Texas Alzheimer's Research Consortium:

Research Update

Stephen C. Waring, DVM, PhD

Research Epidemiologist and Scientific Coordinator

Texas Alzheimer's Research Consortium

Assistant Professor of Epidemiology, Biological Sciences, and Environmental Science

University of Texas School of Public Health

Healthy Aging

Alzheimer's Disease:
Public Health Impact – Prevalence in 2007

- 5.1 million people in US with Alzheimer's disease

Age Group	Percent	People
<65	<1 %	200,000
65 - 74	2%	300,000
75 – 84	19 %	2,400,000
85+	42 %	2,200,000

Every 72 seconds, someone in America develops Alzheimer's disease; by 2050, it will be every 33 seconds

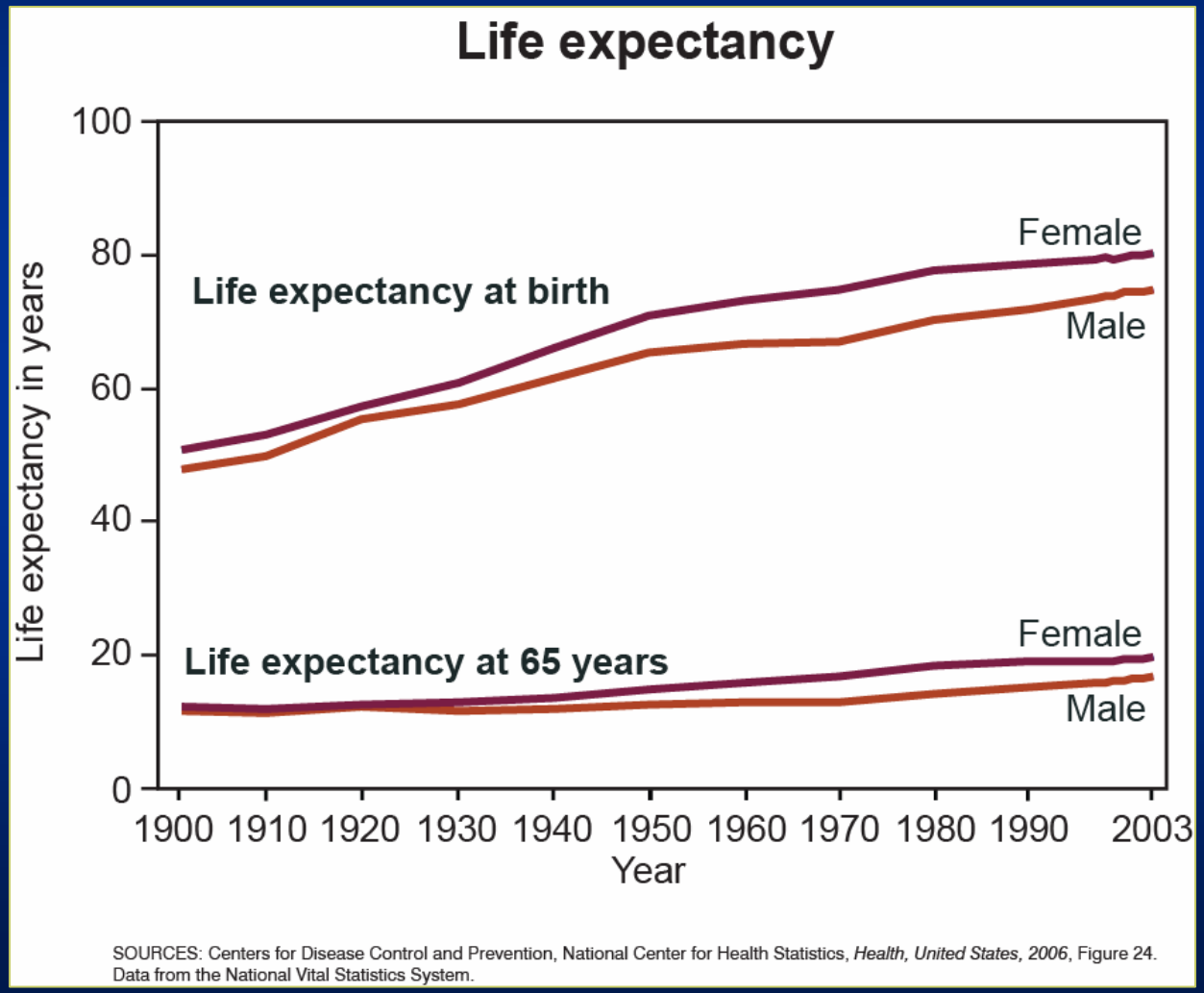
SOURCE: Alzheimer's Association Facts and Figures, 2007

Alzheimer's Disease:
Public Health Impact – Prevalence in Texas (2007)

- There are no formal studies to estimate the true occurrence of Alzheimer's disease in Texas
- Estimated that over 300,000 people in Texas currently have Alzheimer's disease
- Expected to be over 700,000 by the year 2030
- A number of factors need to be taken into account such as the demographic makeup (age, sex, race/ethnicity) of the population

