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Early detection and personalized medicine: Future strategies against Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is the leading cause of dementia and sixth cause of death in elderly adults. AD poses a huge economic burden on society and constitutes an unprecedented challenge for caregivers and families affected. Aging of the population is projected to drastically aggravate the situation in the near future.

To date, no therapy is available to prevent or ameliorate the disease. Moreover, several clinical trials for promising therapeutic agents have failed. Lack of supporting biomarker data for pre-symptomatic enrollment and inaccurate stratification of patients based on genetic heterogeneity appear to be contributing factors to this lack of success.

Recently, the treatment of cancer has seen enormous advances based on the personalized genetics and biomarkers of the individual patient, forming the foundation of precision medicine for cancer. Likewise, technological progress in AD biomarker research promises the availability of reliable assays for pathology staging on a routine basis relatively soon. Moreover, tremendous achievements in AD genetics and high-throughput genotyping technology allow identification of predisposing risk alleles accurately and on a large scale. Finally, availability of electronic health records (EHR) promises the opportunity to integrate biomarker, genomic and clinical data efficiently. Together, these advances will form the basis of precision medicine for AD.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by accumulation of toxic protein aggregates in the brain parenchyma, neuronal death and memory loss. To date, 5 million Americans live with AD costing 305 billion dollars to society in 2020 alone. Fourteen million patients and 1 trillion dollars in costs are projected to burden US society by 2050.[1]

Unfortunately, no therapy is available to delay AD onset, slow down, or halt AD progression. Moreover, several recent promising clinical trials have unfortunately failed. Indeed, several pharmaceutical companies have considered canceling or drastically reducing drug discovery efforts aimed at targeting AD.[2] The general speculation in the field is that clinical trials have not been successful due to enrollment of symptomatic individuals

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already presenting severe and irreversible neurodegeneration. In fact, neural tissue in the CNS is unable to regenerate once significantly damaged, thus making pre-symptomatic treatment necessary for potential positive outcomes.[3] An example of this is heart failure, for which coronary artery disease (CAD) and myocardial ischemia are the main risk factors.[4] Therapeutic approaches aimed at lowering cholesterol, such as statin drugs, show beneficial effects in preventing coronary arteriosclerosis and myocardial infarction. However, they show little efficacy in patients with established heart failure due to myocardial damage.[5] Another main limitation of recent AD clinical trials is the complex genetic heterogeneity of the disease.[6] Just like cancer, most prevalent forms of AD seem to be the combination of common clinical manifestations of different pathogenic mechanisms dictated by individual genetic predisposition and the environment.

Tremendous progress has been accomplished toward the understanding of AD pathogenesis in the last few decades. Moreover, technological advancement in the field of imaging and fluid biomarkers enables us to detect AD earlier and more effectively.[7] The rise of genome wide association studies (GWAS) and whole genome sequencing (WGS) puts clinicians in an optimal position to personalize treatment based on individual genetic background and biomarker positivity. Finally, availability of detailed electronic health records (EHR) presents an unprecedented opportunity to link clinical, genetic and biomarker data for each patient shaping the future therapeutic approach toward pre-symptomatic personalized medicine, ideally for AD prevention. In this manuscript, we discuss this strategy for AD.

2. AD: General background

AD is the most common form of dementia and the sixth cause of death in elderly individuals above 65 years of age. Symptoms range from mild memory impairment to severe cognitive deficits up to loss of basic bodily function and death.[1] AD progresses from an asymptomatic preclinical stage to a mild cognitive impairment stage (MCI) and finally to severe dementia.[8–10]

Generally, AD is classified in two forms: early onset familial AD (EOAD) and late onset sporadic AD (LOAD). EOAD is caused by autosomal dominant mutations in genes involved in amyloid beta (Aβ) production. LOAD results from the interaction between lifestyle factors with over 20 predisposing risk alleles.[6] Age is the strongest risk factor for LOAD, followed by apolipoprotein E (APOE) allele status.[1] Environmental and clinical risk factors such as education level, history of brain trauma, type 2 diabetes, midlife hypercholesterolemia, hypertension, and smoking are also associated with increased incidence of AD.[1]

