Toward precision medicine in Alzheimer's disease

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Abstract: In Western societies, Alzheimer's disease (AD) is the most common form of dementia and the sixth leading cause of death. In recent years, the concept of precision medicine, an approach for disease prevention and treatment that is personalized to an individual's specific pattern of genetic variability, environment and lifestyle factors, has emerged. While for some diseases, in particular select cancers and a few monogenetic disorders such as cystic fibrosis, significant advances in precision medicine have been made over the past years, for most other diseases precision medicine is only in its beginning. To advance the application of precision medicine to a wider spectrum of disorders, governments around the world are starting to launch Precision Medicine Initiatives, major efforts to generate the extensive scientific knowledge needed to integrate the model of precision medicine into every day clinical practice. In this article we summarize the state of precision medicine in AD, review major obstacles in its development, and discuss its benefits in this highly prevalent, clinically and pathologically complex disease.

Keywords: Precision medicine; Alzheimer's disease (AD); genomics

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The concept of precision medicine

The concept of precision medicine, also termed "personalized medicine" or "individualized medicine", is a rapidly advancing field in medical clinical and research settings. In contrast to the "one-size-fits-all-approach", it aims to optimize effectiveness of disease prevention and treatment and minimize side effects for persons less likely to respond to a particular therapeutic, by considering an individual's specific makeup of genetic, biomarker, phenotypic and psychosocial characteristics. The measurement of molecular, environmental, and behavioral factors contributing to a specific disease improves the understanding of disease onset and progression as well as response to treatment. In addition, it allows a more accurate diagnosis and more effective disease prevention and treatment strategies specifically personalized to the individual.

In theory, the concept of precision medicine in clinical practice has been applied since initial efforts to classify disease and administer a specific treatment on the basis of this diagnosis. Longstanding classic examples include the diagnosis and treatment of phenylketonuria in newborns, the use of blood typing to guide blood transfusions, or selection of a specific antibiotic based on known drug sensitivities of the causative bacteria. More recent examples include the testing for specific mutations in the *BRCA1* and *BRCA2* genes in breast cancer patients, or the treatment of cystic fibrosis tailored to target the specific cause underlying the condition in a specific individual. A dramatic recent change in the concept is, however, the vision of applying precision medicine broadly across a vast number of disorders, which now became feasible due to the implementations of large-scale biologic databases (such as databases of human genetic variation), a variety of high-throughput methods for characterizing patient biomarkers of disease (i.e., proteomics, metabolomics, genomics, transcriptomics), coupled with significant advances in the computational tools needed for analyzing the massive amounts of data generated by these technologies. Acknowledging the high impact of improved knowledge on the complex mechanisms underlying a patient's health,

disease or condition for predicting which treatments will be most effective, precision medicine became the focus of major governmental initiatives to transform medical practice.

Epidemiology of Alzheimer's disease (AD)

AD is the most common form of dementia in ageing societies. As populations age, it is expected that this number will quadruple by the year 2050 placing a considerable burden on public health systems (1,2). As the currently available drugs only slightly affect disease severity and progression, AD remains at present effectively untreatable. Interventions preventing, halting, or decelerating the progression would reduce the individual suffering of affects and would significantly relieve public health burden. It has been estimated that delaying the onset of AD by 5 years would reduce the prevalence by ~50% (1).

Clinical and pathological heterogeneity of Alzheimer's disease (AD)

The limited development of drugs is mainly caused by an incomplete characterization of the basic pathologic mechanisms underlying the disease due to significant clinical, pathological and biological complexity. Going from a latency phase (where pathophysiologic processes are active but no signs or symptoms are present), through a prodromal phase (when some limited expression of AD is clinically apparent ("mild cognitive impairment") to full clinical expression, AD is clinically characterized by progressive deterioration in cognition, function and behavior terminating inevitably in complete incapacity and death. Key pathological manifestations in brain include intracellular deposits of hyper-phosphorylated tau protein in the form of neurofibrillary tangles and extracellular β-amyloid (Aβ) protein in diffuse and neuritic plaques, generated through sequential cleavage of the amyloid precursor protein (APP) through β- (BACE1) and ϒ-secretase. In addition, neuronal loss, synapse loss and activated microglia are frequent and broadly distributed (3). Adding to this complexity is frequent clinical and pathological overlap with other pathologies in particular Lewy Body disease (LBD) and cerebrovascular disease (4-6).

Genetic complexity

The clinical and pathological complexity is reflected by the extensive genetic variation underlying AD. Over the past 6 years, large-scale genome-wide association studies (GWAS) and a first round of whole exome sequencing (WES) and whole genome sequencing (WGS) studies have led to significant progress in identifying the underling genetic variants, with mapping of 27 susceptibility loci (*Table 1*) (7-20). These loci pinpoint specific biological pathways, in particular APP metabolism, endocytosis/intracellular trafficking, inflammation and immune response and lipid metabolism. In line with the notion of a genetically complex disease, individually each of these variants has a small effect on disease risk (OR 1.1–1.3). Heritabilities of 58% to 79% for AD indicate that, despite this progress provided by genomic studies, a substantial fraction of the disease remains attributable to unknown genetic factors (21). It is expected that this missing genetic component is in particular composed of rare variants with moderate to large effect sizes that are not readily identifiable by SNP-based methods (22,23). To address this issue, ongoing work is increasingly focusing on targeted resequencing of known risk loci and WGS and WES to reveal additional rare causative variants. Deep genomic endophenotyping determining genes and gene networks contributing to AD is expected to reveal the underlying pathogenic mechanisms and proteins and pathways for drug development.