SOURCE: Alzheimer's Association Facts and Figures, 2007

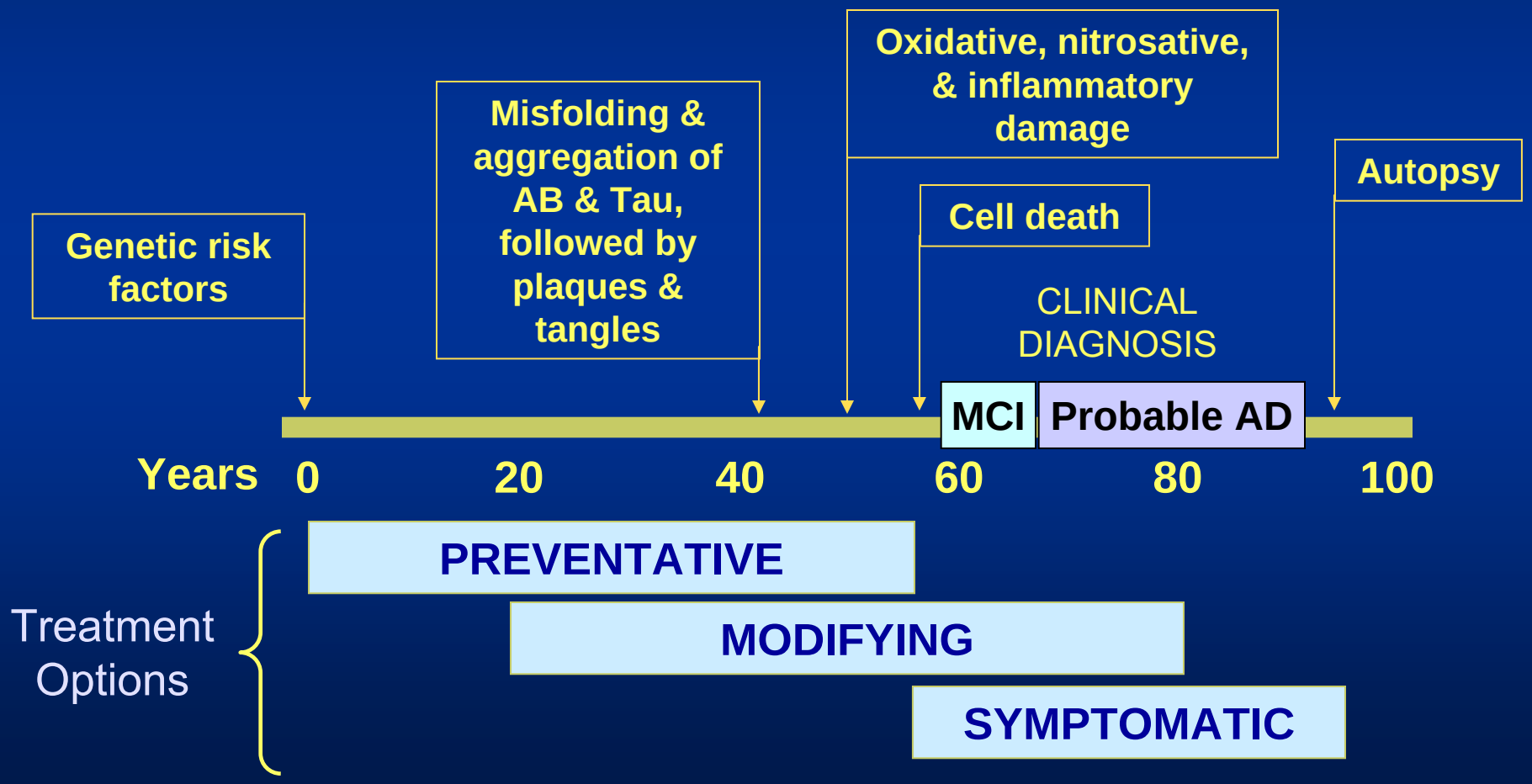
Why AD, Why Now?:
Trends in life expectancy, 1900 - 2003



SOURCES: Centers for Disease Control and Prevention, National Center for Health Statistics, *Health, United States, 2006*, Figure 24. Data from the National Vital Statistics System.