AD brain pathology is characterized by two fundamental hallmarks: accumulation of Aβ plaques and tau neurofibrillary tangles.[11] These toxic protein aggregates promote activation of glial cells, release of inflammatory cytokines, synaptic damage, and neuronal death.[11]

Aβ is produced by sequential cleavage of amyloid precursor protein (APP) along two distinct pathways. Amyloidogenic processing of APP by β- and γ-secretases promotes Aβ accumulation in the brain parenchyma while non-amyloidogenic cleavage of APP by

α- and γ-secretases abrogates Aβ production. The combination of genetic predisposition, aging, and lifestyle factors lead to increased production or reduced clearance of Aβ, which promotes widespread accumulation of amyloid plaques in the AD brain.[12,13] Neuronal processes around Aβ plaques become enlarged and dystrophic possibly due to calcium signaling dysregulation,[14] lysosomal dysfunction[15] and cytoskeletal destabilization.[16] β-Secretase levels increase in the dystrophic neurites to produce Aβ and further drive growth and formation of amyloid plaques.[16] Moreover, cytoskeletal damage may promote tau hyperphosphorylation and aggregation.[17] Several kinases such as cyclin-dependent kinase 5 (CDK5), glycogen synthase kinase β (GSK-3β) and p38 mitogen-activated protein kinases (p38) are involved in tau phosphorylation.[18] Protein phosphatase 2A (PP2A) is the primary phosphatase regulating tau phosphorylation status.[19] Whether tau hyperphosphorylation develops downstream of amyloid pathology or in parallel is still under debate. However, no tau mutation is directly associated with AD and tau brain accumulation follows amyloid pathology from a temporal standpoint. The unhealthy environment of dystrophic neurites significantly damages synaptic terminals[16] impairing neural activity. Glia cells, in particular microglia, activate around dystrophic neurites and attempt to clear Aβ plaques. However, chronic amyloid accumulation overpowers microglial phagocytic capacity leading to inflammatory chemokine release and further neuronal damage.[20] Neuronal death is the result of this vicious cycle, causing irreversible damage to neural circuits involved in memory formation.

3. Genetic heterogeneity of AD

AD is a multifactorial disorder characterized by numerous genetic risk factors. EOAD is associated with autosomal dominant mutations in three genes involved in Aβ production: amyloid precursor protein (APP), presenilin 1 (PSEN1) and presenilin 2 (PSEN2). Aβ is a 38–43 amino acid peptide produced by sequential cleavage by β- and γ-secretase. β-Secretase, also known as BACE1,[21] makes the first cut to produce the membrane-bound β-C terminal fragment (CTF) of APP. Following BACE1 cleavage, γ-secretase cleavage of the β-CTF generates Aβ C-termini of variable lengths.[12,13] Autosomal dominant mutations in APP, PSEN1 and PSEN2 (the latter two being catalytic subunits of the γ-secretase complex) increase pathogenic cleavage of APP by γ-secretase into the longer, more aggregation-prone Aβ-42 isoform, causing early brain deposition of Aβ.[22–26]

LOAD is associated with several genetic risk alleles involved in four main pathways: Aβ metabolism, cholesterol metabolism, endocytosis, and immune response. Apolipoprotein E (APOE) is the most important AD genetic risk factor for LOAD.[27] ApoE is a lipoprotein expressed by astrocytes involved in cholesterol transport, Aβ clearance and tau phosphorylation.[28] APOE has three common isoforms e2, e3 and e4 that differ at two amino acid positions: APOE-ε2 (cys112, cys158), APOE-ε3 (cys112, arg158), and APOE-ε4 (arg112, arg158).[29] Carriers of the e4 variant show 3 times increased odds ratio for LOAD while carriers of the e2 variant are protected against AD. APOE associated risk is allele-dose dependent. In fact, e4 homozygotes display 15 times increased odds ratio for LOAD.[30] The APOE isoforms interact with Aβ differentially in ways that help explain their roles in AD pathogenesis. Indeed, the e4 allele is less efficient in clearing Aβ and promotes its brain deposition.[31] Clusterin (CLU) is a chaperone protein produced

