



What Does the Future Hold in Older Age Underwriting? Building Future Concepts with Current Understanding

Lisa Duckett, MD

Vice President and Medical Director

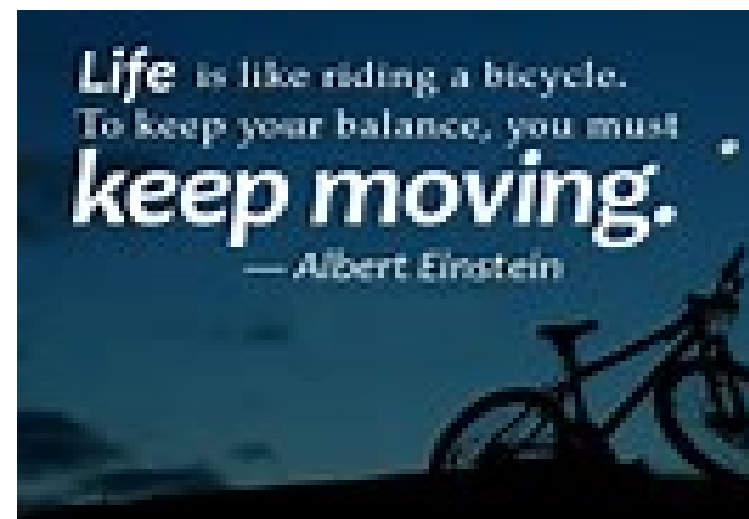
May 2016

Agenda

- I. Older Age Underwriting – Defined as over the age of 70
 - Mortality Trends: shift from infectious diseases to chronic degenerative diseases
 - Current leading causes of death
 - Current underwriting considerations : traditional underwriting tools to assess older age applicant
- II. Dementing illnesses: Alzheimer's Dementia
 - Early detection may aid in risk assessment
 - Biomarkers/ Imaging

Agenda

- III. Lifestyle
 - Inactivity, obesity, malnutrition
 - Medication use based on pharmacogenomics
 - Anticholinergic burden
- 2020 and beyond
 - How to influence behavior?



Mortality Trends

- Currently life expectancies are 76 for men and 81 for women
 - At birth average 79 years
 - USA ranks 34th in the world for life expectancies
 - `Japan is #1 with overall life expectancy of 84 years
- The oldest old (80+) will be the **fastest growing cohort in the population** over the next 25 years
 - Number of people over age 80 will increase by 233% increase
 - Number of people over the age of 65 will increase by 160%
 - Overall population growth : 30% increase over next 25 years

Mortality Trends

CAD, Stroke, Cancer mortality

- Improved mortality has been the trend
 - 1960-1996 54% decrease in CAD deaths
 - 1960-1996 73% decrease in stroke deaths
 - 5 year cancer survival rates have improved from **49%** in the late 1970's to **65%** in 2008
 - 67% increase in cancers of the elderly with the aging population
 - Average age of diagnosis is 66 years and sufferers are more likely to survive their cancer.