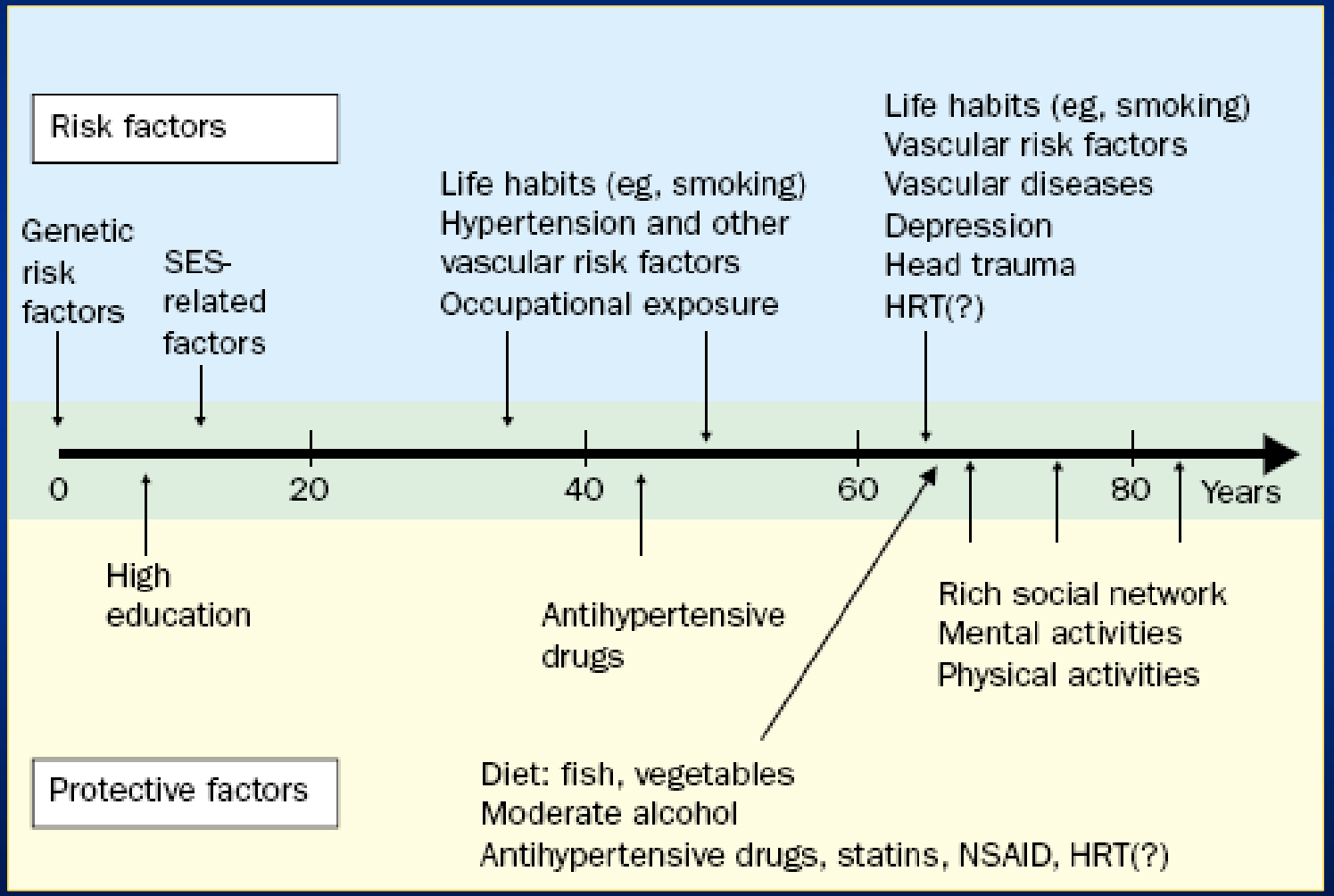
Alzheimer's Disease

Neuropathologic Course over Time



NIA-ADNI, 2005

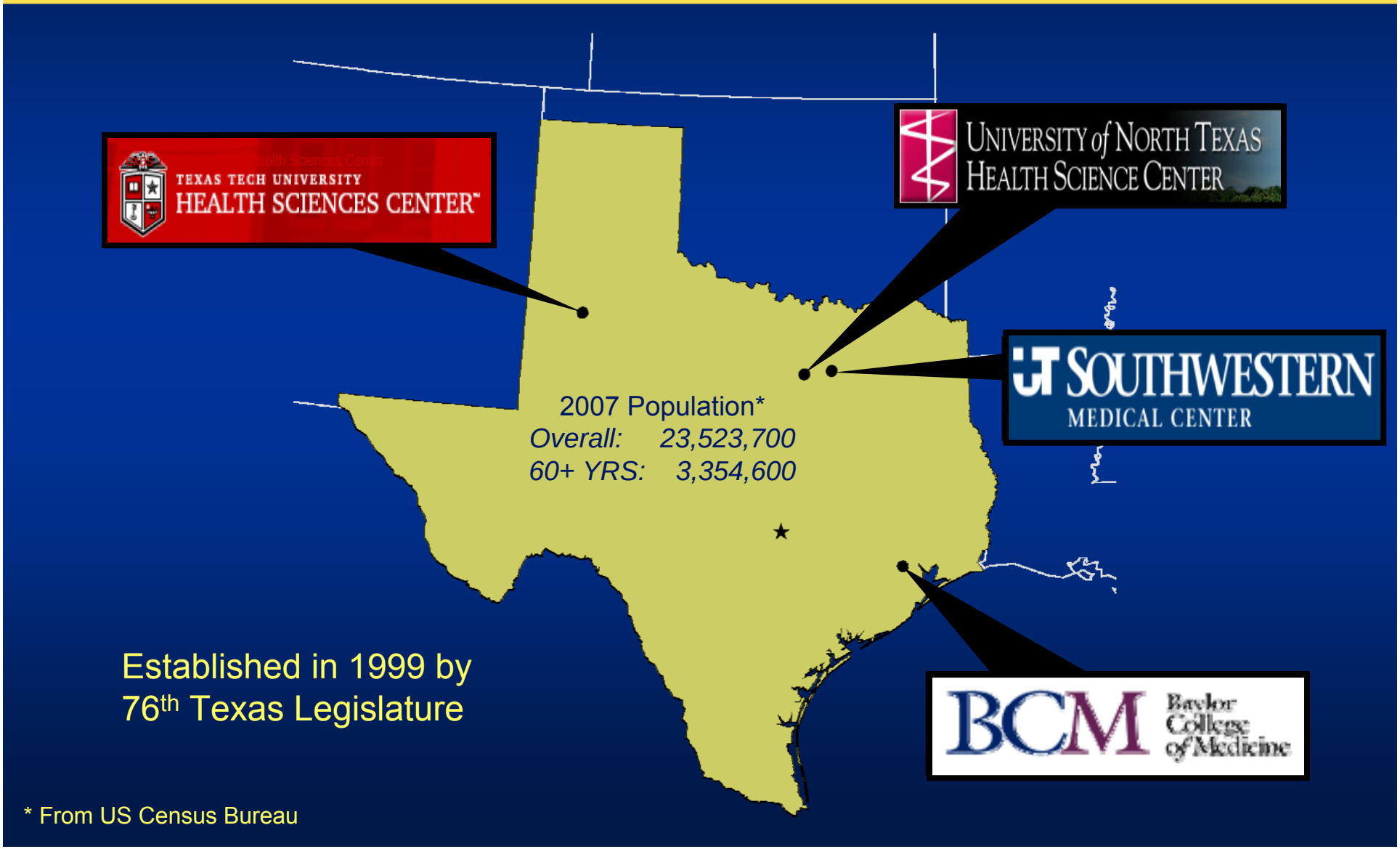
Alzheimer's Disease
Risk/Protective Factor Timeline