by astrocytes involved in lipid transport, apoptosis and immune response.[32] Common CLU variant rs1113600 was associated with reduced AD risk.[33] The exact mechanism by which CLU affects AD susceptibility is unknown. However, CLU binding to Aβ peptide affecting its clearance and deposition seems to be the most likely candidate.[32] ATP-binding cassette transporter A7 (ABCA7) is a membrane transporter expressed in microglia. ABCA7 is the only genetic risk factor associated with AD susceptibility in African-Americans besides APOE e4.[34] Loss-of-function mutations in ABCA7 are associated with increased AD risk due to impaired Aβ clearance by microglia.[35] Sortilin-related receptor 1 (SORL1) is an endocytic receptor involved in trafficking APP to the endosomal compartment.[36] The common variant rs11218343 is associated with increased risk for AD.[37] Bridging integrator 1 (BIN1) is an adaptor protein involved in clathrin-mediated endocytic trafficking of synaptic vesicles. Several SNPs of BIN1 have been associated with increased AD risk, most likely by impairing β-secretase degradation and tau clearance.[38] CD2-associated protein (CD2AP) is a scaffolding protein involved in regulating APP sorting from early endosomes to the lysosomal compartment for degradation.[39] Several CD2AP common variants were associated with AD susceptibility.[40] Phosphatidylinositol-binding clathrin assembly gene (PICALM) encodes for an endocytic protein regulating autophagy of APP C-terminal fragments and endocytosis of γ-secretase. Two SNPs within this gene were associated with reduced AD risk.[33] The CD33 gene encodes for a myeloid- and microglial-specific sialic acid-modified receptor. CD33 signaling regulates microglia activation and inhibits Aβ clearance.[41] Several variants were associated with AD susceptibility within this locus. In particular, the rs386544 variant was associated with increased risk for AD while the rs12459419 variant showed a protective effect.[40] Complement receptor 1 (CR1) is a transmembrane protein expressed in microglia and blood cells. CR1 inhibits the complement cascade and regulates phagocytosis of cellular debris and Aβ. SNPs within CR1 increase AD susceptibility and promote progression of brain pathology.[42] Triggering receptor expressed on myeloid cells 2 (TREM2) is a microglia-specific receptor that mediates innate immune activation and Aβ phagocytosis.[43] First identified in Nasu-Hakola patients exhibiting a frontotemporal dementia-like syndrome, TREM2 has become a crucial genetic risk factor for AD. In particular, the rs75932628 variant, causing an Arg→His substitution in position 47 (R47H), predisposes one to AD by impairing microglial phagocytosis of Aβ.[44] Further risk alleles associated to LOAD have been identified by recent GWAS studies. Some examples are Inositol polyphosphate-5-phosphatase (INPP5D), Human leukocyte antigen (HLA), Ephrin type-A receptor 1 (EPHA1), Protein Tyrosine Kinase 2 Beta (PTK2B), Membrane-spanning 4A (MS4A), Phospholipase C Gamma 2 (PLCG2), Cas scaffolding protein family member 4 (CASS4), Zinc Finger CW-Type And PWWP Domain Containing 1 (ZCWPW1)/Neuronal Tyrosine Phosphorylated Phosphoinositide-3-Kinase Adaptor 1 (NYAP) and Solute Carrier Family 24 Member 4 (SLC24A4)/Ras and Rab interactor 3 (RIN3).[45] However, further studies are needed to better elucidate the mechanisms by which these risk alleles result in LOAD pathophysiology.

Recently, the effects of inheriting multiple predisposing LOAD risk alleles on disease susceptibility and age of onset have been studied. Polygenic risk scores (PRS) were developed to aggregate the effect of each SNP into a unique score. In particular, the effect of several predisposing SNPs was either combined assuming equal effect for each

SNP or the weighted sum for each SNP was calculated for better predictive power.[46] Several studies confirmed the effectiveness of PRS in predicting AD odds ratio and age of onset. Escott-Prince et al. reported how PRS could predict AD with high specificity and sensitivity.[47] Mormino et al. reported that high PRS score was positively associated with increased risk for developing dementia, memory impairment and increased Aβ positron emission tomography (PET) in non-demented elderly individuals.[48] Ge et al. reported that PRS scores were significantly higher in Aβ positive AD/MCI patients compared to healthy amyloid positive controls.[49] Tan et al. reported decreased age of onset in AD and MCI patients with high PRS scores compared to patients with low PRS scores.[50] Unfortunately, PRS show two main limitations for accurately predicting AD susceptibility. PRS scores do not correlate significantly with cerebrospinal fluid (CSF) biomarker data in multiple studies[51,52] and, most importantly, PRS scores were developed from data sets including primarily non-Hispanic, Caucasians of European ancestry. Data for African-Americans and Hispanics are extremely limited, which increases the potential for misclassification of the disease in non-white ethnic groups.

