



Institute  
and Faculty  
of Actuaries

# **Evolving Embodiment of Risk:** **The case of Alzheimer's Disease**

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A grayscale microscopic image showing a dense network of neural structures, including long, thin axons and numerous small, circular cell bodies or synapses, creating a complex, textured background.

Roughly 850,000 now to double to 2050.

Projected increase in people with dementia in UK

Dementia UK London 2014

# Economic impact of dementia

Overall impact £26.3 billion

£4.3 billion on healthcare  
£85 million on diagnostics

£10.3 billion on social care  
£4.5 billion publically funded  
£5.8 billion privately funded

Unpaid care £11.6 billion (44% of cost)

The background of the slide is a grayscale micrograph showing a dense field of biological structures. There are numerous small, circular, light-colored granules or cells scattered throughout. Interspersed among these are several elongated, rod-like structures that appear to have a textured or segmented surface. The overall appearance is that of a microscopic view of a tissue sample or a culture of cells.

Long Term Care expenditure to double to 2050  
– Very high costs in the Netherlands



The background of the slide is a grayscale electron micrograph of brain tissue. It shows a dense network of fine, dark, thread-like structures, likely representing neurofibrillary tangles or amyloid plaques, which are characteristic of Alzheimer's disease. The overall texture is grainy and complex, with varying shades of gray highlighting different cellular components.

# Rhetoric and Dementia

## **Critical update:**

One disease. Millions of lives permanently disrupted.

The Alzheimer's Association, Alzheimer's Disease 2015 Facts and Figures released today, highlights the devastating human and economic costs of the Alzheimer's epidemic. Alzheimer's Disease is taking more than memories — it's taking lives.

(24/3/15)

The background of the slide is a grayscale electron micrograph of neural tissue. It shows numerous long, thin, parallel structures, likely axons or dendrites, interspersed with smaller, more rounded, and granular structures that appear to be amyloid plaques or other cellular components. The overall texture is complex and detailed, typical of high-magnification biological imaging.

# Rhetoric and Dementia

It's a fact that Alzheimer's Disease is an escalating epidemic.

The number of Americans with Alzheimer's Disease and other dementias will grow each year as the size and proportion of the U.S. population age 65-and-older continue to increase. By 2050, the number of people with Alzheimer's may rise as high as 16 million (8/4/15)

# Cautions

Western estimates made on studies from the 1980s

UK - aged 65+ - 22% decline in prevalence in 2011 than was predicted in 1990

Spain - men + decline of 43% between 1987 and 1996

Main reason - decline of cardiovascular disease and its risk factors

Improvements in living conditions and education

<http://www.medscape.com/viewarticle/850437>

# Cautions

Obesity & diabetes on the rise so will this be maintained?

China's obesity prevalence has doubled in 30 years

Call to rebalance research less on diagnostics and treatment than on prevention

"Policies which address determinants of health in earlier life stages and enhance cognitive reserve for populations may have the greatest long term impact on reduction of dementia risk at given ages in later life as well as on population health more generally."

<http://www.medscape.com/viewarticle/850437>



# Modifiable Risk Factors

Obesity

Low educational achievement

Depression

Hypertension

Frailty

Smoking

Type 2 Diabetes

Population attributable risk of 66%

**Meta-analysis of modifiable risk factors for Alzheimer's disease**

J Neurol Neurosurg Psychiatry doi:10.1136/jnnp-2015-310548

## Modifiable Risk Factors

Risk Factor	Relative Risk
Diabetes	1.39
Midlife hypertension	1.61
Midlife obesity	1.60
Depression	1.90
Physical inactivity	1.82
Smoking	1.59
Low education	1.59

[http://www.ilcuk.org.uk/images/uploads/publication-pdfs/ILC\\_Dementia\\_and\\_Prevention.pdf](http://www.ilcuk.org.uk/images/uploads/publication-pdfs/ILC_Dementia_and_Prevention.pdf)

## Modifiable Risk Factors: Diabetes

	2013	2040
Diabetes cases prevented	23k	40k
Life years saved	92.7k	150k
State savings	321M	560M

[http://www.ilcuk.org.uk/images/uploads/publication-pdfs/ILC\\_Dementia\\_and\\_Prevention.pdf](http://www.ilcuk.org.uk/images/uploads/publication-pdfs/ILC_Dementia_and_Prevention.pdf)



# Dementia and Survival

Age	Women	Women + Dementia	Men	Men + dementia
60-64	25.07	9.4	22.3	7.4
65-69	20.8	7.5	18.3	5.9
70-79	16.7	5.8	14.5	4.5
80-89	9.6	4.4	8.2	3.7
90+	4.6	3.9	4.2	3.4

After OHE 2014 + National Life Tables

<http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-365199>



# Dementia vs Alzheimer's Disease

## **Dementia is syndrome**

ICD-10 (WHO)

Memory decline. Particularly learning new information  
Decline in at least one other domain of cognition such as  
judging and thinking, planning and organising etc.