Fratligioni et al. Lancet Neurology 2004

Texas Alzheimer's Research Consortium:

Overview of Current Research



Established in 1999 by
76th Texas Legislature

* From US Census Bureau

Texas Alzheimer's Research Consortium:
Timeline

June 2005 - 79th Texas Legislature appropriated funds to support Consortium research

All activity presented to the Texas Council on Alzheimer's Disease and Related Disorders for approval based on recommendations of the TARC Steering Committee*

Consortium research initiated; creation of minimum database (MDS)	Longitudinal study (LDS) proposals solicited, reviewed, and selected by Oct	Protocols, IRB approvals finalized; recruitment begins	80th legislature appropriated additional funding for next biennium	Plans for research activity for the next biennium finalized
Jun 2006	Sep 2006	Mar 2007	Jun 2007	Sep 2007

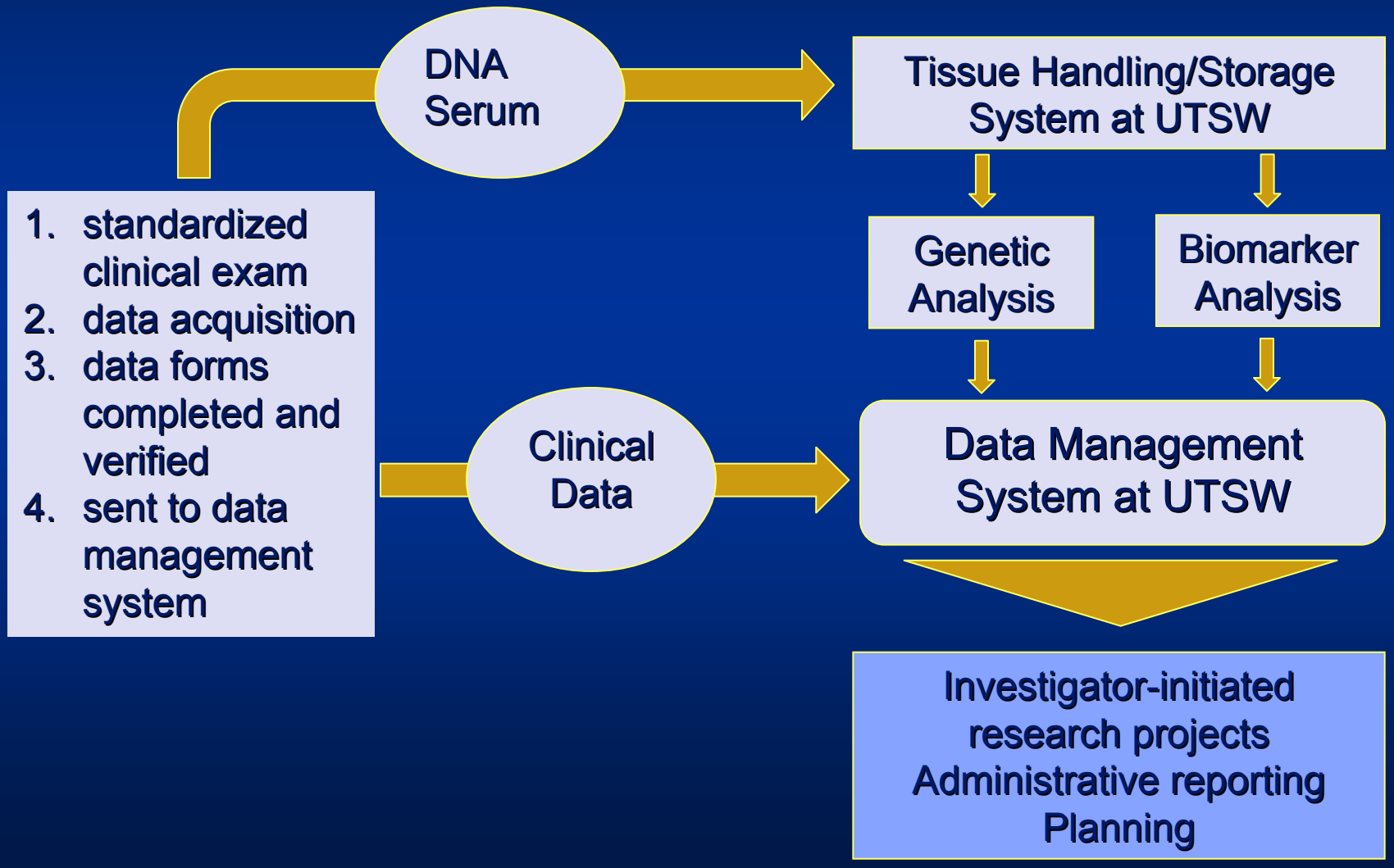
*TARC Steering Committee: Dr. Rachelle Doody (Baylor College of Medicine)
Dr. Randall Schiffer (Texas Tech University Health Science Center)
Dr. Thomas Fairchild (University of North Texas Health Science Center)
Dr. Perrie Adams (University of Texas Southwestern Medical Center)