4. AD biomarkers

In the last few decades technological advancement in the field of brain imaging and fluid biomarker assays have dramatically revolutionized the AD clinical field. PET imaging together with CSF and blood biomarkers have become available for early detection of AD neuropathological change (ADNC). However, blood tests and new PET approaches are still in development, and several limitations still exist in terms of costs, invasiveness and assay reproducibility for AD biomarkers. At the same time, the rapid development of the biomarker field promises early and accurate AD detection on a routine basis in a relatively short time.

Four main types of biomarker have been developed for AD: PET imaging, magnetic resonance imaging (MRI), CSF and blood assays. Moreover, five different hallmarks of the pathology can be characterized with biomarkers: Aβ pathology, tau pathology, neurodegeneration, synaptic dysfunction and glial activation. Furthermore, cognitive tests are available for early detection of memory impairment, including the General Practitioner Assessment of Cognition (GPCOG), the Memory Impairment Screen (MIS), the Mini-Cog test, the Mini-Mental State Exam (MMSE) for detecting dementia, the Clinical Dementia Rating Scale–Sum of Boxes (CDR–SB) and the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog).[1,53,54] Moreover, composite cognitive tests have been developed for detecting pre-clinical cognitive decline.[55] Cognitive tests are excellent tools for early AD diagnosis and monitoring therapy outcomes. However, until cognitive tests become more sensitive, they cannot identify AD patients in a pre-symptomatic stage, which makes them less useful from an early-personalized medicine standpoint.

Aβ PET imaging is to date the most widely used and validated AD biomarker. Three Aβ tracers are currently in use: [^{18}F]florbetapir, [^{18}F] flutemetamol and [^{18}F] florbetaben.[56] Measuring Aβ-42/Aβ-40 ratio in the CSF is another widely established biomarker for amyloid pathology. In fact, the insoluble Aβ-42 isoform significantly decreases in the CSF of AD patients and provides 100% concordance with Aβ PET when expressed as ratio to

Aβ-40.[57] Moreover, decreased Aβ-42/Aβ-40 ratio precedes positive signal in Aβ PET.[58] Aβ-42/Aβ-40 levels can also be tested in the plasma with moderate accuracy against Aβ PET and CSF measurements. However, AD patients display a modest 14% reduction of Aβ-42/Aβ-40 ratio in the plasma compared to 50% in the CSF[59] raising concerns over both specificity and sensitivity. Future optimization of plasma based Aβ biomarkers could circumvent the issues of costs, PET scanner availability and the invasive nature of CSF assays.

Tau PET imaging has been utilized in several clinical trials and shows results concordant with the Braak model for staging location and timeline of brain pathology.[60] Several tracers have been developed for tau PET. The most widely used is the [^{18}F]AV-1451, despite the presence of off-target binding effects.[61] However, a more specific second generation version of AV-1451 has been developed.[62] Both total tau and phospho-tau can be measured in the CSF with close correlation to amyloid brain pathology.[63,64] More recently, plasma tau phosphorylated at positions 181 (P-tau181) and 217 (P-tau217) have gained attention as novel tau biomarkers.[65,66] P-tau181 and P-tau217 strongly correlate with Aβ PET, CSF Aβ-42/Aβ-40 and CSF phospho-tau181 and -tau217. Most importantly, both phospho-tau isoforms accurately predict Aβ PET positivity, harnessing tremendous promise as both a blood diagnostic tool and disease staging biomarker.[67]

Volumetric MRI, CSF and plasma neurofilament light (NFL) are currently utilized as biomarkers for neurodegeneration. Volumetric MRI allows accurate assessment whole brain atrophy, regional atrophy of hippocampus, gray matter atrophy and cortical thickness.[68] NFL levels in both CSF and plasma correlate quite accurately with neurodegeneration in both EOAD and LOAD patients as measured by MRI,[69,70] but elevation of plasma NFL is not specific for AD as it also occurs in other neurodegenerative disorders.

