

# Genetic Testing for Alzheimer's Disease

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# Early Testing for Alzheimer's Disease

- **Genetics / APOE**
- REVEAL Study
- Underwriting
- Managing the risk

# Introduction

- Alois Alzheimer reported Alzheimer's disease (AD) in 50-year-old woman (1907)
- AD causes 2/3 of dementia
- 7.1% of all U.S. deaths due to AD in 1995
  - **Roughly same as cerebrovascular disease (3<sup>rd</sup> cause of death)**
- 2 types
  - Early-onset (familial)- 2% of AD
  - Late-onset (nonfamilial, sporadic, APOE-related)- 98% of AD

## Early-onset (familial)

- Autosomal dominant →  $\frac{1}{2}$  of children affected
- Age at onset
  - 40s, 50s, sometimes even 20s
  - Never after 65
- Caused by 3 genes that disrupt amyloid brain metabolism
  - APP (amyloid precursor protein)
  - Presenilin 1
  - Presenilin 2

## Late-onset (nonfamilial, sporadic, APOE-related)

- The **gene** APOE produces the **lipoprotein** apolipoprotein E (APOE)
- APOE primary component of very low density lipoproteins (VLDL) which carry cholesterol from blood to liver
- APOE important for cholesterol transport within brain

# Apolipoprotein E (APOE) genotypes

- Genotype- Three alleles (versions) of APOE gene
  - e2- Lower AD risk
  - e3- Average AD risk
  - **e4- Higher AD risk**
- APOE genotyping not routine, but many patients request it (**\$299**)

Frequency of APOE genotypes in U.S. and relative risk of AD for controls vs. AD cases*			
A	B	C	D
Genotype	Controls (%)	AD (%)	Relative risk (C / B) <sup>†</sup>
e2/e2	0.8	0.2	0.3
e2/e3	12.7	4.8	0.4
e2/e4	2.6	2.6	1.0
e3/e3	60.9	36.4	0.6
e3/e4	21.3	41.4	1.9
e4/e4	1.8	14.8	8.2
No e4	74.4	41.4	0.6
1 or 2 e4	25.7	58.8	2.2

\* Ashford JW. J Mol Neurosc 2005;23:157-65.

<sup>†</sup> e.g., 1.8% of control group e4/e4, but 14.8% of AD cases e4/e4 (14.8/1.8 = 8.2).

# APOE affects age at onset

- Age at which 50% have AD
  - **e4/e4- Age 68**
  - e3/e4- Age 76
  - e3/e3- Age 84
- By age 80, percent with AD
  - **e4/e4- 91%**
  - e3/e4- 48%
  - No e4- 20%
- e2/e2 overly represented among centenarians
- **No e4/4 has reached 90 without AD**

# Causes of Alzheimer's disease

## Genetic (definite)

APP

Presenilin 1

Presenilin 2

Down's syndrome

Other genes

Most common pathway:  
Environment + genes (APOE, others) + aging

## Nongenetic (possible)

Toxins

Viruses

Prions

Low education

Head trauma

# Pathophysiology

Gene mutation → Increased brain production of amyloid  $\beta$  peptide and/or defective amyloid  $\beta$  peptide

Amyloid  $\beta$  peptide accumulates as plaques that disrupt neurotransmission between neurons

Neurons malfunction / die

Dementia

# Life expectancy after initial clinical diagnosis decreases with older age

Life expectancy after initial clinical diagnosis of Alzheimer's disease in 521 patients compared with the U.S. population, by quartile and age at diagnosis\*†

	Age 70			Age 80			Age 90		
	75%	50%	25%	75%	50%	25%	75%	50%	25%
<b>Female</b>									
U.S population	21.3	15.7	9.5	13.0	8.6	4.6	6.8	3.9	1.8
Alzheimer's	12.3	8.0	5.9	8.7	5.3	3.2	5.2	2.1	1.6
<b>Male</b>									
U.S population	18.0	12.4	6.7	10.8	6.7	3.3	5.8	3.2	1.5
Alzheimer's	5.1	4.4	3.1	6.8	3.6	2.2	4.9	2.7	0.9

\* Larson EB. Ann Intern Med 2004;140:501-9.

† Life expectancy quartile at initial clinical diagnosis can be estimated by factors such as cognitive status (e.g., Mini-Mental State Exam), comorbidity (e.g., cardiovascular disease, cancer, frailty), and instrumental activities of daily living.