To a degree that interferes with daily functioning

Some change in one or more aspects of social behaviour

There should be corroborative evidence that the decline  
has been present for at least 6 months

ICD 10 WHO 1993 Dementia

# Dementia vs Alzheimer's Disease

Acquired, progressive and abnormal deterioration of memory, and at least one other area of cognitive function, which is affecting the daily life of the person, and not due to affective disorders or delirium (Rees, Lipsedge & Ball 1996)

Dementia is a syndrome (essentially brain failure) affecting higher functions of the brain (Barrett & Burns 2014)

## There are many causes of Dementia

Type	Percentage of all people with dementia (rounded figures)			Numbers of people with dementia (rounded figures)
	Female	Male	Both	
Alzheimer's disease	66.2%	54.6%	62.3%	475,000
Vascular dementia	14.8%	20.5%	16.7%	130,000
Mixed (AD & VD)	10.2%	10.9%	10.4%	77,000
Lewy bodies dementia	2.7%	5.6%	3.8%	31,000
Fronto-temporal dementia	1.4%	2.3%	1.7%	15,000
Parkinsons	1.3%	2.7%	1.7%	15,000
Other	3.5%	3.5%	3.5%	27,000

# Dementia Symptoms

Memory loss - recent events, messages, names,

Difficulties organising and planning activities

Confusion in unfamiliar environments

Difficulty finding words

Difficulty with numbers and/or handling money

Changes in personality and mood

Depression



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Memory loss - recent events, messages, names,

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# Not 'just your age dear'

Prevalence Men

Increase to 20% at 90

Prevalence Women

Increases to 30% at 90

Dementia UK 2014



If not 'just your age dear' .....

## Assumptions

Not normal ageing

There is a period when the person is aware of mild problems

A period of cognitive impairment but not yet dementia

## Mild Cognitive Impairment

Jessen et al (2010) Archives General Psychiatry 67. 414 et seq.

# Mild Cognitive Impairment

10 to 15% per year progress to dementia

1 in 4 patients remain with MCI

Normal people 1 to 2 percent per year convert to dementia and 5 percent convert over five years

Over three years:-

- 1/3 improve
- 1/3 remain the same
- 1/3 develop dementia

(Bartlett & Burns 2014)



A grayscale electron micrograph showing numerous amyloid plaques, which are dense, circular clusters of protein, and neurofibrillary tangles, which are long, thin, and thread-like structures. These are characteristic of Alzheimer's disease pathology.

## The pathway from preclinical disease to dementia

<http://www.alz.uci.edu/alzheimers-disease/what-is-alzheimers/mild-cognitive-impairment>

A grayscale electron micrograph of brain tissue. It shows numerous small, dark, circular amyloid plaques scattered throughout. Interspersed among these are several long, thin, and sometimes branching neurofibrillary tangles made of tau protein. The background is a lighter, granular texture representing the surrounding brain tissue.

## **What makes Alzheimer's Disease, Alzheimer's Disease?**

Tangles - made of Tau

Plaques – made of Amyloid

<http://petridishtalk.com/2011/05/>

A grayscale electron micrograph showing numerous long, thin, and slightly curved amyloid fibrils scattered across the field of view. Some fibrils appear as straight lines, while others are more tangled or branched. The background is a granular texture.

# Amyloid Cascade Hypothesis

Accumulation of amyloid triggers neuronal degeneration

Accumulation triggers cell death

Amyloid interferes with mitochondrial function

Amyloid interferes with neurotransmitters and glucose use

[http://www.medscape.org/viewarticle/769590\\_slide](http://www.medscape.org/viewarticle/769590_slide)

# Failure to develop treatments

Trial design

Excessive side-effects biased enrolment

Heterogeneity of the AD process

No linear relationship between amyloid and cognition

No amyloid cognitive impairment (20%)

**Too late and/or the wrong target**

DOI: 10.1002/ana.24227





## Biomarkers and embodying risk

**‘(Genetic) technologies permit us to speculate with much greater precision than was formerly the case about who may be struck by misfortune...’**

Lock, M. (2013) The Alzheimer’s Conundrum.

