

# Charting NIH Milestones to Implement the Recommendations from the Alzheimer’s Disease Research Summit

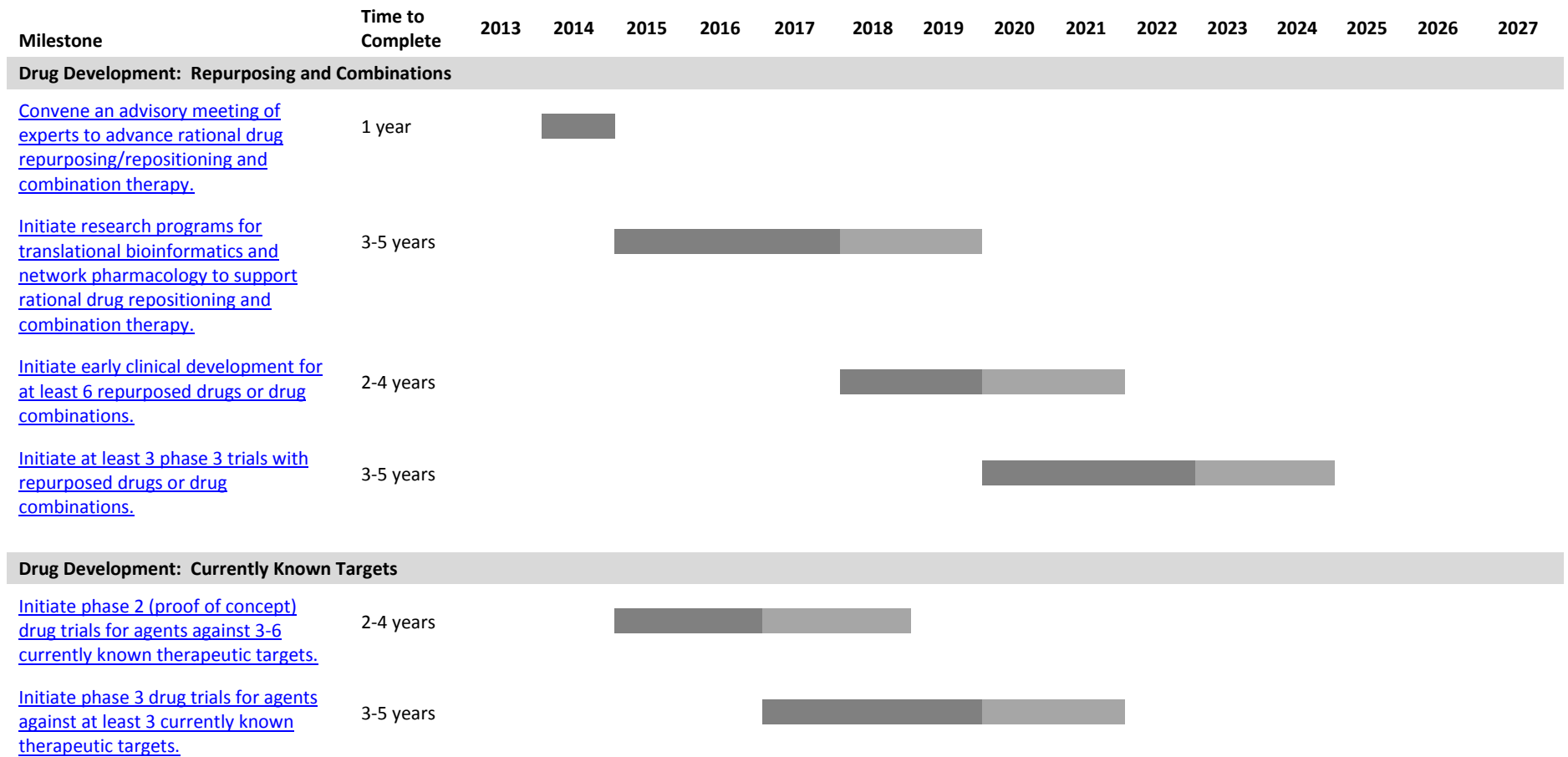
## Contents

Milestone Chart.....2

Full Milestone Statements .....8

Alzheimer’s Disease Research Summit Recommendations – May 2012.....18

## Milestone Chart



Milestone	Time to Complete	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027
<b>Drug Development: Novel Targets</b>																
<a href="#">Establish a searchable, open access database for the purpose of identifying regions of the genome that contain novel targets.</a>	4-5 years	█	█	█	█	█										
<a href="#">Establish a consortium of genetics and genomics experts to execute a large scale sequencing project to identify AD risk and protective gene variants in subjects with late onset AD.</a>	5-8 years	█	█	█	█	█	█	█	█							
<a href="#">Identify, characterize, and complete early validation for at least 6 novel therapeutic targets for AD.</a>	5-7 years		█	█	█	█	█	█	█	█						
<a href="#">Initiate a drug discovery effort to develop novel therapeutic agents against at least 6 novel therapeutic targets.</a>	5-7 years					█	█	█	█	█	█	█				
<a href="#">Initiate phase 2 (proof of concept) drug trials for agents against 3-6 novel therapeutic targets.</a>	2-4 years								█	█	█	█				
<a href="#">Initiate phase 3 drug trials for agents against at least 3 novel therapeutic targets.</a>	3-5 years										█	█	█	█	█	