Shift from Mortality to Morbidity

Identify the high functioning elderly with minimal disease burden



Factors that May Influence the Trends

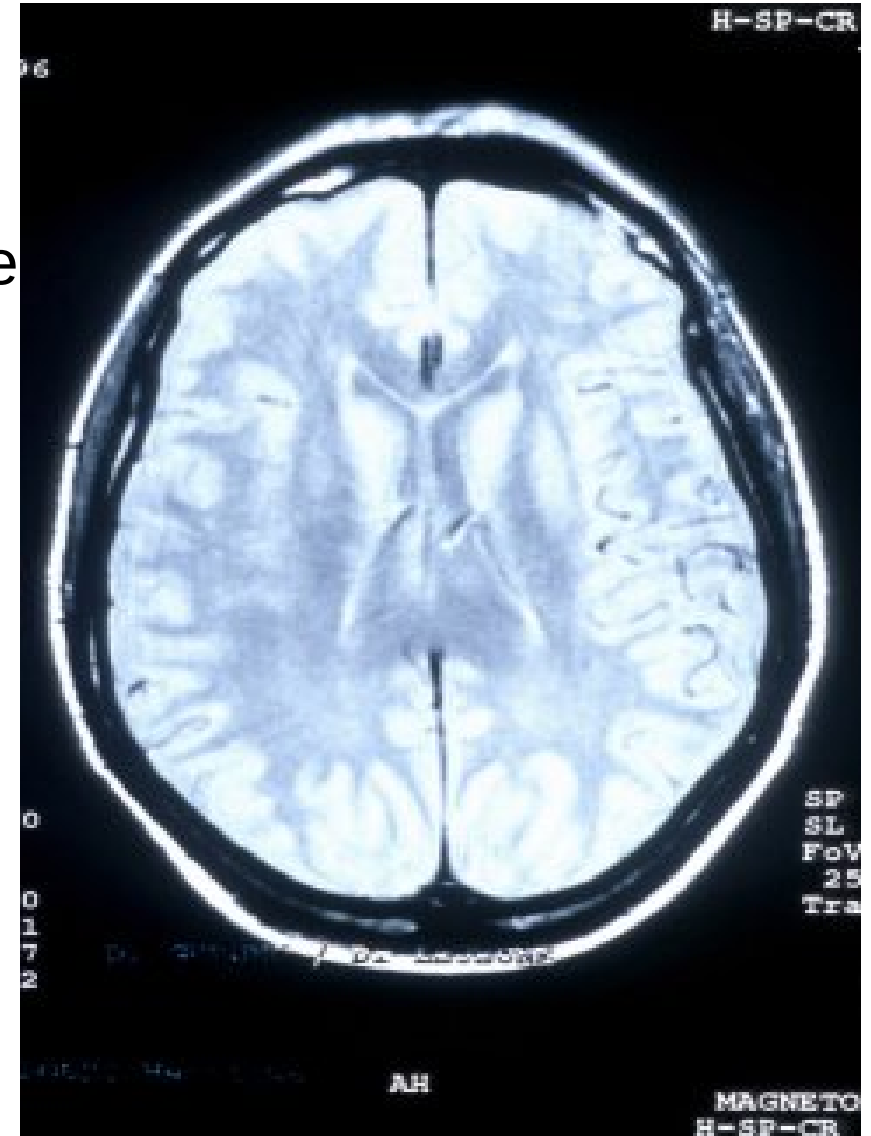
- Lifestyle choices: Inactivity, obesity, smoking
- Genetic information and its use to choose appropriate medications and modify or prevent diseases = Precision Medicine
- How to translate information into behavior change?

Top 10 leading causes of death

- Heart Disease accounts for ~ 24 % of deaths in the USA
 - Accounts for 40% of all deaths worldwide
 - Related to risk factor control: Smoking, Diabetes, Lipids, HTN
 - Increasing prevalence with increasing age
- Cancer accounts for ~ 23%
 - Lung cancer is the most common form of cancer for both men and women
 - Smoking related
- Chronic lower respiratory disease is the 3rd leading cause of death
 - 80% of respiratory diseases attributable to cigarette smoking
- Accidents are the 4th most common cause of death in USA
 - 75% of deaths related to falls occur in individuals over the age of 65 years
 - Rate of falls increase exponentially with age over 75 years of age
 - 12 month mortality rate post hip fracture is up to 67%

Top 10 leading causes of death

- Stroke- One out of 20 deaths/ 5th Leading cause
 - Ischemic stroke predominant type 87%
 - Leading cause of long term disability
- Alzheimer's disease
- Diabetes
- Influenza and pneumonia
- Kidney disease
- Suicide