# Treatment not good, will improve

- May slow progression for 6-12 months (some better than others)
  - Razadyne® (galantamine)- Anticholinergic
  - Exelon® (rivastigmine)- Anticholinergic
  - Aricept® (donepezil)- Anticholinergic
  - Cognex® (tacrine)- Anticholinergic
  - Namenda® (memantine)- Glutamate regulator
  - Evista® (raloxifene)- Selective estrogen receptor blocker
- Ineffective
  - Vitamin E (NEJM 2005;352:2379-88)
  - Statins (Arch Neurol 2005;62:1047-51)
- Experimental (lab mice)
  - Amyloid  $\beta$  peptide vaccine for prevention / treatment of existing AD

# Early Testing for Alzheimer's Disease

- Genetics / APOE
- **REVEAL study**
- Underwriting
- Managing the risk

**REVEAL first study to show that genetic information changes how people buy insurance**

## **Genetic Testing For Alzheimer's Disease And Its Impact On Insurance Purchasing Behavior**

Widespread genetic testing for Alzheimer's susceptibility could present dilemmas for long-term care insurance

by Cathleen D. Zick, Charles J. Mathews, J. Scott Roberts, Robert Cook-Deegan, **Robert J. Pokorski**, and Robert C. Green

**Health Affairs 2005 (March);24:483-90**

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

- Randomized controlled trial to evaluate impact of genetic education (**learning APOE genotype**) on **148 adult children of AD patients**
- **Control group** (46 subjects)- Told of AD risk based on age / gender / family history
- **Intervention group** (102 subjects)- Told of AD risk based on age / gender / family history / **APOE genotype**

# Subjects with family history of AD more likely to have already purchased LTC

- Percentage with insurance at beginning of study
  - Health- 97%
  - Life- 78%
  - Disability- 40%
  - LTC- 20%
- In U.S., **7%** of aged 65+ have LTC insurance, compared to **20%** baseline in REVEAL
- **Even before APOE known, subjects with family history of AD were 3 times more likely to have already purchased LTC**
  - Other possible reasons for greater baseline LTC coverage were higher income / education / socioeconomic status

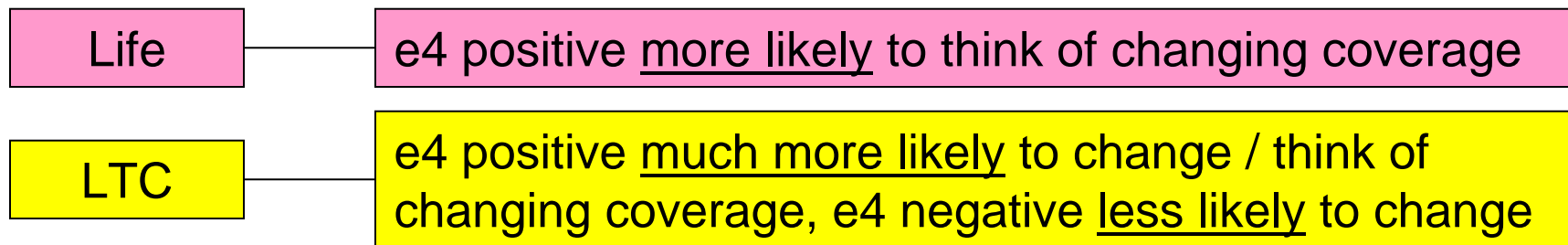
# Results

Percentage of subjects who changed / thought about changing insurance coverage in year after learning of AD risk based on age, sex, family history, and APOE

Type of Insurance	Percent reporting a change			Percent thinking about a change		
	No APOE disclosure (n = 46)	E4 Negative (n = 54)	E4 Positive (n = 48)	No APOE disclosure (n = 46)	E4 Negative (n = 54)	E4 Positive (n = 48)
Health	6.5	5.6	12.5	23.9	13.0	25.0
Life	6.5	7.4	2.1	4.4	5.6	16.7
Disability	4.4	3.7	4.2	8.7	7.4	18.8
LTC	<b>4.4</b>	<b>1.9</b>	<b>16.7</b>	<b>32.6</b>	<b>22.2</b>	<b>45.8</b>

Pokorski RJ, et al. Health Affairs 2005 (March);24:483-90.

In all cases, change meant “increase” coverage.