Milestone	Time to Complete	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027
<b>Development of Non-Pharmacological Interventions</b>																
<a href="#">Convene an advisory meeting to delineate an interdisciplinary research agenda focused on advancing non-pharmacological interventions for the cognitive and behavioral symptoms of AD.</a>	1 year		█													
<a href="#">Convene an advisory meeting to inform the design of therapeutic approaches combining pharmacological and non-pharmacological treatments.</a>	1 year			█												
<a href="#">Initiate interdisciplinary research programs aimed at gaining an in depth mechanistic understanding of the impact of non-pharmacological interventions on AD.</a>	5 years				█	█	█	█	█	█						
<a href="#">Initiate Phase 2 and 3 clinical trials for at least 3 non-pharmacological interventions aimed at AD prevention.</a>	4-5 years					█	█	█	█	█	█					
<a href="#">Initiate Phase 2 and 3 clinical trials for at least 3 interventions combining pharmacological and non-pharmacological interventions for AD treatment or prevention.</a>	4-5 years							█	█	█	█	█	█			
<a href="#">Review results of past and existing grants for the purpose of developing new technologies that promote prevention and treatment trials.</a>	1 year		█													
<a href="#">Issue Funding Opportunity Announcements for research aimed at developing new technologies that improve clinical care, care giver support and in-home monitoring.</a>	3-5 years				█	█	█	█	█	█						

Milestone	Time to Complete	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027
<b>Biomarkers of Disease Progression</b>																
<a href="#">Initiate synthesis and testing of novel PET ligands and develop and test novel CSF/blood biomarkers for assessment of disease related pathological burdens.</a>	5 years		█	█	█	█	█	█	█							
<a href="#">Initiate development of imaging and/or fluid biomarkers to demonstrate target engagement for 5 novel therapeutic targets for AD.</a>	5 years		█	█	█	█	█	█	█							
<a href="#">Incorporate imaging and/or fluid biomarkers into Phase II (proof of concept) drug trials to provide proof of mechanism and/or evidence of target engagement for novel targets.</a>	3-5 years					█	█	█	█	█	█					
<a href="#">Incorporate imaging and/or fluid biomarkers into Phase III (pivotal) drug trials to select subjects and/or provide evidence of target engagement for novel targets.</a>	3-5 years							█	█	█	█	█	█			
<a href="#">Initiate studies to develop minimally invasive biomarkers for detection of cerebral amyloidosis and other AD pathophysiology.</a>	5 years			█	█	█	█	█	█	█						
<a href="#">Initiate studies to link peripheral blood-based biomarkers and central imaging and CSF biomarkers.</a>	5 years				█	█	█	█	█	█	█					
<a href="#">Launch research programs to develop and validate sensitive neuropsychological assessment measures to detect and track the earliest clinical changes of AD.</a>	5 years		█	█	█	█	█	█	█							
<a href="#">Develop and test methods for the standardization of immunoassays and mass-spectrometry and the collection and analysis of MRI and PET neuroimaging data.</a>	5 years		█	█	█	█	█	█	█							

Milestone	Time to Complete	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027
<b>Epidemiology</b>																
<a href="#">Establish an expert panel of epidemiologists and clinical scientists to make recommendations for best practices in the use of existing epidemiology of dementia databases.</a>	1 year		█													
<a href="#">Initiate expansion of epidemiology of dementia cohorts to include subjects in midlife and use data generated to inform clinical trial design.</a>	5-7 years		█	█	█	█	█	█	█							
<b>Research Resources</b>																
<a href="#">Develop a common Alzheimer's Disease research ontology for comparative analysis of US and international AD research portfolios and create a publicly available database (IADRP) that will house the AD portfolios.</a>	2-3 years		█	█	█											
<b>Partnerships to Accelerate AD Drug Development</b>																
<a href="#">Convene an advisory meeting focused on facilitating public private partnerships (PPP) aimed at accelerating the development and testing of effective therapies for AD treatment and prevention.</a>	1 year		█													
<a href="#">Convene meetings of PPP working groups for the purpose of formulating concrete steps aimed at accelerating the timeframe of AD drug development.</a>	1 year		█													

Milestone	Time to Complete	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027
<b>Infrastructure</b>																
<a href="#">Create a network of Translational Centers aimed at preclinical development and testing of AD therapeutics.</a>	3-5 years		█	█	█	█	█									
<a href="#">Establish an NIH working group to develop an expedited review track for translational AD research applications.</a>	1 year			█												
<a href="#">Create a National IRB.</a>	2 years		█	█	█											
<a href="#">Establish a working group to identify standard outcome measures necessary for data comparisons across a variety of clinical studies.</a>	1 year		█													
<a href="#">Initiate 3-4 clinical research studies using common standard outcome measures.</a>	3-5 years		█	█	█	█	█									
<b>Study Recruitment and Participation</b>																
<a href="#">Increase knowledge among research scientists of best practices for recruitment and retention of research participants.</a>	2 years		█	█												
<a href="#">Establish a working group including clinical trial recruitment experts to dynamically evaluate and update the materials and information provided in the central resource.</a>	1 year		█													
<a href="#">Increase awareness of large-scale registries that encompass the spectrum of the disease from healthy to at-risk asymptomatic to symptomatic individuals willing to participate in clinical research aimed at AD prevention and treatment.</a>	2 years		█	█												
<a href="#">Increase the rate of enrollment for AD clinical trials and increase the participation of underrepresented populations.</a>	5 years		█	█	█	█	█	█	█	█	█	█	█	█	█	█