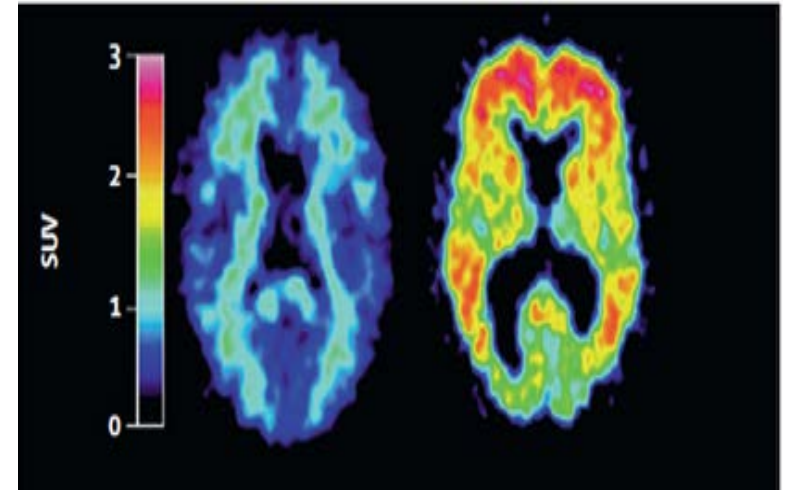
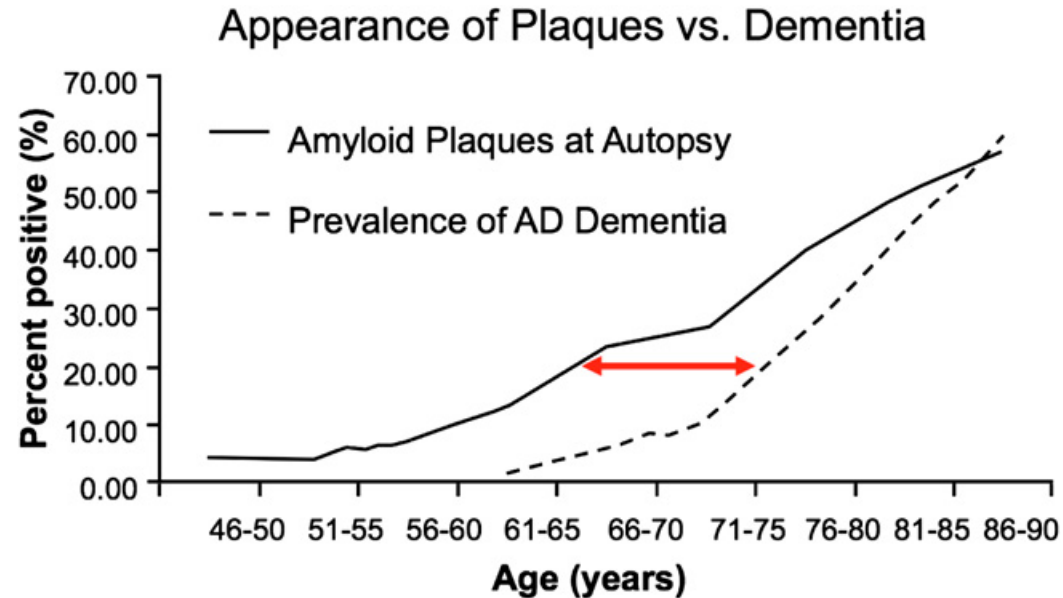
CDC/NCHS, National Vital Statistics System, *Mortality* 2013

CDC, NCHS. Underlying Cause of Death 1999-2013 on [CDC WONDER Online Database](https://wonder.cdc.gov/), released 2015. Data are from the Multiple Cause of Death Files, 1999-2013, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Accessed Feb. 3, 2015.