# AD “perfect storm” for LTC antiselection

- “Perfect storm”
  - High likelihood of needing care
  - APOE gives significant (but incomplete) predictive information
  - LTC private market in U.S.
- Overall, e4 positive subjects **5.8 times** more likely to increase LTC coverage
- Authors suggest **LTC purchase might increase further with older age**, i.e., no perceived need to buy LTC at age 52 (average age of study subjects)

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- Managing the risk

# Incidence rate of AD doubles every 5 years

Age 62- 1 new case per 1000 people

Age 79- 1 new case per 100 people

Age 94- 1 new case per 10 people

Age 105- Incidence rate equals mortality rate

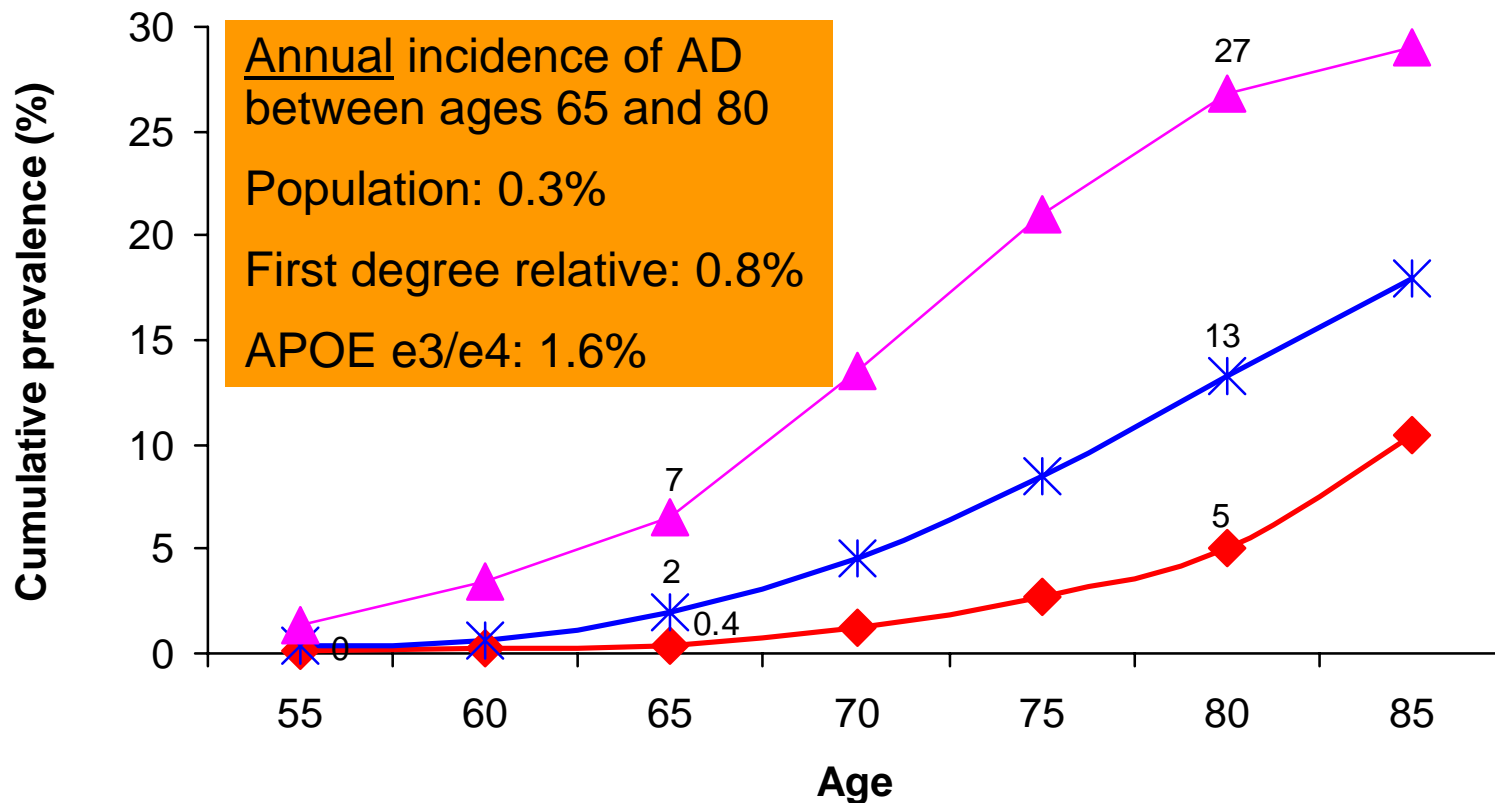
Are underwriting requirements, especially cognitive testing, in line with AD incidence rates?