## Full Milestone Statements

Drug Development: Repurposing and Combinations		
Milestone	Success Criteria	Time Required
<ul style="list-style-type: none"> <li>Convene an advisory meeting of experts from the pharmaceutical industry, government, academia, the FDA, and the non-profit sector to advance rational drug repositioning and combination therapy based on translational bioinformatics and network pharmacology approaches and to explore opportunities for new public-private partnerships to facilitate drug rescue/repurposing and combination therapy. [Summit 4.A, 4.B, 4.C, and 4.D]</li> </ul>	<p>Development of recommendations for rational repositioning and combination therapy development.</p> <p>Development, negotiation, and implementation of appropriate agreements among the stakeholders involved in repositioning and combination therapy of drugs for AD. These agreements should address legal issues, intellectual property rights, and liability to expedite rigorous clinical testing of repurposed drugs.</p>	<p>1 year 2014</p>
<ul style="list-style-type: none"> <li>Initiate research programs for translational bioinformatics and network pharmacology to support rational drug repositioning and combination therapy from discovery through clinical development. [Summit 4.A, 4.B, 4.C, and 4.D]</li> </ul>	<p>Identification of at least 6 existing drugs suitable for repurposing and/or combination therapy for AD prevention or treatment.</p> <p>The drugs selected for repurposing or combination therapy will be prioritized based on:</p> <ul style="list-style-type: none"> <li>– Evidence that they modulate disease relevant pathways/networks gained from computational and empirical approaches.</li> <li>– Preclinical proof-of-efficacy in a relevant model system.</li> <li>– Availability of biomarkers to monitor target engagement in humans.</li> <li>– Sufficient evidence of safety for the intended target population.</li> </ul>	<p>3-5 years 2015-2019</p>
<ul style="list-style-type: none"> <li>Initiate early clinical development for at least 6 existing drugs or drug combinations for the treatment or prevention of Alzheimer’s disease. [Summit 4.A, 4.B, 4.C, and 4.D]</li> </ul>	<p>Completion of at least 4 phase II trials with repurposed drugs and/or drug combinations. Successful trials will provide conclusive evidence of therapeutic mechanism/target engagement.</p>	<p>2-4 years 2018-2021</p>



<ul style="list-style-type: none"> <li>Initiate at least 3 phase III trials with repurposed drugs or drug combinations. Of these at least one trial will be in an asymptomatic at-risk population and at least one for individuals with advanced disease. Of the trials initiated in patients with advanced disease, at least one trial will target the neuropsychiatric symptoms of Alzheimer's disease. [Summit 4.A, 4.B, 4.C, and 4.D]</li> </ul>	<p>Comprehensive success/failure analyses of data from at least 3 phase III trials.</p>	<p>3-5 years 2020-2024</p>
<b>Drug Development: Currently Known Targets</b>		
Milestone	Success Criteria	Time Required
<ul style="list-style-type: none"> <li>Initiate phase II (proof of concept) drug trials for agents against 3-6 currently known therapeutic targets. Of these at least 2 will be for targets involved in asymptomatic stages of disease. These trials will be designed to provide or confirm proof of mechanism and/or evidence of target engagement for the therapeutic agent being tested. [Summit 3.A, 3.B, 3.F, and 5.E]</li> </ul>	<p>Completion of 3-6 phase II drug trials for agents against currently known targets, providing conclusive evidence of therapeutic mechanism/target engagement.</p>	<p>2-4 years 2015-2018</p>
<ul style="list-style-type: none"> <li>Initiate phase III drug trials for agents against at least 3 currently known therapeutic targets. Of these at least one trial will be asymptomatic, at risk populations. These trials will incorporate a combination of biomarkers (fluid and imaging) and cognitive measures as outcomes and include collection of DNA and other bio-samples for interrogation of responsiveness. [Summit 3.A, 3.B, 3.F, and 5.E]</li> </ul>	<p>Comprehensive success/failure analysis of data from at least 3 phase III trials.</p>	<p>3-5 years 2017-2021</p>