Texas Alzheimer's Research Consortium:
Goals of the Consortium

- Establish a scientific focus that puts us at the forefront of Alzheimer's disease research
- Attract collaborations with researchers throughout the Consortium member institutions as well as outside
- Compete for external funding from government and non-government entities in crucial areas of Alzheimer's disease research such as genetic, molecular, clinical epidemiology, pharmacogenomics, treatment/prevention trials

Texas Alzheimer's Research Consortium:

Research Database Structure and Flow



Texas Alzheimer's Research Consortium:
Overview of Current Research

Research Personnel

- At each member Institution
  - Investigators
    - Director, Neurologists, Clinicians, Nurses, Psychometricians, Neuropsychologists, Neurogeneticists, Epidemiologists, Neuroscientists, Neurobehavioral Scientists, Research Support
  - Project Coordinator
  - Data Management Team
- Consortium Data Coordination and Management
  - Statisticians, Data Analysts, Programmers, Data Entry, Bioinformatics, Epidemiologists, Website development/Management
- Analysis
  - Statisticians, statistical genetics, geneticists, molecular scientists, bioinformatics

Texas Alzheimer's Research Consortium:
Overview of Current Research

- Minimum Database (MDS)
  - To provide cross-sectional demographic and limited clinical information on individuals recruited for studies of aging and dementia at all member sites
  - Similar format and content to the National Alzheimer's Coordinating Center (NACC) Minimum Data Set (MDS)
  - Provides a 'gateway' to information useful for planning studies or analyses

Texas Alzheimer's Research Consortium:
Overview of Current Research

MDS Baseline Characteristics

	Overall	Initial Visit 2001 – 2006
Sex		
Male	2067	1002
Female	3494	1852
Race/Ethnicity		
Caucasian	4521	2362
Black	438	174
Hispanic	489	221
Other	36	28
Diagnosis		
AD	2790	1238
Non-AD dementia	672	264
MCI or CDR=0.5	322	220
Non-demented control	1230	742

Data lock: 10/01/06

Texas Alzheimer's Research Consortium:
Overview of Current Research

MDS Presentation/Publication

Staging Dementia Severity with CDR Sum of Box Scores: An investigation by the Texas Alzheimer's Disease Research Consortium (TARC)

Sid E. O'Bryant, Stephen Waring, Munro Cullum, James Hall, Laura Lacritz, Paul Massman, Rachelle Doody, Philip Lupo, Joan Reisch, and the Texas Alzheimer's Research Consortium

Abstract in press:*Archives of Clinical Neuropsychology*

- MDS allowed a study of Clinical Dementia Rating (CDR) scale to be presented at the annual conference of the National Academy of Neuropsychology, November 11-14, 2007 in Scottsdale, AZ
- Manuscript to be submitted to peer-review journal

Texas Alzheimer's Research Consortium:
Overview of Current Research

Longitudinal Database Study (LDS)

Research Objectives:

- To identify potential genetic factors associated with earlier age at onset among patients with AD
- To examine the association between inflammation and AD and determine whether inflammation mediates the effect of cardiovascular risk factors on development of AD

Texas Alzheimer's Research Consortium:
Overview of Current Research

Longitudinal Database Study (LDS):

Specific Aim 1

To identify novel genes associated with earlier age of onset among patients with AD.

Employing sophisticated bioinformatic and statistical genetic tools to perform a genome-wide association analyses on 500 well characterized AD patients

Texas Alzheimer's Research Consortium:
Overview of Current Research

Longitudinal Database Study (LDS):

Specific Aim 2.

To identify polymorphisms in genes related to inflammatory function that are associated with earlier age of onset of AD

Utilizing the same tools and methods applied in Specific Aim 1, genome-wide association analyses will be performed on 100 well characterized cognitively normal controls and compared to results generated for the 500 AD patients

Texas Alzheimer's Research Consortium:
Overview of Current Research

Longitudinal Database Study (LDS):

Specific Aim 3

To test the hypothesis that patients diagnosed with Alzheimer's disease (AD) will demonstrate a significantly different inflammatory profile relative to healthy controls.

Inflammatory markers (α1-antichymotrypsin, IL-1ra, IL-1β , IL-4, IL-6, IL-8, IL-10, INFγ, CRP, and TNFα) will be analyzed from serum samples collected on all participants and subjected to a multivariate analysis of variance profile analysis.

Texas Alzheimer's Research Consortium:
Overview of Current Research

Longitudinal Database Study (LDS):

Specific Aim 4

To test the hypothesis that inflammation mediates the relation between cardiovascular disease and Alzheimer's disease.