Traditional Underwriting Older Age Applicant

- Underwriting for the most common causes of death
 - Difficult to underwrite geriatric syndromes
 - Dementia, Frailty, Falls
- What are we missing?
 - **Ways to detect dementia**
 - **Alzheimer's research has developed methods to study the brain in vivo with imaging of amyloid plaques**
 - **Goal of research to detect asymptomatic, preclinical dementia and intervene early in disease**

10 year Lag Time: Amyloid to Dementia



Dementia: Early Recognition

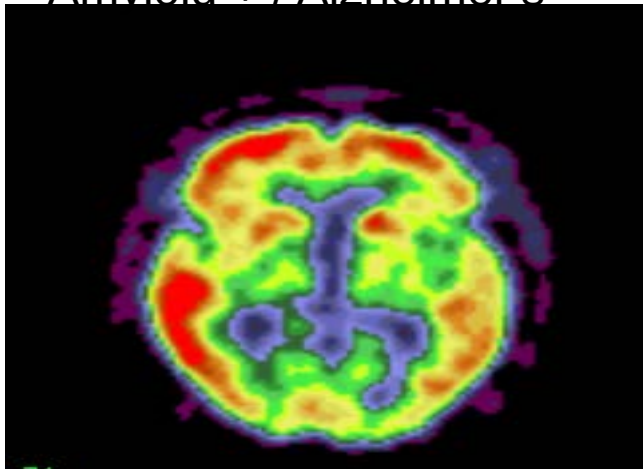
Name of the Game !

- Clinical medicine: biomarkers for AD
 - Adjunctive information to substantiate disease presence
- Lumbar puncture
 - A pattern of low Amyloid B42 and elevated phosphorylated tau
 - Phosphorylated tau is more specific
 - Distinguish AD from ALS, Parkinson's, Lewy body and Frontotemporal dementia
 - Commercially available from Athena Diagnostics
 - In one published prospective study of MCI:
 - Sensitivity 89% and Specificity 77%
 - Positive Predictive value 73% vs Negative Predictive value 91%
- Not ready for prime time – YET, but it's coming !

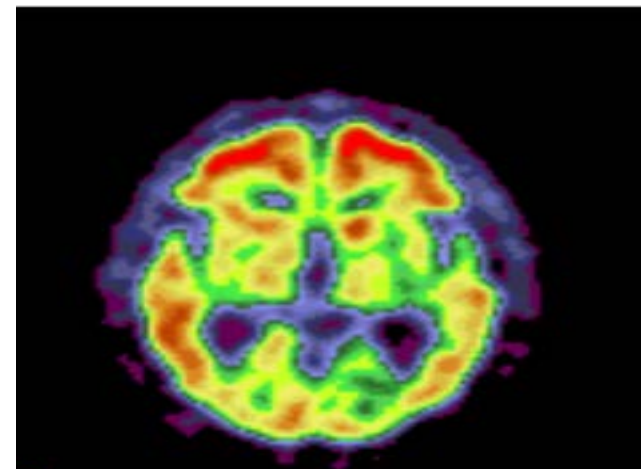
Advanced Imaging in Detection of Amyloid Plaque

- Florbetapir-F18 is an injectable radiopharmaceutical agent (Amyvid/ Eli Lilly) developed for PET use. It binds to amyloid plaque and thus can be used in the diagnosis of Alzheimer's Disease.
 - FDA approved for the evaluation of cognitive impairment (MCI)
 - Scan sensitivity was estimated at 92% and specificity at 95% in autopsy proven cases

Amyloid + / Alzheimer's



Amyloid+ / Normal



When Will Biomarkers and Amyloid Imaging Be Used?

Diagnostic Dilemmas : Not universal for a while

- Mild cognitive impairment with equivocal traditional testing
 - Mortality ratio for any degree of MCI ~ 200%
 - 5-10% risk for AD development
- Distinguishing dementia from depression
- Cognitive changes in a young individual
- Asymptomatic but high risk and highly motivated individuals
- Clinical trials

New insights into dementia

Sleep studies may be warranted in cognitive impairment ?