Drug Development: Novel Targets		
Milestone	Success Criteria	Time Required
<ul style="list-style-type: none"> <li>Establish a searchable, open access research database that contains all clinical, biomarker, and epidemiological data, and related genotypes and phenotypes from existing genetic studies; analyze these data to identify regions of the genome that are targets for AD therapeutics. [Summit 1.C]</li> </ul>	At least one novel target, pathway or therapeutic approach identified through use of the database.	4-5 years 2013-2017
<ul style="list-style-type: none"> <li>Establish a consortium of genetics and genomics experts to develop and execute a large scale sequencing project to analyze the genomes of a large number of well characterized individuals including multi-ethnic subjects using next generation sequencing approaches; identify a broad range of AD risk and protective gene variants in subjects with late onset AD (LOAD). [Summit 1.C]</li> </ul>	Identification of new risk and protective alleles for LOAD that lead to the identification of at least one novel therapeutic approach, drug target or pathway for prevention.	5-8 years 2013-2020
<ul style="list-style-type: none"> <li>Identify, characterize, and complete early validation for at least 6 <i>novel</i> therapeutic targets for AD (a minimum of 3 targets for presymptomatic and early stage disease and a minimum of 3 for advanced disease). [Summit 1.A, 1.B, 1.D, and 5.A]</li> </ul>	Validation based on availability of the following for each <i>novel</i> target: a systems-level understanding of the gene, protein and metabolic networks within which they operate, one or more cell based/animal models that are freely available to the research community, a quantitative assessment of the integrative response to the modulation of the target in one or more model organisms, and identification of pharmacodynamic biomarker(s) for target engagement.	5-7 years 2014-2020
<ul style="list-style-type: none"> <li>Initiate drug discovery efforts to develop novel therapeutic agents against at least 6 <i>novel</i> therapeutic targets (a minimum of three targets for presymptomatic and early stage disease and a minimum of three for advanced disease). [Summit 1.A, 1.B, 1.D, and 5.A]</li> </ul>	Complete preclinical development, through IND filing, of therapeutics agents against at least 3 <i>novel</i> targets.	5-7 years 2017-2023

<ul style="list-style-type: none"> <li>Initiate phase II (proof of concept) drug trials for agents against 3-6 novel therapeutic targets. These trials will provide proof of mechanism and/or evidence of target engagement of the target being tested. [Summit 3.A, 3.B, 3.F, and 5.E]</li> </ul>	Completion of 3-6 phase II drug trials for agents against novel targets, providing conclusive evidence of therapeutic mechanism/target engagement.	2-4 years 2020-2023
<ul style="list-style-type: none"> <li>Initiate Phase III drug trials for agents against at least 3 novel therapeutic targets. These trials will incorporate a combination of biomarkers (fluid and imaging) and cognitive measures as outcomes and include the collection of DNA and other bio-samples for the interrogation of responsiveness. [Summit 3.A, 3.B, 3.F, and 5.E]</li> </ul>	Comprehensive success/failure analysis of data from at least 3 phase III trials.	3-5 years 2022-2026
<b>Development of Non-Pharmacological Interventions</b>		
Milestone	Success Criteria	Time Required
<ul style="list-style-type: none"> <li>Convene an advisory meeting to delineate an interdisciplinary research agenda focused on: (i) advancing non-pharmacological interventions for the cognitive and behavioral symptoms of AD by non-pharmacological treatments, (ii) informing the design of therapeutic approaches combining pharmacological and non-pharmacological treatments and (iii) identification of best practices for implementation of non-pharmacological interventions. [Summit 5.B, 5.C, 5.D, and 5.F]</li> </ul>	Recommendations developed for advancing non-pharmacological interventions for AD treatment and prevention to enable successful implementation of effective non-pharmacological interventions.	1 year 2014
<ul style="list-style-type: none"> <li>Convene an advisory meeting to inform the design of therapeutic approaches combining pharmacological and non-pharmacological treatments. [Summit 5.B, 5.C, 5.D, and 5.F]</li> </ul>	Recommendations developed for design of clinical trials combining pharmacological and non-pharmacological interventions.	1 year 2015

<ul style="list-style-type: none"> <li>Initiate interdisciplinary research programs that integrate epidemiological and mechanistic research including cutting edge systems biology approaches to gain an in depth understanding of the mechanisms by which various non-pharmacological interventions impact brain health and the course of AD. [Summit 5.B, 5.C, 5.D, and 5.F]</li> </ul>	<p>Identification of at least 3 new therapeutic targets for neuroprotection based on knowledge of mechanisms mediating the impact of non-pharmacological interventions of brain health in aging and AD.</p> <p>Preclinical proof-of-concept for at least 3 types of non-pharmacological interventions that can inform clinical trial design.</p>	<p>5 years 2016-2020</p>
<ul style="list-style-type: none"> <li>Initiate clinical trials for at least 3 non-pharmacological interventions aimed at AD prevention. Of these at least one trial will be a pivotal, phase III trial. [Summit 5.B, 5.C, 5.D, and 5.F]</li> </ul>	<p>Completion of at least 2 phase II trials for non-pharmacological interventions aimed at AD prevention. Successful trials will provide conclusive evidence of therapeutic mechanism.</p> <p>Comprehensive success/failure analysis of data from at least one phase III trial.</p>	<p>4-5 years 2017-2021</p>
<ul style="list-style-type: none"> <li>Initiate clinical trials for at least 3 interventions combining pharmacological and non-pharmacological interventions for AD treatment or prevention. Of these at least one trial will be a pivotal, phase III trial. [Summit 5.B, 5.C, 5.D, and 5.F]</li> </ul>	<p>At least 2 phase II trials completed for interventions combining pharmacological and non-pharmacological interventions for AD treatment or prevention with conclusive evidence of therapeutic mechanism.</p> <p>Comprehensive success/failure analysis of data from at least one phase III trial.</p>	<p>4-5 years 2019-2023</p>
<ul style="list-style-type: none"> <li>Review results of past and existing grants to develop technologies that promote prevention and treatment trials. Assess areas where technologies have been adopted, where there are promising results that should be followed up, and where there are remaining needs. [Summit 5.G]</li> <li>Initiate research programs (R01), Small Business Innovative Research (SBIR) or Small Business Technology Transfer (STTR) focused on developing and testing new technologies or modifying and testing existing technologies to improve clinical care, caregiver support (e.g., improved caregiver quality of life, improved ability to provide effective care to the care recipient), and in-home monitoring. [Summit 5.G]</li> </ul>	<p>At least two new technologies are developed, prove useful in formal or informal care, and are widely adopted.</p>	<p>1 year 2015</p> <p>3-5 years 2016-2020</p>

