accelerate discovery of novel genetic susceptibility loci for cognitive impairment in PD.

Precision Medicine

In precision medicine, because greater knowledge about genetic risk fuels development of interventions tailored to specific molecular drivers, there will be growing need for the third component, detection of pathophysiologic processes as early as possible, ideally during latency. There has been strong progress in this area of research, with many groups around the world pursuing a variety of technologies. Notable successes in AD are positron emission tomography imaging for cerebral amyloid³⁹ and, more recently, pathological tau,⁴⁰ and cerebrospinal fluid concentrations of A β ₄₂ (a major component of SPs) and tau species (a major component of NFTs).^{41–45} Although early, experience with imaging of pathological tau suggests that the regional distribution may be critically important, a possibility reinforced by our quantification of PHF-tau. A similar approach and outcomes have been achieved in PD with neuroimaging and measurement of cerebrospinal fluid biomarkers.^{45–50} Interestingly, cerebrospinal fluid α -synuclein concentration (a major component of LB) may not only aid in diagnosis of LBD, but also improve the diagnostic accuracy of AD biomarkers.⁵¹ Molecular neuroimaging for pathological α -synuclein is a high priority for development.⁵²

Although envisioned primarily as diagnostic aides or potential surrogates for pharmacological activity,⁵³ results suggest that biomarkers may also serve to group patients by underlying pathophysiologic processes that apparently can cross classic diagnostic boundaries. From this perspective, neuroimaging and biofluid biomarkers might, in the future, serve as evidence for selection of therapeutics in addition to assignment to a clinical diagnostic category.

Success in precision medicine for diseases that cause dementia will require much more work to fill gaps in our knowledge regarding risk stratification, surveillance for preclinical pathophysiologic processes, and development of new interventions that are tailored to key molecular drivers of disease. Of these, we are having the most success in identifying genetic risk and developing tools to detect pathophysiologic processes; major advances in the repertoire of disease-modifying therapies are needed. Despite our incomplete knowledge, several groups are now beginning to incorporate the approach of precision medicine into clinical trials for AD and PD. Indeed, determination of genetic risk as a partial window into molecular drivers of disease, coupled with neuroimaging and biomarkers of underlying pathophysiologic processes, has been incorporated into the design of several clinical trials. These include the Dominantly Inherited Alzheimer Network Trials Unit,⁵⁴ the

Alzheimer's Prevention Initiative,⁵⁵ and Anti-Amyloid Treatment in Asymptomatic Alzheimer Disease⁵⁶ trial, which all focus on subgroups of individuals with known genetic risk for AD, and biofluid biomarkers or neuroimaging to detect onset of disease. In addition, major research initiatives are underway to advance therapeutics that oppose the functional outcomes of mutations in *LRRK2* or *GBA* that increase risk of PD. We expect this is only the beginning for a precision medicine approach to clinical and biological complexity of AD and PD.

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