- Research found a correlate between indices of hypoxia in PSGs predict MCI in a cohort of elderly women
 - Oxygen desaturation index and percentage time in apnea or hypopnea associated with incident MCI
 - These measures may better quantify the sleep related gas exchange disturbances
 - Intermittent vs continuous hypoxia associated with greater cellular oxidative stress
 - Not only has sleep disordered breathing (SDB) been associated with MCI
 - Higher levels of beta- amyloid deposition in the brains of those with both MCI and SDB has also been shown in very small studies measured by PET-PiB

Anticholinergic Cognitive Burden Scale

- Tool for clinicians that identifies the severity of anticholinergic effects on cognition
 - Research has found that the low risk drugs are those with affinity for muscarinic receptors without cognitive impairment
 - High risk medications are those that readily cross the blood brain barrier and are associated with delirium
 - Possible anticholinergic activity (ACB=1)
 - Moderate anticholinergic activity (ACB=2)
 - Severe anticholinergic activity (ACB=3)

Anticholinergic Cognitive Burden Scale

- The definite anticholinergic medications have been linked to
 - Decline on performance on MMSE
 - Increased risk for MCI
 - Increase risk of mortality
 - Cause and effect correlation not established
 - May be that anticholinergic medications are commonly used in disease states with high morbidity and mortality
 - Further research to elucidate the relationship

Anticholinergic Burden Scale

Possible Anticholinergic Effects ACB score = 1	Definite Anticholinergic Effects ACB = 2	Definite Anticholinergic Effects score = 3
Alprazolam Atenolol Captopril Codeine Diazepam Digoxin Furosemide Prednisone Nifedipine Warfarin	Amantadine Belladonna Cyclobenzaprine Cyproheptadine Carbamazepine Loxapine Meperidine	Amitriptyline Brompheniramine Chlorpheniramine Clomipramine Clozapine Diphenhydramine Hydroxyzine Paroxetine Promethazine

Mobility models for the future

- “NIH investigators have identified several markers, including grip strength, gait (walking) speed, circulating levels of the protein IL-6, and measures of lung function, that can be used to predict the onset of limitations in mobility. Researchers are currently conducting a genome-wide association study to identify genes and genomic regions associated with trajectories of change in each of these markers.”

Methods to assess Falls

Primarily historical data

- Falls are a result of many factors
 - Difficult to assess the risk due to multifactorial nature
- Look at risk factors
 - Look at the medications, medications, medications
 - Polypharmacy data shows that risk increases with 4-5 or more medications/ regardless of type
 - Benzodiazepine use increases risk 44% (residents of nursing homes)
 - Psychoactive drugs, diuretics, Class 1A antiarrhythmics, digoxin
 - Prior fall?
 - Those with impaired gait/ balance high risk for falling

Fall Risk Assessment

- Walking speed – indicator for mobility
 - If impaired predicts future dependence
- Hand grip strength – indicator for overall muscle strength
 - Predicts future disability independent of chronic disease
- TUG – indicator for lower extremity strength and balance
 - Predicts falls

Grip Strength Test

Another tool for risk assessment?

- Hand dynamometers measure hand grip force
 - Provides information about lean muscle mass
 - Marker for frailty, sarcopenia, and nutritional well being
 - Predictive of other conditions: Bone mineral density in postmenopausal women
 - Increased cardiovascular and cancer mortality

Mean and Std deviation and Hand Grip Strength in kilograms

Men 70+	Right 33(7.8)	Left 32(7.5)	BMI 27.2(3.9)	Women 70+	Right 20(5.8)	Left 19(5.5)	BMI 27(4.7)
------------	------------------	-----------------	------------------	--------------	------------------	-----------------	----------------

Kärkkäinen M, Rikkinen T, Kröger H, Sirola J, Tuppurainen M, Salovaara K, Arokoski J, Jurvelin J, Honkanen R, Alhava E: Physical tests for patient selection for bone mineral density measurements in postmenopausal women. Bone. 2009, 44 (4): 660-665.

Gale CR, Martyn CN, Cooper C, Sayer AA: Grip strength, body composition, and mortality. Int J Epidemiol. 2007, 36 (1): 228-35. 10.1093/ije/dyl224.