Biomarkers of Disease Progression		
Milestone	Success Criteria	Time Required
<ul style="list-style-type: none"> <li>Initiate synthesis and testing of novel PET ligands and develop and test novel CSF/blood biomarkers for assessment of disease related pathological burdens such as tau, inflammation, synaptic dysfunction. [Summit 1.E]</li> </ul>	Development and testing of 3-5 novel PET ligands and/or CSF/blood biomarkers for assessment of AD pathology.	5 years 2014-2018
<ul style="list-style-type: none"> <li>Initiate development of imaging and/or fluid biomarkers to demonstrate target engagement for 5 novel therapeutic targets for AD. [Summit 1.E]</li> </ul>	Identification of 3 imaging and/or fluid biomarkers for which there is proof of engagement of novel therapeutic targets.	5 years 2014-2018
<ul style="list-style-type: none"> <li>Incorporate imaging and/or fluid biomarkers into Phase II (proof of concept) drug trials to provide proof of mechanism and/or evidence of target engagement as trials for 3-6 existing and 3-6 novel therapeutic targets are initiated. [Summit 1.E]</li> </ul>	Initiation and completion of 5 Phase II (proof of concept) drug trials using imaging and/or fluid biomarkers for proof of target engagement.	3-5 years 2017-2021
<ul style="list-style-type: none"> <li>Incorporate imaging and/or fluid biomarkers into Phase III (pivotal) drug trials to select subjects and/or provide evidence of target engagement as trials for 3-6 existing and 3-6 novel therapeutic targets are initiated. [Summit 1.E]</li> </ul>	Initiation of 3 Phase III (pivotal) drug trials using imaging and/or fluid biomarkers to select at risk subjects and/or for proof of target engagement.	3-5 years 2019-2023
<ul style="list-style-type: none"> <li><i>Biomarkers Usable in Community Studies</i> Initiate studies to develop minimally invasive biomarkers for detection of cerebral amyloidosis and other AD pathophysiology. [Summit 1.F and 1.G]</li> </ul>	Development and testing of 5 biomarkers that utilize biofluids or other minimally invasive imaging, electrophysiological recording, or other methodologies to assess the burden of AD pathophysiology that could be used in community based and epidemiological studies of AD.	5 years 2015-2019
<ul style="list-style-type: none"> <li>Linking peripheral and central biomarkers Initiate studies to link peripheral blood-based biomarkers and central imaging and CSF biomarkers. [Summit 1.F and 1.G]</li> </ul>	Identification of 3 peripheral blood-based biomarkers that have a high correlation with central imaging and/or CSF biomarkers.	5 years 2016-2020

<ul style="list-style-type: none"> <li>Launch research programs to develop and validate sensitive neuropsychological assessment measures to detect and track the earliest clinical manifestations of Alzheimer's disease. [Summit 3.D]</li> </ul>	Development of at least one sensitive neuropsychological assessment measure that has been validated for the detection or tracking of the earliest clinical manifestations of AD.	5 years 2014-2018
<ul style="list-style-type: none"> <li><b>Biomarker Standardization</b> Develop and test methods for the standardization of immunoassays and mass-spectrometry/single reaction monitoring assay or other methodologies for CSF A<math>\beta</math> &amp; tau and other biomarkers as they become clinically applicable. Develop and test methods for standardization of collection and analysis of MRI and PET neuroimaging data. [Summit 3.E]</li> </ul>	CLIA laboratory qualification in US & the equivalent certification in the EU for at least one CSF biomarker of disease pathology. For neuroimaging data, qualification of at least one biomarker for use in clinical trials by the FDA and/or the EMA.	5 years 2014-2018
<b>Epidemiology</b>		
<b>Milestone</b>	<b>Success Criteria</b>	<b>Time Required</b>
<ul style="list-style-type: none"> <li>Establish an expert panel of epidemiologists and clinical trialists to make recommendations for best practices in the use of existing epidemiology of dementia databases to individualize treatments in clinical trials for AD in heterogeneous populations. [Summit 3.C and 3.G]</li> </ul>	Clinical trialists and epidemiologists implement best practices and work together in the design of clinical trials for AD.	1 year 2014
<ul style="list-style-type: none"> <li>Initiate expansion of epidemiology of dementia cohorts to include subjects in midlife and use data generated to inform clinical trial design. [Summit 3.C and 3.G]</li> </ul>	Three or more active cohorts that cover age range from midlife to late-life as a study population for investigating and reporting findings on changing risk profiles from younger to older ages.	5-7 years 2014-2020