Markers of cardiovascular disease and cardiovascular risk factors (hypertension, hyperlipidemia, and diabetes) will be examined to first replicate the previously established relation between cardiovascular disease and AD and then to determine whether inflammatory markers mediate this relationship.

Texas Alzheimer's Research Consortium:
Overview of Current Research

Longitudinal Database Study (LDS): Methods

- Study population
  - 500 Individuals with Probable AD
    - All participating in genetic study
    - 100 participating in biomarker pilot study
  - 100 Cognitively normal individuals
    - All participating in both genetics and biomarker study
- Eligibility
  - Must be at least 55 years of age and meet criteria for Probable AD or normal control
  - Must have requisite study information and provide DNA (genetics study) and serum (biomarker study participants only)
  - Excluded if have preexisting conditions that would influence findings
- IRB approved consent obtained on all participants

Texas Alzheimer's Research Consortium:
Overview of Current Research

Longitudinal Database Study (LDS): Methods

- Examination procedures
  - Clinical evaluation - clinical , neurological examination, establish age at onset, document cardiovascular disease and risk factors
  - Neuropsychological Core Battery
    - Global cognitive functioning/status (MMSE and CDR)
    - Attention (Digit Span and Trails A)
    - Executive function (Trails B and Clock Drawing)
    - Memory (WMS Logical Memory I and WMS Logical Memory II)
    - Language (Boston Naming and FAS Verbal Fluency)
    - Premorbid IQ (AMNART)
    - Depression (Geriatric Depression Scale (GDS)

Texas Alzheimer's Research Consortium:
Overview of Current Research

Methods: Laboratory analysis

- Genome-wide association study
  - involves rapidly scanning large samples for markers (SNPs) across complete sets of DNA to find genetic variations associated with a particular disease or trait
  - new genetic associations identified lead to development of better strategies to detect, treat and prevent disease
  - particularly useful in finding genetic variations that contribute to common, complex diseases, such as AD among others (diabetes, cardiovascular, etc)
  - Association of genetic variations with disease (or trait) in these markers serve to point to the region of the human genome where the disease-causing problem resides and ultimately identification of the actual gene involved
  - TARC will be using the Affymetrix 6.0 GeneChip®
    - allows interrogation of ~1,000,000 SNPs
    - In use by several large studies of diabetes, cardiovascular disease, and others
  - Genotyping of first samples to begin in September, expected to be completed by end of year (500 cases, 100 controls)

Texas Alzheimer's Research Consortium:
Overview of Current Research

Methods: Laboratory analysis

- Biomarker study
  - Serum samples on 100 cases and 100 controls will be shipped to Rules Based Medicine in Austin, Texas for analysis
  - multiplex assays of α1-antichymotrypsin (ACT), interleukin-1 receptor antagonist (IL-1ra), IL-1β, IL-4, IL-6, IL-8, IL-10, interferon gamma (INFγ), C - reactive protein (CRP), and tumor necrosis factor alpha (TNFα)
  - takes advantage of emerging technology offered by RBM called Multi-Analyte Profiles (MAPs), a large panel of tests that provide accurate and precise measurement of numerous biological markers of cancer, infectious disease, autoimmunity, cardiovascular risk, as well as hormones, growth factors, and numerous other proteins in the blood

TARC Study of the Genetics of AD
Background: Known Genetic Models of Disease

To date, three genes identified (familial AD)

- younger age at onset (< 55 yrs of age)
- rare, fully penetrant autosomal dominant mutations
- cause abnormal amyloid precursor protein (APP) processing, overproduction of A-β_{1-42}
  - amyloid precursor protein (APP) gene - CH21
  - presenilin 1 (PSEN1) gene - CH14
  - presenilin 2 (PSEN2) gene - CH1
- account for <5% of all AD (majority due to PSEN1)

TARC Study of the Genetics of AD
Background: Genetic Risk Factors

Apolipoprotein E - Chromosome 19

- Best characterized polymorphism
- accounts for up to 50% of late onset AD
- ε-4 allele associated with increased risk of developing AD
  - heterozygous (2/4, 3/4) - 2-5 fold increase
  - homozygous (4/4) - 10-15 fold increase
- earlier age at onset
  - heterozygous (2/4, 3/4) - 5-10 yrs
  - homozygous genotype (4/4) - 10-20 yrs
- also risk factor for atherosclerosis, myocardial infarction, and stroke

TARC Study of the Genetics of AD
Background: Genetic Risk Factors

Recent findings

SORL1 (Chromosome 11; Rogaeva et al. Nature Genetics 2007)

- SORL1 levels are reduced in in brains of individuals with AD
- SORL1 binds to APP; overexpression reduces Aβ production
- SORL = sortilin-related receptor lipoprotein

DAPK1 (Chromosome 9; Li et al. Hum Mol Genetics 2006)

- DAPK1 plays a pro-apoptotic role in the programmed cell death cascade, including neuronal apoptosis
- predominantly expressed in the brain (hippocampus, cortex most severely affected regions)
- DAPK = death associated protein kinase

TARC Study of biomarkers in AD
Background: Biomarker Basics

Definition

- characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (NIH Working Group, 2001)

Types (Vasan Circulation 2006)

- marker of the natural history of a disease and correlates longitudinally with known clinical indices
- marker that captures the effects of a therapeutic intervention in accordance with its mechanism of action
- marker intended to be a surrogate end point expected to predict clinical benefit/lack of benefit/harm based on scientific evidence (clinical, epidemiological, treatment trials, etc)