A grayscale electron micrograph showing numerous long, thin, and slightly curved amyloid fibrils. These fibrils are densely packed in some areas and more sparse in others, with many small, dark, circular spots (possibly nuclei or other cellular components) visible in the background. A semi-transparent gray rectangular box is overlaid on the left side of the image, containing the text 'CT scan' and a URL.

CT scan

<http://www.medscape.com/features/slideshow/alzheimers>

A grayscale electron micrograph showing numerous long, thin, and slightly curved amyloid fibrils scattered across the field of view. The fibrils have a characteristic striated or periodic appearance. The background is dark and filled with small, bright, circular spots, likely representing individual protein monomers or small oligomers.

# MRI Scan

<http://www.dialogues-cns.com/publication/imaging-in-alzheimers-disease>

A grayscale electron micrograph showing numerous long, thin, and slightly curved amyloid fibrils scattered across the field of view. The fibrils have a characteristic striated or periodic appearance. The background is dark and contains many small, bright, circular or spherical particles, likely representing other cellular components or contaminants.

## FDG – PET scan

<http://www.dialogues-cns.com/publication/imaging-in-alzheimers-disease>



A grayscale electron micrograph showing numerous long, thin, and slightly curved amyloid fibrils scattered across the field of view. The fibrils have a characteristic striated or banded appearance. A semi-transparent gray rectangular box is overlaid on the center of the image, containing text.

Amyloid PET

Amyloid PET scan

<http://www.dialogues-cns.com/publication/imaging-in-alzheimers-disease>

A grayscale electron micrograph showing numerous long, thin, and slightly curved fibrillar structures, which are characteristic of amyloid-beta aggregates. These fibrils are scattered across the field of view, with some appearing more densely packed than others. The background is a granular, light gray texture.

# Cerebrospinal fluid

## **Amyloid-beta(1-42):**

Reduction amyloid-beta

## **Total Tau:**

Increase in Total Tau

Total Tau predicts conversion of MCI

## **Phosphorylated Tau:**

Phosphorylated Tau distinguishes AD from other conditions

A grayscale electron micrograph showing numerous long, thin, and slightly curved amyloid fibrils scattered across the field of view. Interspersed among these fibrils are many small, spherical particles, which are likely tau protein aggregates or oligomers. The background is dark and granular.

Poorer survival with low AB amyloid and raised tau

[https://www.genevaassociation.org/media/58196/ga\\_ed\\_382\\_10\\_smalley\\_health,dementia,underwriting.pdf](https://www.genevaassociation.org/media/58196/ga_ed_382_10_smalley_health,dementia,underwriting.pdf)



A grayscale electron micrograph showing numerous amyloid plaques and neurofibrillary tangles, which are characteristic of Alzheimer's disease. The plaques appear as dense, circular clusters, while the tangles are more elongated and fibrous structures.