Research Resources		
Milestone	Success Criteria	Time Required
<ul style="list-style-type: none"> <li>Develop a common Alzheimer's disease research ontology, as a unified classification system for comparative analysis of research portfolios, and strategic planning, and create a publicly available database that will house the AD research portfolios from AD funding agencies in the US and abroad.</li> </ul>	Recruitment of all federal and non-federal funding agencies in the US as well as AD funding agencies from countries that have an AD National Plan to participate in this database.	2-3 years 2013-2015
Partnerships to Accelerate AD Drug Development		
Milestone	Success Criteria	Time Required
<ul style="list-style-type: none"> <li>Convene an advisory meeting focused on facilitating public-private partnerships aimed at accelerating the development and test of effective therapies for AD treatment and prevention. [Summit 1.H, 1.I, 1.K, and 6.C]</li> </ul>	Established working groups on: (i) Rapid Data Sharing and Analysis, (ii) Enabling Bidirectional Translation in AD drug development, (iii) Eliminating IP barriers for Target Validation through clinical proof of concept.	1 year 2013
<ul style="list-style-type: none"> <li>Convene meetings of the working groups for (i) Rapid Data Sharing and Analysis, (ii) Enabling Bidirectional Translation in AD drug development, (iii) Eliminating IP barriers for Target Validation through clinical proof of concept. Each working group will formulate concrete steps needed to accelerate the timeframe of AD drug development. [Summit 1.H, 1.I, 1.K, and 6.C]</li> </ul>	<p>Recommendations developed on (i) the creation of an open access, web based resource that integrates complete, diverse multidimensional biological and chemical data that will be useful in advancing information on drug targets, including mechanistic information that will aid in the development of measures of target engagement (PD readouts); (ii) creation of computational tools for development of biological network models of AD and normal aging; (iii) creation of tools that will foster development of bio network models that provide a predictive framework for using drugs in combination or singly (iv) removing legal and IP barriers surrounding data sharing.</p> <p>One or more partnerships established to accelerate key steps in AD drug development.</p>	1 year 2014

Infrastructure		
Milestone	Success Criteria	Time Required
<ul style="list-style-type: none"> <li>Create a network of translational centers that bring together expertise and technology needed for integration of multi-modal data analysis, mathematical modeling and empirical testing and apply a systems biology/systems pharmacology approach to the most challenging aspects in preclinical therapy development such as: (i) therapeutic target selection and initial target validation, (ii) predictive toxicology, (iii) rigorous preclinical efficacy testing and development of translatable, preclinical biomarkers. The centers will provide training programs for the new generation of translational scientists. [Summit 2.A and 2.B]</li> </ul>	Creation of at least 3 Translational Centers that will apply the principles of quantitative and systems pharmacology to AD drug development.	3-5 years 2014-2018
<ul style="list-style-type: none"> <li>Establish an NIH working group to develop an expedited review track for translational AD research applications (from target identification/validation drug discovery through Phase III clinical trials). [Summit 2.D]</li> </ul>	New NIH policy in place for fast tracking of AD translational research application.	1 year 2015
<ul style="list-style-type: none"> <li>Create a National IRB. [Summit 3.H]</li> </ul>	Initiation of at least one multi-center clinical trial that utilizes a national IRB.	2 years 2014-2015
<ul style="list-style-type: none"> <li>Establish a working group to identify standard outcome measures necessary for data comparisons across a variety of clinical studies. [Summit 5.E]</li> </ul>	Identification of at least two standard outcome measures for data comparison in clinical research.	1 year 2014
<ul style="list-style-type: none"> <li>Initiate 3-4 clinical research studies using common standard outcome measures. [Summit 5.E]</li> </ul>	Data comparisons conducted from clinical studies using common standard outcome measures.	3-5 years 2014-2018



Study Recruitment and Participation		
Milestone	Success Criteria	Time Required
<ul style="list-style-type: none"> <li>Increase knowledge among research scientists of best practices for recruitment and retention of research participants.</li> </ul>	Central resources for both references and tools, including videos and presentation materials created and available.	2 years 2014-2015
<ul style="list-style-type: none"> <li>Establish a working group including clinical trial recruitment experts to dynamically evaluate and update the materials and information provided in the central resource.</li> </ul>	Recommendations for successful recruitment methods.	1 year 2014
<ul style="list-style-type: none"> <li>Increase awareness of large-scale registries that encompass the spectrum of the disease from healthy to at-risk asymptomatic to symptomatic individuals from early midlife to late life willing to participate in clinical research aimed at AD prevention and treatment.</li> </ul>	A central repository of AD related registries and cohorts created and publicized.	2 years 2014-2015
<ul style="list-style-type: none"> <li>Increase the rate of enrollment for AD clinical trials and increase the participation of underrepresented populations.</li> </ul>	Increased rates of enrollment and inclusion of underrepresented populations for AD clinical trials as evaluated using the existing NIH system for NIH funded clinical research.	5 years 2014-2018