Synaptic dysfunction is currently assayed by fluorodeoxyglucose (FDG) PET, synaptic vesicle protein 2A (SV2A) PET, and CSF dendritic protein neurogranin (NG). Several studies reported [^{18}F]FDG PET hypometabolism in AD vulnerable brain areas. FDG PET strongly correlates with cognitive decline in AD patients.[71] A recent study reported a 40% reduction in SV2A PET in AD hippocampus.[72] However, further validation is needed. Finally, NG is significantly increased in the CSF of AD patients and correlates more accurately than other fluid biomarkers with cognitive decline.[73]

Glial activation can be measured with two main biomarkers: translocator protein (TSPO) PET and soluble Triggering Receptor Expressed on Myeloid Cells 2 (s-TREM2) CSF levels. TSPO is a surface protein expressed on pathogenic activated microglia. TSPO PET retention is significantly increased in AD brains and strongly correlates with cognitive decline.[74] However, a SNP in the TSPO gene needs to be considered when assessing TSPO PET data, since the SNP affects TSPO ligand binding.[75] Indeed, TSPO genotyping is necessary to classify TSPO binding capacity of study participants. Another marker for glial activation is CSF s-TREM2. AD patients display increased s-TREM2 CSF levels with good correlation to CSF Aβ-42 and total-tau. However, s-TREM2 levels usually peak in the MCI stage while slightly decreasing in more advanced stages of the pathology,[76] making cut-point determination difficult.

In conclusion, several biomarkers are available to assess different hallmarks of AD pathology and characterize disease staging. However, each different technology presents limitations due to costs, availability, invasive nature of the assay, or short plasma half-life. Indeed, they seem the less likely candidate for routine screening of patients. All CSF assays, despite being very accurate, are extremely invasive and present enormous patient compliance constraints. Finally, although plasma biomarkers are the least invasive, several of the plasma assays are not as accurate as their CSF counterparts. However, plasma P-Tau181 and P-Tau217 assays show tremendous promise given their very high levels of accuracy, concordance with other biomarkers and great potential for routine application. In the near future, plasma phospho-Tau could become the routine screening tool for asymptomatic patients. Patients displaying positive signals for P-Tau or carrying specific predisposing risk alleles could undergo further testing with CSF biomarkers such as Aβ-42/Aβ-40, NFL, NG and s-TREM. Imaging techniques such as Aβ PET, tau PET, volumetric MRI, FDG PET and TSPO PET could be used in more specialized circumstances, such as in symptomatic patients, for accurate disease staging. Familial EOAD patients could be directly diagnosed with the three technologies for early detection of neurodegeneration and cognitive decline.

5. Current drug pipeline for AD

Five drugs are currently FDA approved to treat AD. Three cholinesterase inhibitors (galantamine, rivastigmine and donepezil), one NMDA receptor blocker (memantine) and memantine-donepezil in combination.[1] Unfortunately, these current treatments can only provide short-term mitigation of symptoms but do not show disease-modifying effects.

As reviewed by Cummings et al., 121 drugs are in clinical trials for AD in 2020. In particular, 19 have disease-modifying potential, 12 are cognitive enhancing agents and 12 aim to target neuropsychiatric symptoms. Moreover, 36 phase III clinical trials are assessing efficacy for 29 potential therapeutics targeting brain amyloidosis, tau pathology, neuroinflammation, synaptic integrity, neurotransmitter receptors, metabolic processes and vascular health.[2]

For the first time since 2003, a new therapeutic reached approval for AD by the National Medical Products Administration (NMPA) in China, sodium oligomannate (GV-971).[77] This agent ameliorates dysbiosis of the gut microbiome and reduces neuroinflammation. An international multicenter phase III trial is underway in the Unnited States, Europe and China.