## Genetics: Early Onset Alzheimer's Disease

### Presenillin 1

Early age of onset – 15% Familial cases

### Presenillin 2 –

Later onset and not all progress to dementia

### Amyloid Precursor Gene (APP)

Together fewer than 1 in 100 cases

Excess production of Amyloid

Lock, M. (2013) The Alzheimer Conundrum





## Genetics: Late Onset Alzheimer's Disease

APOE gene - Identified in 1983

Three common forms e 2, 3 and 4

5 common genotypes 2/3, 3/3, 2/4, 3/4, 4/4

e4 present in 25-30% population

e4/4 variant 10 times the risk

Not everyone with e4 develops the disease

Between 1/3 and 1/2 of those with LOAD do not have e4

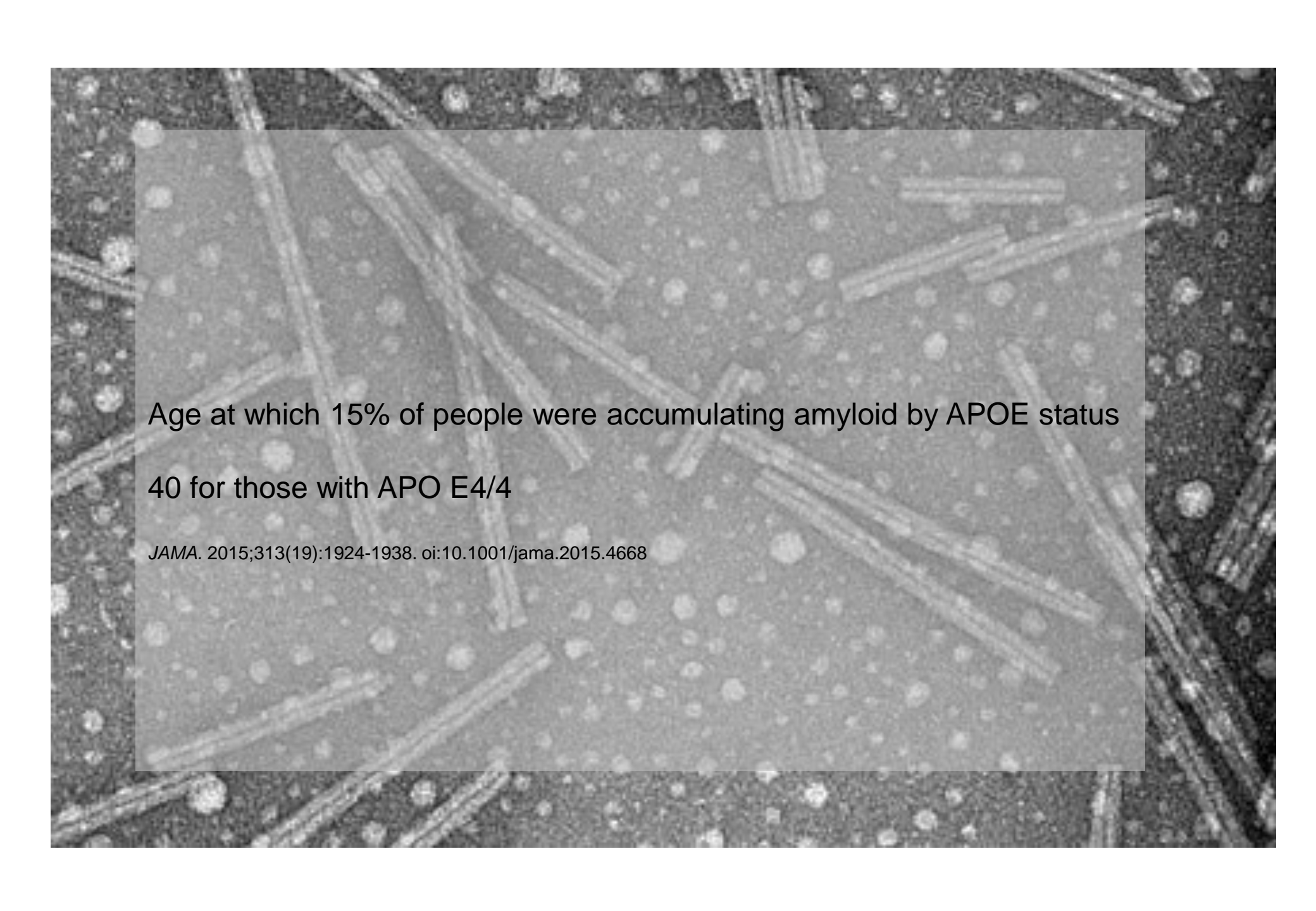
A grayscale electron micrograph showing a dense field of amyloid plaques and neurofibrillary tangles, characteristic of Alzheimer's disease pathology. The plaques appear as small, dark, circular structures, while the tangles are represented by long, thin, dark, thread-like structures.