## Alzheimer's Disease Research Summit Recommendations – May 2012

### Session 1: Interdisciplinary Approach to Discovering and Validating the Next Generation of Therapeutic Targets for Alzheimer's Disease

- A. Intensify scientific efforts to deepen the understanding of the complex pathobiology of Alzheimer's disease, and diversify target identification to better address the multifactorial nature of the disease. These efforts should include the use of systems biology approaches and tools, as well as cutting-edge stem cell technology.
- B. Develop a better systems-level understanding of how the many discoveries that have already been made (e.g., genetic, pathological, biochemical, radiological, neuropsychological) and the contributory factors that have already been identified (e.g., A $\beta$ , tau, apoE4,  $\alpha$ -synuclein, TDP-43, aging, proteostasis failure, mediators of inflammation, comorbidities) are related mechanistically.
- C. Facilitate the conversion of existing genetic information into mechanistic insights and therapeutic advances and continue to generate new genetic data using exome and genomic sequencing approaches to identify rare genetic variants of large functional effect.
- D. Generate new experimental models (e.g., different animal species, human induced pluripotent stem [iPS] cells, in silico models) that better simulate the multifactorial etiology of Alzheimer's disease and use these models to identify modulators of disease pathways and to assess combination treatments which may be required to defeat this disease. Ensure that these new tools and models are freely shared.
- E. Develop in vivo imaging agents (tracers for PET scans) to assess target engagement and the burden of brain pathology to enable successful drug development for existing and new therapeutic targets.
- F. Develop robust biomarkers that can feasibly be obtained in large cohorts of volunteers, including metabolic signatures to develop and validate diagnostic, prognostic, and surrogate biomarkers for Alzheimer's disease and biomarkers for disease subtypes.
- G. Establish links among peripheral biochemical changes (e.g. blood-based markers) and imaging and cerebrospinal fluid changes to identify and validate peripheral biomarkers of disease.
- H. Enable rapid sharing of new data via web-based resources with the capacity to store large and diverse datasets (such as data about clinical phenotypes, genetics, epigenetics, proteomics, and metabolomics) that can be used for testing different models or hypotheses at the computational level.
- I. Enable analysis of new data before publication, using approaches such as collaborative challenges open to all citizens and scientists.
- J. Maximize the use of existing infrastructure and resources (e.g., research centers, biobanks, and repositories) by publicizing their availability to researchers.
- K. Facilitate the creation of new translational teams to expedite the discovery and validation of new therapeutic targets. These teams should include epidemiologists, basic research scientists, geneticists, computational biologists, medicinal chemists, pharmacologists, toxicologists, pharmacogenomics experts, clinicians, and project managers, collaborating within and across institutions.

## Session 2: Challenges in Preclinical Therapy Development

- A. Develop infrastructure and resources to increase the likelihood that preclinical therapeutic development efforts for Alzheimer's disease will translate to success in the clinic by:
  - Creating expert advisory committees for all aspects of preclinical and early clinical drug development to assist academic drug discovery efforts
  - Establishing a network of Alzheimer's disease preclinical therapy centers integrated with existing and proposed translational infrastructure and resources (e.g., Alzheimer's Disease Neuroimaging Initiative, Alzheimer's Disease Centers)
  - Establishing an open-access resource for reviewing and publishing negative and discrepant data.
- B. Develop broad capabilities in quantitative and systems pharmacology to understand the impact of drugs on organisms, to predict dosing, to reduce toxicity, and to facilitate drug repurposing and the identification of combination therapies. This will require a wide collaboration among NIH Institutes, government, academia, industry, voluntary health organizations, and foundations including the establishment of new training programs.
- C. Increase the predictive power of preclinical testing in animal models by:
  - Establishing a standardized and rigorous process for the development and characterization of animal models, and ensuring their maximal and rapid availability to all researchers for preclinical drug development
  - Aligning the pathophysiological features of Alzheimer's disease animal models with the corresponding stages of clinical disease using translatable biomarkers
  - Establishing guidelines for rigorous preclinical testing in animal models and reporting of both positive and negative findings.
- D. Provide an expedited review track for applications focused on drug discovery, preclinical, and clinical drug development for Alzheimer's disease to mitigate difficulties with intellectual property and commercialization issues that are imposed by the current lengthy review/grant cycle at the NIH. Establish multi-disciplinary review panels with adequate expertise to evaluate all aspects of translational research.