TARC Study of biomarkers in AD
Background: Ideal Candidates for AD

- Candidate markers fall under four main biological rationales:
  - specific markers of AD neuropathology
  - non-specific markers of neurodegeneration
  - markers of oxidative stress
  - markers of neural inflammation

Baily Can J Neurol Sci 2007

TARC Study of biomarkers in AD
Background: Ideal Candidates for AD

- Consensus panel on molecular and biochemical markers of AD, ideal biomarker should:
  - detect a feature of underlying pathology of AD
  - have high sensitivity and specificity
  - be reliable, *non-invasive, easy to perform, and inexpensive*
  - be validated in peer-reviewed publications

Growdon JH Arch Neurol 1999

TARC Study of biomarkers in AD

Background: Best Candidates to Date

Source	Biomarker	Associated Pathology
CSF	low Aβ 1-42	amyloid plaques
CSF	elevated p-tau	neurofibrillary tangles
MRI	medial temporal atrophy	neuronal cell/synaptic loss

TARC Study of biomarkers in AD
Role of Inflammatory Factors

- Several reports of inflammatory proteins involved in AD
  - both anti- and pro-inflammatory mechanisms
    - α1-antichymotrypsin
    - Interleukins (IL-6, IL-1β, IL-1ra)
    - C-reactive protein (CRP)
    - tumor necrosis factor-α. (TNFα)
    - others

No studies have simultaneously evaluated a range inflammatory markers to compare inflammatory profiles of AD patients to that of non-AD control participants.

TARC Study of biomarkers in AD
Role of Cardiovascular Disease and Risk Factors

- Numerous reports linking cardiovascular disease and AD
  - midlife hypertension as a risk factor for development of AD
  - diabetes, hyperlipidemia, smoking, and obesity have been linked with AD in several studies
  - presence of multiple CVD factors puts an individual at increased risk over and above any one marker
  - possible role of inflammation on the associations between CVD and AD remains largely uninvestigated
  - Only two studies have reported on this but only assessed a very limited group of markers (CRP, TNF-alpha / IL-10 ratio)

We will examine the role of inflammation as a mediating variable between CVD and AD and will have the significant advantage of including multiple inflammatory markers.

What we need to know:
Clinical utility of genetic/biomarker discovery

- Improved understanding of pathophysiology
- Potential for rational drug development
- Potential for pharmacogenomic effects, targeted treatments and preventive strategies
- Potential role in early detection and early intervention
- Potential role in risk assessment and prophylaxis

What we need to know:
How do we get there from here?

- Alzheimer's disease likely results from genetic variants that alter either the production or processing of β-amyloid and other proteins
- Large scale initiatives
  - Texas Alzheimer's Research Consortium to identify genes and biomarkers
  - NIA LOAD Genetics Initiative to identify genes with large and small effects and gene-gene, gene-environment interactions
  - NIA ADNI (Neuroimaging Initiative) to assess role of clinical, imaging, biomarkers over time
- Coordinated efforts with cardiovascular and other studies not only efficient but may improve 'the fit' in determinant models
- Impact of disease on caregiver health