## **Genetics: Late Onset Alzheimer's Disease**

**APO E 3 and 4**

**The effects of a single amino acid change**

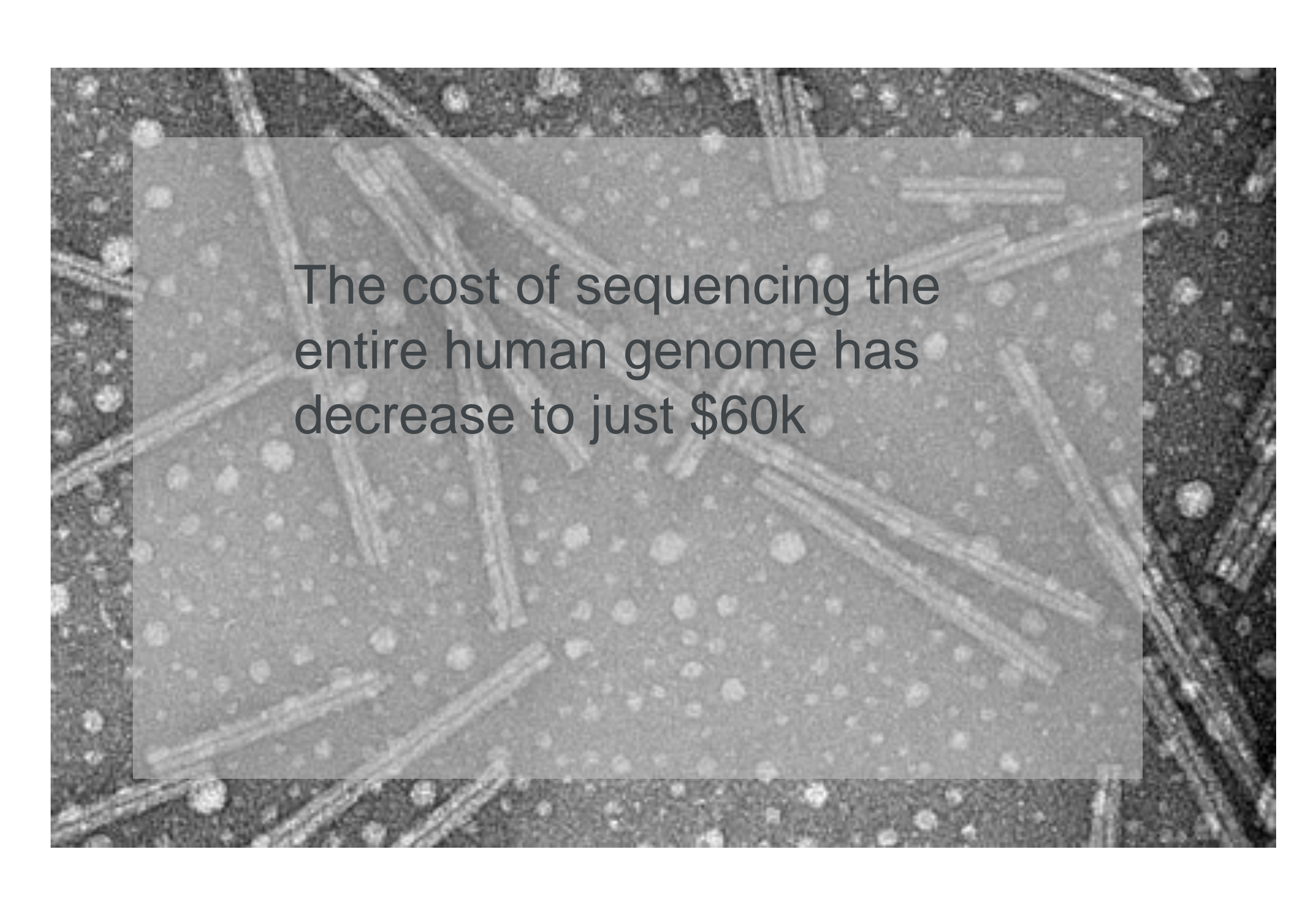
<http://gladstoneinstitutes.org/node/11431>

A grayscale electron micrograph showing numerous long, thin, and slightly curved amyloid fibrils scattered across the field of view. The fibrils appear as light-colored, thread-like structures against a darker, granular background. A semi-transparent gray rectangular box is overlaid on the center of the image, containing text.

Age at which 15% of people were accumulating amyloid by APOE status  
40 for those with APO E4/4

*JAMA*. 2015;313(19):1924-1938. oi:10.1001/jama.2015.4668



A grayscale microscopic image showing a dense field of small, circular, light-colored structures, possibly cells or spores, interspersed with elongated, rod-like structures. The background is dark and textured.