Frailty

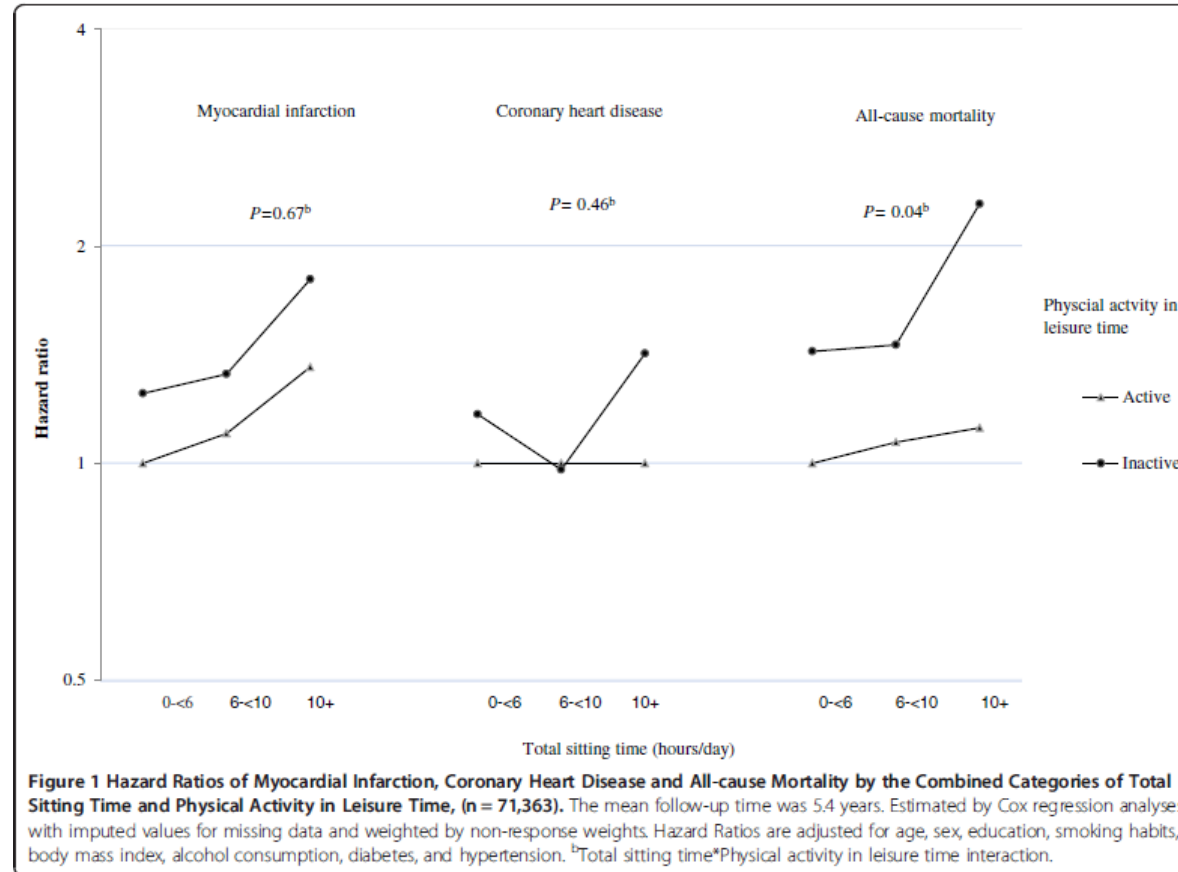
- Not limited to those with low BMI
 - Sarcopenic obesity
 - Muscle mass loss with poor protein intake
 - Muscular atrophy due to inactivity
- Best serum marker is prealbumin
 - Specific marker for protein synthesis
 - Less influenced by liver synthesis
 - Insurance lab: cholesterol and albumin