In the United States, the most promising therapy is aducanumab, the monoclonal antibody against Aβ fibrils developed by Biogen. Despite initial reports of a failed futility analysis, including additional trial participants in the analysis showed reduced cognitive decline, amyloidosis and tau brain accumulation at higher doses, thus meeting the primary endpoint in one of two trials and leading to application for FDA approval by Biogen.[2] Two more monoclonal antibodies against fibrillary Aβ, BAN2401 and gantenerumab, are showing promising results in phase III trials.[78,79] However, passive immunotherapy against oligomeric and monomeric Aβ with crenezumab and solanezumab, respectively, has failed.[2] Other approaches aimed at Aβ production, such as β-secretase inhibitor and γ-secretase modulators, were halted due to toxicity, off-target effects and cognitive worsening.[80]

In other therapeutic approaches, one tau-targeting agent is enrolled in phase III trials: tau aggregation inhibitor methylene blue (LMTX). Other tau-targeting approaches such as passive immunotherapy and anti-sense nucleotides are in phase I and II trials.[2] Apart from GV-971, several neuroinflammation-targeting drugs reached phase II and III. Some examples are cromolyn-ibuprofen (ALZT-OP1), gingipain inhibitor COR388 and tyrosine kinase inhibitor masitinib.[2] Another class of therapeutics reaching phase II and III are synaptic integrity/neuroprotective agents. The most compelling candidates in the class are SV2A modulator AGB101 and troriluzole.[2] Several compounds targeting neurotransmitters receptors are involved in phase II and III trials. In particular, sigma-1 agonists, NMDA antagonists, α-adrenergic agonist and D2 agonists are under evaluation.[2] Finally, drugs targeting metabolic processes such as insulin sensitizer metformin and vascular enhancing agents such as angiotensin II receptor blocker (losartan) reached phase III.[2] Moreover, preclinical research is producing approaches that have great potential for the future. Some examples are APOE immunotherapy, TREM2 modulation and gut microbiome manipulation.[81–83]

6. Personalized medicine for AD

As defined by the FDA, precision medicine aims at tailoring disease treatment and prevention for each specific individual accounting for their genetic makeup and lifestyle. In particular, precision medicine seeks to move clinical practice away from the “one therapy fits all” approach taking into account how each patient, or subgroup of patients, might be susceptible to a specific disease or respond to a therapy based on their genetic background, lifestyle and environment. In the last few decades, aging-associated, chronic, multifactorial diseases such as cancer, heart disease and dementia have become the biggest challenge to human health. Preclinical and clinical research in the field of cardiovascular disorders and cancer has demonstrated how a single “magic bullet approach” is unlikely to work. A combination of several therapeutics targeting multiple pathogenic pathways are required to treat cardiovascular disorders. For cancer, patient stratification in subgroups based on predisposing risk alleles, such as BRCA1 and BRCA2, has become the most advanced strategy. The AD field is quickly catching up in characterizing pathogenic mechanisms and predisposing risk factors. Increasing evidence points toward substantial genetic heterogeneity for AD. Several predisposing risk alleles involved in different pathogenic pathways have been identified. In addition, several lifestyle habits correlate with AD susceptibility. Finally, compelling data from AD clinical trials have shown that the etiopathology and proper staging of disease is fundamental for understanding the best timeline for treatment. In fact, pre-symptomatic intervention seems to be necessary to ensure potential disease-altering effects.

Technological progress has been achieved in the genomic, transcriptomic and proteomic fields. GWAS studies and WGS projects provide the means to identify common and rare risk alleles with much greater sensitivity and accuracy. The biomarker field has also progressed rapidly, making new technology for disease stratification available and promising routine AD biomarkers assays in the near future. These accomplishments create an optimal environment to move the AD field toward precision medicine. In fact, the clinician of the near future could be capable of identifying specific predisposing risk alleles in young