## Session 3: Whom to Treat, When to Treat, and What Outcomes to Measure

- A. Initiate treatment trials in asymptomatic, at-risk individuals (e.g., individuals at risk genetically, older adults positive for biomarkers for Alzheimer's disease) using uniform biomarkers and cognitive outcomes, informed by data from Alzheimer's disease trials using patients with more advanced disease.
- B. Collect DNA and other biosamples from these studies to enable subsequent interrogation based on treatment response and predictors of decline in the groups receiving placebo.
- C. Expand large-scale registries and natural history cohorts of healthy individuals from early midlife to late-life, as well as individuals with subjective and/or objective cognitive impairment and use the data generated to inform clinical trial design. These cohorts should be population-based and should oversample underrepresented ethnic minorities and groups with lower education.
- D. Develop, validate, and standardize sensitive neuropsychological and other clinical and behavioral measures to detect and track the earliest clinical manifestations of Alzheimer's disease and to predict long-term clinical and functional outcomes. These measures should be sensitive to change and capture the variability in cognitive function that may be an important predictor of treatment response.

- E. Optimize biomarkers for detecting and monitoring the progression of Alzheimer's disease, and focus particularly on standardization. These biomarkers will be used to elucidate the temporal trajectories over the course of preclinical and prodromal Alzheimer's disease, to assess the proximity to onset of clinical symptoms, and to predict long-term clinical response to treatment.
- F. Develop treatments for patients with symptomatic Alzheimer's disease and support proof of concept studies to validate novel targets for cognitive and neuropsychiatric symptoms across all disease stages.
- G. Develop approaches to stratify and individualize treatments based on the heterogeneity of symptomatic patient populations.
- H. Support broad infrastructure changes that will accelerate and improve the efficiency of prevention initiatives, including the formation of a national centralized Institutional Review Board for multi-center Alzheimer's disease trials and the development of agreements for data sharing of de-identified data from both placebo and treatment arms via public databases.

#### **Session 4: Drug Repurposing and Combination Therapy**

- A. Expand publicly available libraries of drugs, drug signatures, and Alzheimer's disease tissues and publicize their availability to the Alzheimer research community. Consider including cell-type and region-specific expression differences in the brain and periphery at varying stages of Alzheimer's disease, as different stages may require different drugs. Expression libraries from cognitively normal adults positive for amyloid imaging and CSF Alzheimer's biomarkers and from centenarians without dementia could be used to identify Alzheimer's disease-resistant expression signatures that correlate with specific drug signatures for prevention studies.
- B. Maintain rigor in the development of repurposed drugs with respect to scientific rationale, as well as design of clinical trials. Provide adequate prior clinical trial evidence for safety in populations with or at risk for Alzheimer's disease.
- C. The optimal therapy for Alzheimer's disease may involve the use of drug combination cocktails and require different composition of these cocktails at different stages of the illness. To facilitate the development of effective combination therapies, develop translational workgroups that include experts in network biology and network pharmacology.
- D. Encourage the evaluation of drugs that simultaneously target multiple disease pathways (e.g., insulin, selective estrogen receptor modulators).
- E. Develop translational groups across institutions that focus on specific therapy development efforts (e.g., apoE therapeutics, combinatorial therapeutic strategies, drug repurposing, neuropsychiatric symptoms).

#### **Session 5: Nonpharmacological Interventions**

- A. Integrate epidemiological studies with mechanistic research to explore underlying pathways by which risk and protective factors contribute to the disease process.
- B. Continue to identify the molecular mechanisms by which non-pharmacological interventions operate and employ systems biology approaches to examine brain health in relation to, and in concert with, other organ systems.
- C. Initiate rigorously designed clinical trials in asymptomatic and cognitively impaired older adults to establish the effectiveness of physical exercise, cognitive training, and the combination of these interventions for Alzheimer's disease treatment and prevention.

- D. Combine nonpharmacological (e.g., behavioral, lifestyle, environmental) interventions with pharmacological treatments to maximize possible therapeutic benefit. Use epidemiologic information, mechanistic research in animal models, and network analysis to inform trial design and drug selection.
- E. Develop standard outcome measures to enable data comparisons across studies. These include but are not limited to ecologically valid measures of real world function, quality of life, and physical and cognitive function.
- F. Pursue the science of behavioral change for successful implementation of effective nonpharmacological interventions.
- G. Invest in research to develop technologies that promote prevention and treatment trials, clinical care, caregiver support, and in-home monitoring.

### **Session 6: New Models of Public Private Partnerships**

- A. Promote and enable partnerships across all sectors involved in basic, translational, and clinical research to successfully implement an integrated translational research agenda.
- B. Increase awareness of the importance and value of public private partnerships among federal agencies, other stakeholder organizations, and the public and engage the full spectrum of the Alzheimer's disease community in various partnership activities for the advancement of AD therapy development.
- C. Enable partnerships for:
  - Data sharing (with standardized ontologies and metadata)
  - Creating, validating and sharing tools for translational research (e.g., instruments and biomarkers, animal models, high-throughput screening assays, iPS cells).
  - Expanding the precompetitive space using new models of public private partnerships such as the Arch2POCM partnership for target validation and also for product development partnerships.
- D. Develop a National Institutional Review Board for Alzheimer's disease studies accessible to both public and private funding research organizations.