Immune Risk Phenotype

- Biomarkers that suggest poor immune function INCREASE risk for mortality
 - Multiple inflammatory markers have been studied
 - CRP, IL-6, TNF, WBC
- Gene polymorphisms located within the promoter regions for production of proinflammatory cytokines have shown different susceptibilities to diseases
 - Successful aging subjects attenuate the inflammatory response better than those who do not age as successfully
 - $CD4/CD8 < 1$
 - Low levels of B cells
 - Increased HsCRP
 - Increased both IL-6 and TNF

Sitting is the new smoking

Sitting > 10 hrs/day 2X all cause mortality



Obesity

- “The full long-run consequences of increased obesity rates at the aggregate level are probably not yet visible, but there are enough warning signs to suggest that past trends showing better health among the elderly may be ending—unless other societal changes or medical advances can compensate for the effects of unhealthy weight gain.”



Exercise Reduces Risk of Cardiovascular Mortality

- Prospective follow up analyses, stronger predictor of mortality than traditional risk factors
- Response to exercise training, specifically aerobic capacity is variable and ranges from 0% to 100%
 - Some individuals do not improve aerobic capacity despite intense aerobic training
 - The estimated heritability for gains in cardiorespiratory fitness ~ 50% with training
- Active individuals live longer 6.2 years in men and 5.6 years in women
 - Jogging 1 - 2.4 h per week lowest mortality with multivariable hazard ratio of 0.29 compared to sedentary

Response to Exercise and Improved Aerobic Capacity Genetically Linked

11 gene SNPs explained 23% of the variance in gains in fitness (VO2max) *

- Theorized that aerobic capacity is the factor that can be manipulated to prevent cardiovascular disease
- Forecast gains in aerobic capacity using a “peripheral gene signature”
 - Research found that ~ 20% of the subjects studied did not improve aerobic capacity with intense endurance training / high intensity interval training
 - Research also found that ~ 30% did not enhance their insulin sensitivity
 - Concludes that genetic information can tailor lifestyle modifications
 - Promote alternative exercise intervention programs
 - Targeted therapies : intense pharmacologic and dietary protocols to overcome genetic predisposition

Risk Factor Modification for Dementia

Does it decrease prevalence rate?

Triple the number of AD cases in the next 40 years

- Yes it does !
 - Up to 50% of AD cases attributable to modifiable risk factors
- Diabetes : Randomized control trials reviewed
 - RR for dementia in those with diabetes is 1.39 and up to 1.50 RR for all dementias
 - Possible mechanisms:
 - Hyperinsulinemia may inhibit brain insulin production
 - Impaired amyloid metabolism and clearance

Risk Factor Modification for Dementia

Does it make a difference?

- Depression : RR 1.91 for development of dementia
 - Life time presence of depression
 - Anticholinergic medications can worsen cognitive function
- Physical Inactivity RR 1.82 for development of dementia
 - Highest levels of inactivity in women, that are older, living in urban areas
 - 2009 rates of inactivity in US
 - 32.5% of adults over age 18 inactive : mirrors the obesity figures
 - 32.5% have some leisure time activity
 - 34.9% regularly active

Risk Factor Modification for Dementia

Does it Make a Difference?

- Hypertension : RR 1.61 for dementia
 - The association between HTN and dementia is complex
 - Age and BP control related; although, not a consistent finding
 - Older age onset of htn no association
 - Hypotension is linked to the development of dementia particularly in individuals with treated htn
- Obesity : RR 1.60 for dementia
 - BMI ≥ 30 kg/m²
 - Midlife development of obesity portends risk

Risk Factor Modification for Dementia

Does it decrease prevalence rate?