asymptomatic adults. Moreover, the disease could be diagnosed pre-symptomatically thanks to cutting-edge biomarkers. Biomarker assays could become routinely available and easy to administer, as in the case of P-Tau181 and P-Tau217. Therapeutic approaches could be administered based on genetic background and biomarker profile. Amyloid-targeting therapies could be administered to AD patients before symptoms manifest. Tau therapeutics could be beneficial in combination with Aβ drugs, especially at symptomatic stages of the disease. Therapeutic approaches targeting inflammatory pathways could be directed at patients carrying mutations for TREM2, CR1 and CD33, but also at individuals exhibiting amyloid and tau pathologies that trigger neuroinflammation. Patients carrying mutations for lysosomal genes such as SORL1, BIN1, CD2AP and PICALM could be candidates for therapies targeting Aβ and tau aggregation, synaptic health and neurotransmitter release. Patients carrying risk alleles for APOE and ABCA7 could benefit from Aβ-targeting drugs, tau therapeutics, APOE immunotherapy, and drugs targeting metabolic processes and vascular health. Clinical trials could be designed upon genetic predisposition and disease stage for better stratification of patients. A broad range of biomarker assays could help determine efficacy of drugs tested in clinical trials more rapidly than is now possible.

7. Conclusion

Despite numerous failures in developing disease modifying therapies for AD, current technological progress in the fields of biomarker assays and genetics present an unprecedented opportunity to reshape AD therapeutic strategies toward precision medicine. Blood biomarker assays such as P-Tau will allow easy and accurate detection of the disease in the pre-symptomatic stage. Other biomarkers, such as PET, MRI and CSF assays, will determine disease staging and possibly help identify etiology. Genetic testing will enable the future clinician to better identify disease etiology based on SNPs, rare variants, and polygenic risk alleles.

Precision medicine strategy could be based on the following staged approach (Fig. 1):

- Step 1: Yearly physical examination with blood tests for Aβ accumulation and tau pathology (Aβ42, P-Tau, etc.) starting in middle age. The same individuals will undergo one time genetic testing for AD risk alleles at 50 years of age. All individuals are as yet asymptomatic.
- Step 2: For individuals showing positive results, further blood tests for neurodegeneration, inflammation, synaptic markers, etc., would be warranted to determine disease stage and pathophysiologic mechanisms. Cognitive testing would be performed at this stage to detect memory impairment. Individuals showing either positive blood biomarkers, cognitive impairment or both will be treated early with the most appropriate drug cocktail (step 4).
- Step 3: For symptomatic patients, in addition to the above blood tests, Aβ and Tau PET and MRI imaging may be performed, along with CSF tests if necessary, for precise disease staging to inform the appropriate treatment strategy.
- Step 4: The patient would be treated with the most appropriate drug cocktail specifically designed for their individual etiology and stage of AD.

Steps 1 and 2 would be fundamental for early detection and disease prevention in asymptomatic AD. Step 3 would be crucial to identify disease etiology and staging for individuals with cognitive impairment in symptomatic AD.

To conclude, early identification of patients in the pre-symptomatic stage (with routine biomarker assays) and accurate stratification of patients based on genetic predisposition could offer enormous potential for individualized prevention and treatment of AD. Close collaboration between regulatory agencies, research institutions and pharmaceutical companies across the globe will be fundamental for moving the AD research field toward the coming era of precision medicine.

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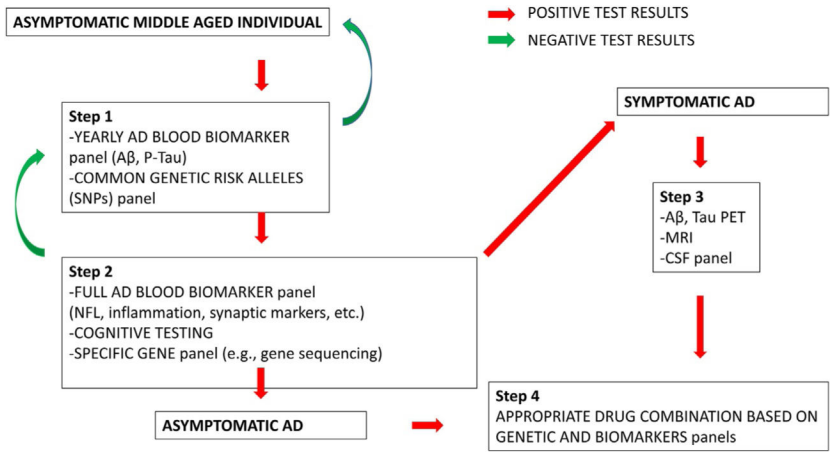

Fig. 1.

Hypothetical steps for personalized early detection and treatment strategy for a precision medicine approach for Alzheimer's disease.