# Family history (FH)

- 25% of late-onset AD have close relative with AD
- **Ask older applicants about FH**
  - “At what age was condition **diagnosed** (e.g., AD, heart disease, cancer),” not “At what age did **death** occur from condition”
- FH important if
  - Any AD under age 60
  - AD in two or more elderly parents, siblings, aunts, uncles

# Likelihood of AD varies with age, family history, APOE

## Prevalence of Alzheimer's disease, males



Cupples LA, et al. Genet Med 2004;6:192-6.

—◆— Population —\*— First degree relative —▲— APOE e3/e4

# Attending physician's statement often not helpful

Physician usually does not know about mild AD

Physician may not record AD diagnosis in records

“Potential harm of early identification of dementia relates to repercussions of the label of cognitive impairment, including inability to obtain life or health insurance” (J Am Geriatr Soc 2000;48:1430-34)

# Memory loss = AD until proven otherwise

## If memory loss

- **Full evaluation by specialist**
  - Cognitive tests- Borderline low score often / usually = early AD
  - MRI, blood, etc., for other impairments- Depression, brain tumor, multi-infarct dementia, systemic illness
- **Time (12 months, minimum)** for physician to follow patient, repeat tests (mild cognitive impairment → AD at 10%-15% per year)

# Applicants with known AD

- Suicide risk- Claims within contestable period might be “accidental death”
- Moral risk if beneficiary initiates insurance purchase
- Legal risk- Often cannot contest misrepresentation (applicant forgot past medical history)
- Risk classification difficult because great variation in survival data in medical literature

# AD major concern for LTC & products with LTC rider ... even without APOE issue

- AD already most common / most costly / longest LTC claim
- Dementia definition weak
  - Easy to misrepresent “Significant impairment on cognitive test”
  - Easy to misrepresent “Need for continuous supervision”
- REVEAL
  - People with FH of AD **3 times** more likely to **already have** LTC
  - e4 positive subjects **5.8 times** more likely to **increase** LTC coverage

# AD incidence will increase

- Growing emphasis on screening for prevention / early treatment (when better treatment becomes available)
- **Routine screening in future for people with early memory loss, family history of AD, “worried well,” healthy elderly**
  - [www.medafile.com](http://www.medafile.com)
  - Free online memory test for early identification of AD
  - Suggested frequency- Age 50-65, each year; 65+, every 3 months

# Tests to screen for AD

Neuropsychological tests

Delayed word recall, other

Brain scans

1. MRI- Small hippocampus (memory)
2. PET (positron emission tomography) scan- Slower glucose metabolism

Electroencephalograph (EEG)

Abnormal pattern predicts AD

Scratch and sniff test

Abnormal with AD (strawberry, lemon, smoke, lilac, leather), online purchase

Genetic predisposition

Family history, apolipoprotein e4

Mathematical models

Combine data from above to predict AD

# Claims scenarios when AD incidence increases

What happens if incidence of AD increases in **2010** due to routine screening?

## No breakthrough in treatment

↑ number of claims, ↑ claim duration

## Breakthrough in treatment

↑ number of claims, ↑ claim duration

↑ number of claims, ↓ claim duration

↓ number of claims, ↑ claim duration

↓ number of claims, ↓ claim duration

What happens if AD cured, controlled, or prevented in **2025**?

↓ ↓ ↓ in number, duration of claims

# What insurers can do when / before AD incidence increases

Underwriting

1. More cognitive tests based on age, amount at risk, cost / benefit analysis
  - e.g., age 60- \$500,000+
  - e.g., age 65- \$250,000+
2. Use family history to modify risk
3. Physician's statement often won't reveal existing AD