Application of precision medicine to Alzheimer's disease (AD)

Although the hypotheses concerning disease mechanisms underlying AD have yielded drugs that have been tested in large clinical trials, the results of the trials completed to date have been disappointing and the current treatment strategies for AD have only minimal effect. While these failures have driven researchers to initiate clinical trials earlier in the course of the disease out of expectation that earlier intervention might be more effective, another major reason for the failure to identify an effective treatment is likely the consideration of AD as a homogeneous disease. The risk and molecular profiles of persons with AD show vast variation, and grouping patients with different risk or molecular profiles into a single entity can be expected to hide small subgroups potentially responsive to a certain treatment regime.

The aim of precision medicine, which is applicable to any disease including AD, is specifically targeting the issue of underlying molecular and clinical heterogeneity by identifying a person's specific pattern of risk factors,

Table 1 Major molecular pathways involved in LOAD etiology that were identified by genomic studies

Gene	Molecular pathway
APOE, SORL1, CLU, CR1, PICALM, BIN1, ABCA7, CASS4, PLD3	Amyloid pathway
CLU, CR1, EPHA1, ABCA7, MS4A4A/MS4A6E, CD33, CD2AP, HLA-DRB5/DRB1, INPP5D, MEF2C, TREM2/TREML2	Immune system/inflammation
APOE, CLU, ABCA7, SORL1	Lipid transport and metabolism
CLU, PICALM, BIN1, EPHA1, MS4A4A/MS4A6E , CD33, CD2AP, PTK2B, SORL1, SLC24A4/RIN3, MEF2C	Synaptic cell functioning/endocytosis
BIN1, CASS4, FERMT2	Tau pathology
PTK2B	Cell migration
MEF2C, PTK2B	Hippocampal synaptic function
CELF1, NME8, CASS4	Cytoskeletal function and axonal transport
INPPD5	Microglial and myeloid cell function
FBXL7	Phosphorylation-dependent ubiquitination

by identifying the specific underlying pathophysiologic processes, and finally by aiming to administer a preventive or therapeutic intervention that is specifically personalized to the identified molecular pattern of risk and disease processes.

Determination of risk profile

As described above, for risk assessment of AD, particularly much effort is currently put into disentangling the genetic risk. However as AD has in addition a considerable non-genetic component, it will also be essential to identify underlying environmental factors and gain insight into the existing gene-environment interactions. Established examples of known environmental factors increasing risk for AD are cerebrovascular disease, traumatic brain injury (TBI) or intellectual activity. Cerebrovascular changes such as hemorrhagic infarcts, small and large ischemic cortical infarcts, vasculopathies, and white matter changes, increase the risk of dementia. A meta-analysis incorporating data from 22 hospital-based and eight population-based cohorts found that 7.4% of patients with first-ever stroke developed poststroke dementia (24). Possible mechanisms through which stroke could lead to cognitive impairment and AD include direct damage of brain regions that are important in memory function (such as the thalamus), an increase in Aβ deposition, an induction of inflammatory responses impairing cognitive function, and overexpression of cyclin-dependent kinase 5 (CDK5; a serine–threonine kinase critical to synapse formation and synaptic plasticity) caused by hypoperfusion.

Retrospective studies (25-27) suggested that individuals with a history of TBI had a higher risk of dementia than individuals with no history of such injury. Two meta-analyses (28,29) demonstrated that among patients with TBI, the risk of dementia was higher in men than in women. While prospective studies of the relationship between TBI and AD have proved inconsistent (30-32), postmortem and experimental studies support a link between these conditions (33). Evidence also exists that after human brain injury, the extent of Aβ pathology and tau pathology increases in brain tissue, cerebrospinal fluid (CSF) Aβ levels are elevated and APP is overproduced (34).

Following initial reports that elderly people with higher levels of education had a lower incidence of dementia than individuals with no education, cognitive activity was suggested to decrease the risk of cognitive decline by increasing cognitive reserve. Several prospective studies subsequently found that both young and old (35,36) people who engage in cognitively stimulating activities, such as learning, reading or playing games, were less likely to develop dementia than individuals who did not engage in these activities. RCTs have shown a beneficial effect of intellectual interventions on cognitive function in elderly, dementia-free individuals although the benefits of cognitive training seem to be domain specific (37). It is important to recognize that "risk" is an estimate of the likelihood to develop a disease in the future, not a measurement of ongoing pathophysiologic processes. In line with this notion, a person with a genetic variant increasing risk such as the APOEe4 allele or the TREM2 R47H variant is regarded at being at increased risk compared to a person

without this variant, but may not develop the disease until decades later or may not develop it at all.