The cost of sequencing the  
entire human genome has  
decrease to just \$60k



A grayscale electron micrograph showing numerous long, thin, and slightly curved amyloid fibrils. These fibrils are densely packed in some areas and more sparse in others, with many small, dark, spherical particles (possibly lipid droplets or other cellular components) scattered throughout the background.

# **Genome Wide Association Studies**

Strongest evidence for APOE involvement

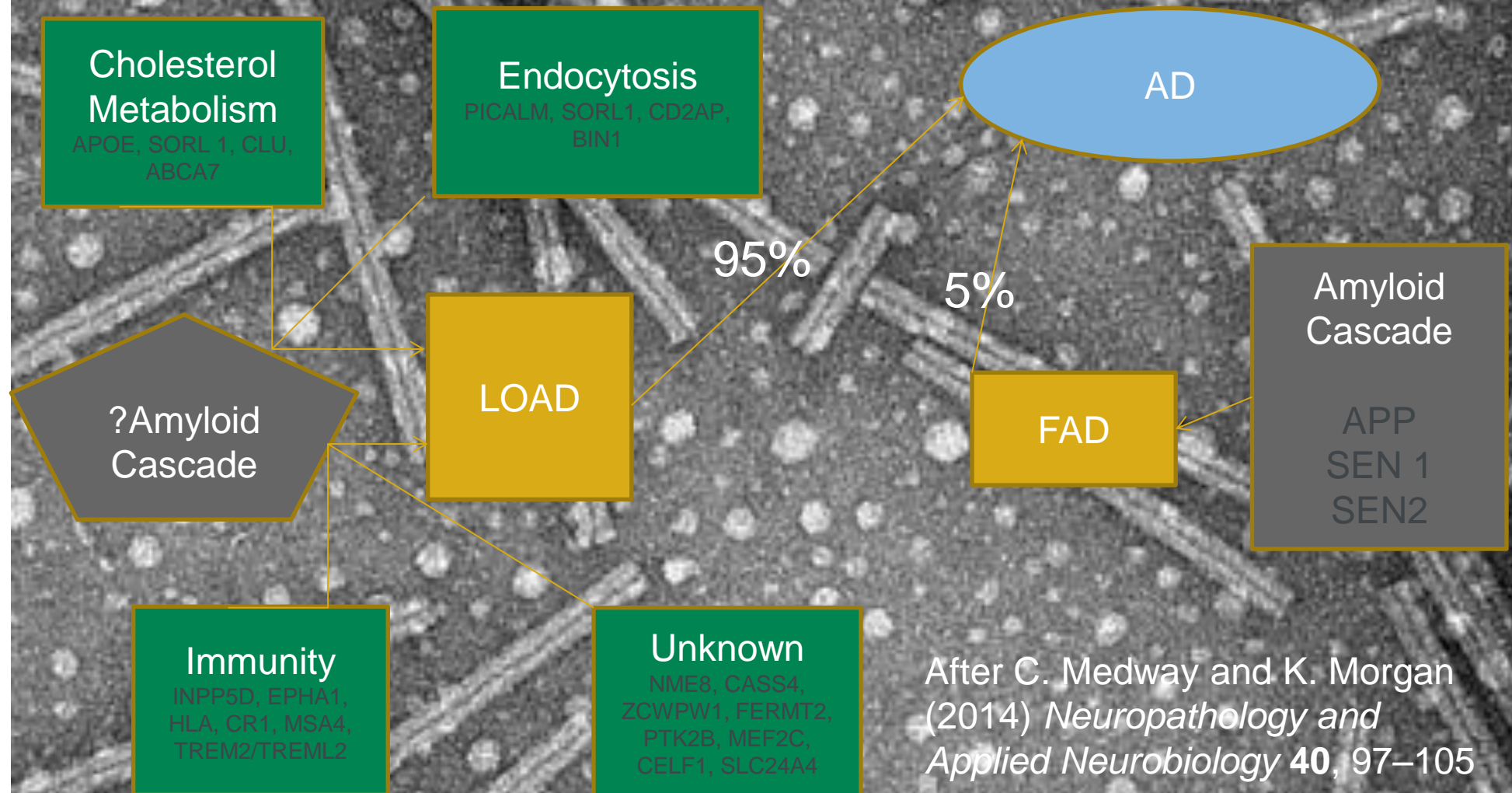
Complex interaction between multiple genes

## **Epigenetics**

The expression of these genes depends on interaction with the environment

Potential to alter the expression of these genes

# Genome Wide Association Studies



A grayscale electron micrograph showing numerous long, thin, and slightly curved amyloid fibrils scattered across the field of view. Some fibrils appear as straight lines, while others are more curved or bundled. The background is dark with some granular texture.