Claims

More restrictive benefit criteria

Pricing

Increase price

Product design

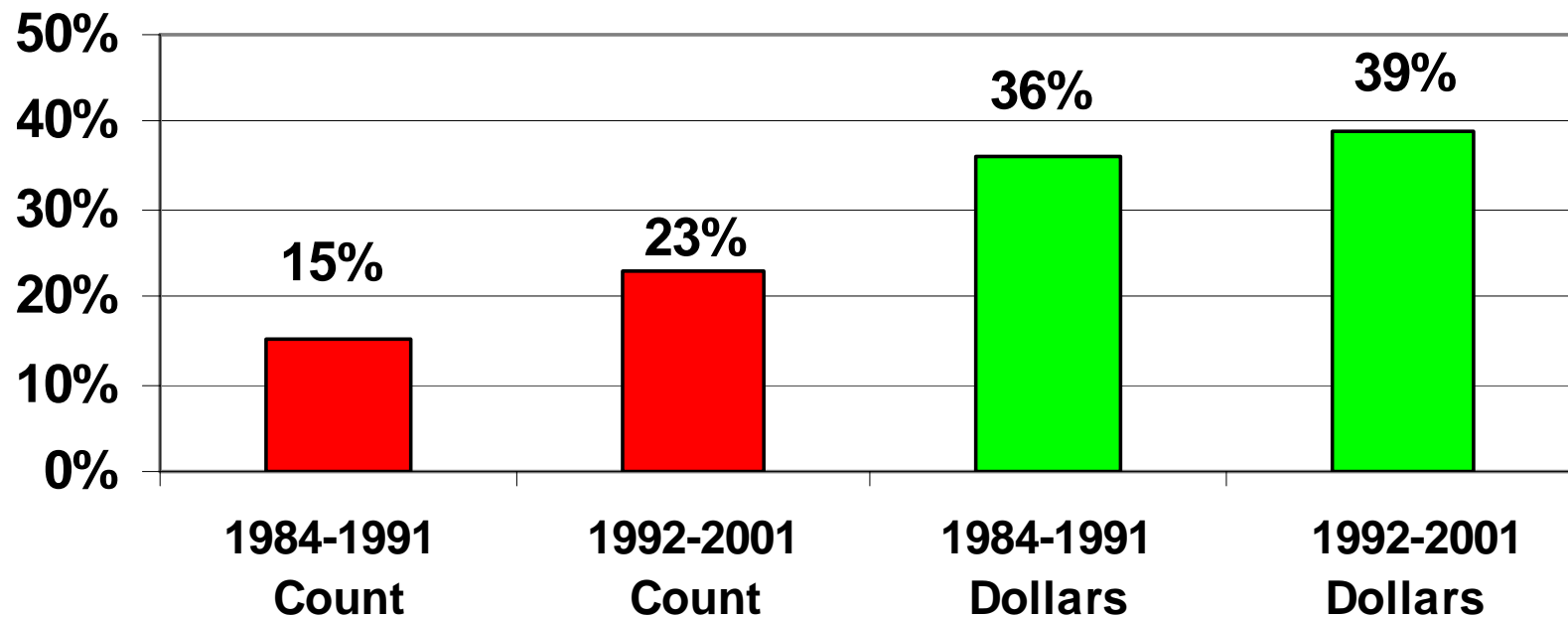
Reduce risk per contract provisions

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- **Managing the risk**

## AD already very important cause of claim

**Alzheimer's disease as a cause (%)  
of LTC Claims, by issue year**



Source: SOA LTC Intercompany Experience Study

# Managing the risk

- Pricing
  - Antiselection certain → size of impact uncertain, but likely significant
  - Low market penetration compounds antiselection

## Product benefits

- Higher / lower AD risks likely to choose higher / lower benefits
  - Continue to offer wide choice of benefit options?
  - Continue to offer unlimited lifetime benefit?
  - Offer new benefits for AD prevention / treatment?
- Product wording
    - Claim trigger defensible against claims for pre-symptomatic / mild AD?

# Managing the risk

- Marketing
  - Will agents / financial planners recommend APOE testing?
  - Will emphasizing AD in marketing attract more applicants with positive family history / e4?
  - Will AD tests encourage existing insureds to test for AD?
    - Cancel policy if negative?
    - Upgrade to “better” policy if positive?
- Claims
  - Pay only on objective criteria in contract wording?
  - Fear of lawsuits → pay on AD diagnosis / early dementia?

# Managing the risk

- New underwriting questions
  - Family history of AD?
  - **Had any test indicating higher likelihood of developing AD?**
- Regulatory
  - Most states allow use of genetic information for LTC, a few do not
- Public Relations
  - Fair / unfair to use genetic information? Only a risk, not an impairment? Not my fault?
  - Fair that low risk subsidize high risk insureds?
  - Private insurance optional → vulnerable to antiselection
  - Public programs that mandate participation less vulnerable

# Why insurance companies do dumb things\*

- Denial of problem
- Tension between short- and long term goals
  - e.g., need to meet quarterly sales targets greater than worry about long term risks

\* Crompton, Robert B. Why insurance companies do dumb things. Contingencies Nov/Dec 2003, p. 8-12

# Why insurance companies do dumb things

Antiselection not a problem

Don't need more cognitive tests

Underwriting protects us

Claims people protect us

Treatment will decrease claims

We've priced for this

We'll sort this out next quarter

We can always raise rates if mistakes in product design

Market share our #1 goal (same as many former LTC insurers)

I'll be long retired by then

Do any of these beliefs apply to LTC insurance?

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