Determination of underlying molecular mechanisms

The importance of detection of latent underlying pathophysiologic processes lies in the both in the expectation that earlier detection enables more effective prevention and intervention, and the potential to use biomarkers of these processes to group patients in clinical trials or for treatment. A common example of the assessment of underlying pathological processes in everyday clinical practice is the measurement of plasma lipid profile, fasting glucose concentration, blood pressure and electrocardiography to determine presence and severity of cardiovascular disease. Treatment decisions largely depend on the outcomes of such tests.

Approaches for detection of latent pathophysiologic processes in AD have made significant advances over the past years and include in particular a variety of brain imaging technologies including structural brain imaging and brain amyloid and tau imaging, and the quantification of biomarkers in blood and CSF. In particular the neuroimaging technologies are highly promising as they rapidly gain ability to assess brain function at increasing levels of organization. On structural MRI, AD is characterized by atrophy in the medial temporal lobe in particular in the hippocampus, parahippocampus and the amygdala; in addition, white matter changes may be present. Compared to non-demented individuals several brain areas of persons with AD (38-40) and MCI (40-42) show a decrease in white matter integrity in diffusion tensor imaging (DTI) suggesting that these changes occur early in the disease process, in line with enhanced white matter degradation in preclinical and presymptomatic carriers of familial AD mutations compared to non-carriers (43). On arterial spin labeling (ASL)-MRI, cerebral blood flow is reduced in AD (44-46), on ^{18}F-fluorodeoxyglucose (FDG)-PET cerebral glucose metabolism is decreased (47,48). Amyloid specific imaging tracers, which include the Pittsburgh compound B (PIB), Florbetaben (^{18}F-BAY94-9172), Florbetapir (^{18}F AV-45) and ^{18}F-flutemetamol) binding selectively to cortical and striatal Aβ plaques, show a strong positive correlation with AD diagnosis (46,48,49) and fibrillary amyloid plaques at autopsy (49-51) although there is also substantial tracer retention in non-demented individuals (51) and it remains to be clarified whether this retention represents preclinical AD. The recent development of selective in-vivo tau PET imaging ligands such as [^{18}F]THK523, [^{18}F]THK5117, [^{18}F]THK5105 and [^{18}F]THK5351, [^{18}F]AV1451(T807) and [^{11}C]PBB3 has provided valuable information on the role of tau in the early phases of neurodegenerative diseases and disease progression, and is expected to help select appropriate patients and provide proof of mechanism and efficacy in clinical trials. Established CSF biomarkers of LOAD are decreased Aβ1-42 and increased t-tau and p-tau levels (52). Quantification of molecules in other biofluids such as serum, plasma, or even urine has been investigated repeatedly but has not yielded reproducible biomarkers.

Interventions personalized to an individual's molecular risk and disease pathology profile

As described above, at present, there are no effective preventive or therapeutic measures for AD. The therapies currently applied largely focus on cholinesterase inhibitors including donepezil (Aricept), galantamine (Razadyne) and rivastigmine (Exelon) and suppression of ionotropic glutamatergic signaling by memantine (Namenda), which are all only given after onset of symptoms. Common side effects of these drugs include diarrhea, nausea and sleep disturbances.

As described above, most of the clinical trials performed to date have neglected the underlying clinical and molecular heterogeneity of the disease. In an attempt to address this methodological shortcoming, a first round of ongoing trials including the Dominantly Inherited Alzheimer Network (DIAN) (53), the Alzheimer's Prevention Initiative (54) and A4 trial (55) are now incorporating information of underlying pathological mechanisms, selecting patients considered most likely to respond to the anticipated action of the therapeutic tested. It is hoped that these trials prove to be more successful.

Future directions

The ultimate aim of precision medicine is to enable clinicians to accurately and efficiently identify the most effective preventive or therapeutic intervention for a specific patient. For this, clinicians apply tools (i.e., clinical tests and information-technology) that are implemented in the routine clinical practice, are economically feasible, and help to disentangle the biological complexity underlying human disease.

Used for decades in the management of some rare

diseases and now broadly applied in cancer care, the precision medicine approach is now beginning to be adapted to dementia.

Capitalizing in particular on the advances in genomic and imaging technologies, over the past 5 years in particular progress in identifying underlying genetic risk variants pinpointing specific molecular pathways, and developing tools to detect pathophysiologic processes has been made. In addition, to advance the development of therapeutic targets, precision medicine is now beginning to be incorporated into clinical trials: the Alzheimer's Prevention Initiative (54), the Dominantly Inherited Alzheimer Network Trial (56), and the Anti-Amyloid Treatment in Asymptomatic Alzheimer Disease (57) trial all are focusing on subgroups of individuals with known genetic risk for AD and biofluid biomarkers or neuroimaging to detect onset of disease. Although successful application of precision medicine to AD will demand extensive additional work to identify risk groups, the underlying pathological processes and develop new interventions, and will continue to require significant involvement of biologists, physicians, technology developers, data scientists, patient groups and others, it is anticipated that this is only the beginning of a broad precision medicine approach targeting the clinical and biological complexity of AD and building the evidence base needed to guide clinical practice.

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Footnote

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