# Blood

Easily accessible but not in contact with the brain

Blood is a complex fluid

Single molecule studies not useful

Proteomics – Identify a protein signature for a disease

Potentially a cheap and acceptable biomarker for presymptomatic AD



A grayscale electron micrograph showing numerous long, thin, and slightly curved amyloid fibrils scattered across the field of view. The fibrils have a characteristic striated or periodic appearance. The background is dark and filled with small, light-colored granular particles.

# Proteomics

<http://neurology.stanford.edu/memory/alzheimers/diagnosing.html>



A grayscale electron micrograph showing numerous long, thin, rod-like structures, likely viral particles, scattered across the field of view. These structures are surrounded by a dense population of smaller, spherical particles. The background has a granular texture.

# Proteomics

Replication studies inconsistent e.g. Kiddle et al (2014)

Non-specific e.g Chiam et al (2015)

But quite exciting Hye et al (2014)



# Ideal Biomarker

Sensitive and specific

Identifies pathological process before clinical symptoms

Can be used for screening

Is proportionate to the severity of that process

Can be used as a marker for therapy

Cheap, acceptable

A grayscale electron micrograph showing numerous amyloid plaques and neurofibrillary tangles, which are pathological hallmarks of Alzheimer's disease. The plaques appear as dense, circular clusters, while the tangles are more elongated and fibrous structures.

# Relationship of biomarkers to the onset of cognitive problems

Jack CR, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, Shaw LM, Vemuri P, Wiste HJ, Weigand SD, Lesnick TG, Pankratz VS, Donohue MC, Trojanowski JQ. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol.* 2013 Feb;12(2):207-16



# National Institute on Aging- Alzheimer's Association (NIA-AA) Classification 2011

## Preclinical Stage

No cognitive impairment but biomarkers present

## Mild Cognitive Impairment due to AD

Impairment on cognitive testing  
Biomarker evidence  
No impairment functioning

## Dementia due to Alzheimer's Disease

[http://www.alzheimersanddementia.com/article/S1552-5260\(11\)00099-9/pdf](http://www.alzheimersanddementia.com/article/S1552-5260(11)00099-9/pdf)





## The *Risk Evaluation and Education for Alzheimer's Disease* (REVEAL)

Educational session about AD

APOE testing

Informed of results and three further sessions over 12 months

At one year – 27% remembered accurately

50% had the broad gist correct

23% nothing or incorrectly

Lock, M. (2013) The Alzheimer Conundrum

A grayscale electron micrograph of neural tissue, showing numerous dark, circular amyloid plaques and lighter, elongated neurofibrillary tangles, which are characteristic of Alzheimer's disease pathology.

# Increasing Complexity

Complex susceptibility genes identified

Modified by epigenetic factors

How do doctors manage these issues?

Effects

..... "can initiate or inhibit action, and increase or reduce, or transform anxiety about genetic embodiment"

Lock, M. (2013) The Alzheimer Conundrum

A grayscale microscopic image showing a dense network of fibers and small, bright, circular structures, possibly cells or bacteria, against a dark background.

‘I know what you told me but this is what I think’

Communicated risk not taken at face value even in those who recalled risk correctly at six weeks

69.3% higher, 30.7% lower

‘Anchoring and adjustment bias’

Linnenbringer et al (2010) Genet Med. 12. 219 –227

Kinscapes, Timescapes and Genescapes

<http://orca.cf.ac.uk/39555/1/Kinscapes,Timescapes,and%20genescaes.pdf>

Remain major problems in imparting and understanding probabilistic information about susceptibility

Information eclipsed by lay understanding



A grayscale microscopic image of a textured surface, possibly a material or biological sample, showing numerous small, circular features and elongated, fibrous structures. A semi-transparent rectangular box is overlaid on the image, containing the text "THE FUTURE!!!".

THE FUTURE!!!



# Challenges

‘(Genetic) technologies permit us to speculate with much greater precision than was formerly the case about who may be struck by misfortune...’ Lock (2013)

Life insurance

Critical Illness

Retirement annuities

Long term care

Vehicle insurance

Public liability

Employers liability

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