What we need to know:
Goals of AD Research

Slowing progression

- enhance quality of life for patient and family

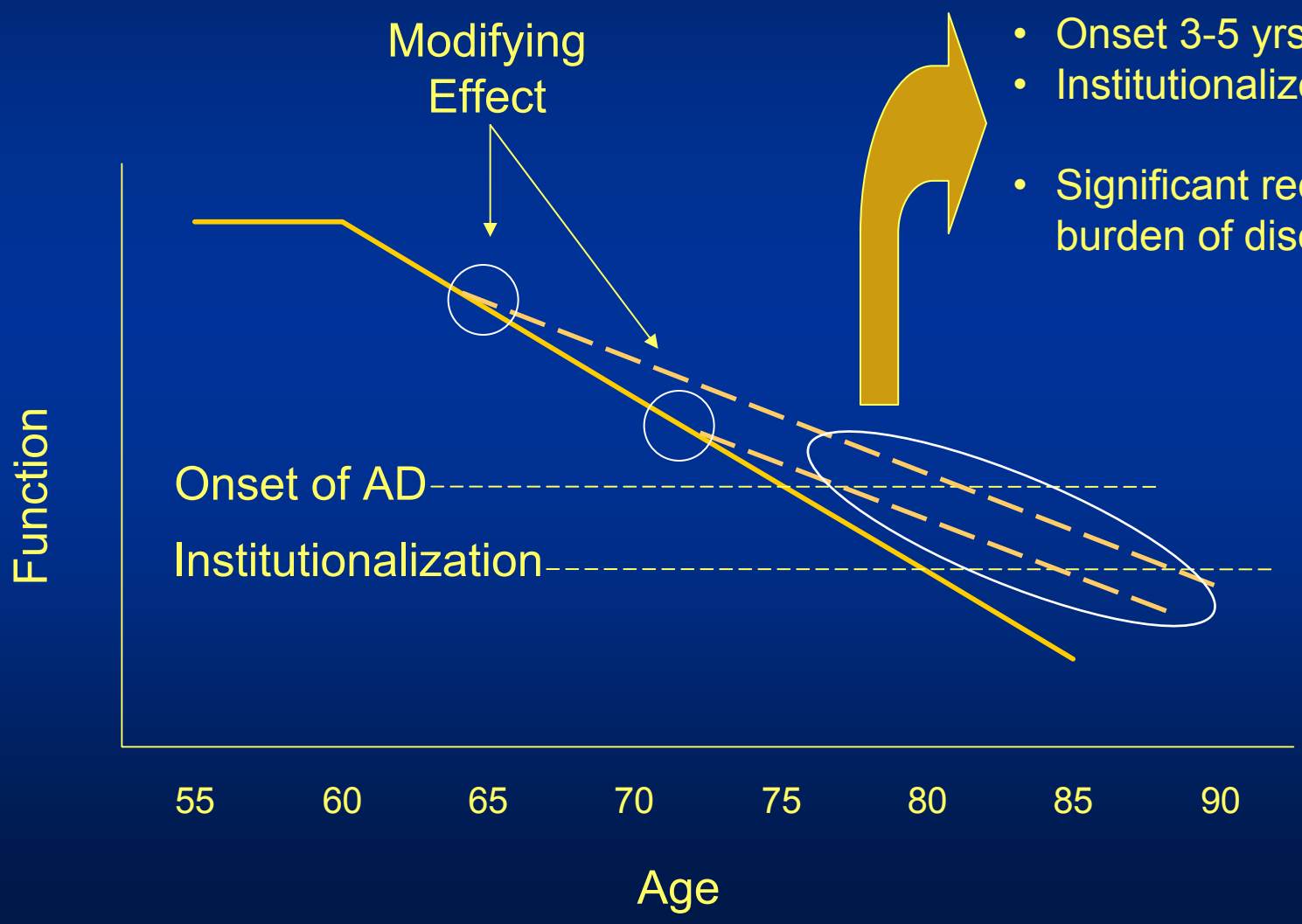
Delaying onset

- lower prevalence; reduce burden on health care

Prevention

- any reduction in incidence is a significant impact

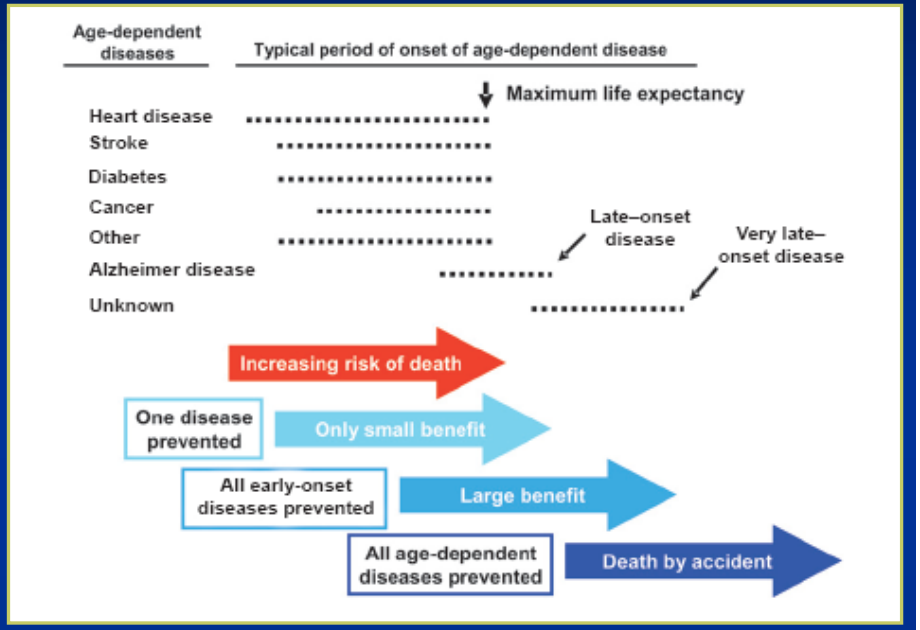
Public health impact of delaying effect



- Onset 3-5 yrs later
- Institutionalized 5-10 yrs later
- Significant reduction in PH burden of disease

Impact of Healthy Aging
Combined Effects of Age and Age-Related Disease

Theoretical effect of preventing age-related diseases
(Hekimi Nature Genetics 2006)



History of age-dependent diseases development	Percentage of 424 unrelated centenarians	
	Males	Females
Survivors	13	17
Delayers	36	34
Escapers	51	49

Morbidity profiles of centenarians
(Evert et al, J Gerontol 2003)

Texas Alzheimer's Research Consortium:
Summary

- Research focus is centered on novel genetic and biomarker studies to address questions that take advantage of the collective expertise and research interest at each member site.
- Multidisciplinary study will provide a robust dataset of prospectively collected clinical, genetic, and biological data from subjects with sufficient follow-up to address an unlimited number of research questions now and into the future.
- This study population is not currently available at individual sites and would be difficult to assemble at a single site due to inherent budget, resource, and recruitment constraints.

Texas Alzheimer's Research Consortium:
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Texas Council on Alzheimer's Disease and Related Disorders

We don't stop playing because we grow old;
we grow old because we stop playing

George Bernard Shaw

Where to find additional information

- NIA (National Institute on Aging): www.nia.nih.gov
- ADEAR (AD Education and Referral): www.alzheimers.org
- Alzheimer's Association: www.alz.org
- Alzheimer's Research Forum: www.alzforum.org