- Smoking : RR for dementia is 1.59
- Prevalence rate of smoking in the USA as of 2009 20.6% adults
 - Former smoking does not appear to increase the risk
 - Contributes to vascular disease
 - Neurotoxins in smoke, oxidative stress, and inflammatory processes

Precision Medicine

 [BRIEFING ROOM](#) [ISSUES](#) [THE ADMINISTRATION](#) [PARTICIPATE](#) [1600 PENN](#)

THE PRECISION MEDICINE INITIATIVE



[PRECISION MEDICINE](#) [INITIATIVE](#) [PRINCIPLES](#) [STORIES](#) [f](#) [t](#) [GO TO TOP](#)

“Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type — that was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?”

- President Obama, January 30, 2015

Precision Medicine

Future landscape of medicine – Heavy influence on genetic information

- Personalized medical care based on genomics
 - Consideration of lifestyle and environment
 - Genetic profiling to guide medical therapy: 1 million Americans enrolled
 - Initiative to accelerate research in the area of cancer treatment short term and then range of health and disease in the long term
 - More accurate risk stratification optimizing preventative strategies and patient care
- Targeted therapies: Give the right drug, at correct dose, to achieve specific targets
 - Pharmacogenomics

Pharmacogenomics Drug Labels

PharmGKB annotates drug labels containing pharmacogenetic information approved by the [US Food and Drug Administration](#) (FDA), [European Medicines Agency](#) (EMA), the [Pharmaceuticals and Medical Devices Agency, Japan](#) (PMDA), and [Health Canada \(Santé Canada\)](#) (HCSC). PharmGKB annotations provide a brief summary of the PGx in the label, an excerpt from the label and a downloadable highlighted label PDF file. A list of genes and phenotypes found within the label is mapped to label section headers and listed at the end of each annotation. PharmGKB also attempts to interpret the level of action implied in each label with the "PGx Level" tag.

See the [legend](#) for more information about drug label sources and PGx Levels.

We welcome any information regarding drug labels containing PGx information approved by the FDA, EMA, PMDA, HCSC or other Medicine Agencies around the world - please contact [feedback](#).

[view legend](#)

☐ **B** Only Biomarker labels

Search:

Drug	FDA	EMA	PMDA	HCSC
abacavir	B Genetic testing required	Genetic testing required	Informative PGx	Genetic testing required
abiraterone	Informative PGx			
acetaminophen	B Actionable PGx			Actionable PGx
aliskiren		Informative PGx		
amitriptyline	B Actionable PGx			
anastrozole	B Genetic testing required			Genetic testing required
arformoterol	B Informative PGx			
aripiprazole	B Actionable PGx	Actionable PGx		Actionable PGx
arsenic trioxide	B Genetic testing required	Genetic testing required	Genetic testing required	Genetic testing required
atazanavir		Genetic testing recommended		
atomoxetine	B Actionable PGx		Actionable PGx	Actionable PGx
atorvastatin	Actionable PGx		Actionable PGx	Actionable PGx
axitinib		Informative PGx		
azathioprine	B Genetic testing recommended		Actionable PGx	Actionable PGx
belimumab	Informative PGx	Informative PGx		
belinostat	Actionable PGx			
boceprevir	B Informative PGx	Informative PGx		Informative PGx
bosutinib	B Genetic testing required	Genetic testing required		Genetic testing required
brentuximab vedotin	Informative PGx	Genetic testing required		

- 13 of 45 New drugs
 - FDA approved in 2015
 - Personalized medicines

Coumadin Dosing based on Cytochrome P-450 System

Required Patient Information

Indication: Atrial fibrillation

Liver Disease: Yes

Smokes: No

CYP2C9 Genotype: CYP2C9*3/*3

Slow metabolizer and Warfarin sensitive

VKORC1-1639/3673 Genotype: AA

Statin/HMG CoA Reductase Inhibitor: Pravastatin/Pravachol®

INR3: 1.5

AM

Target INR: 2.5

Dose 1 estimated: 2.6 mg/day

Dose 2 estimated: 1.2 mg/day

Dose 3 estimated: 1.2 mg/day

Warfarin

mg

Dose 1 actual:

3

PM

Dose 2 actual:

3

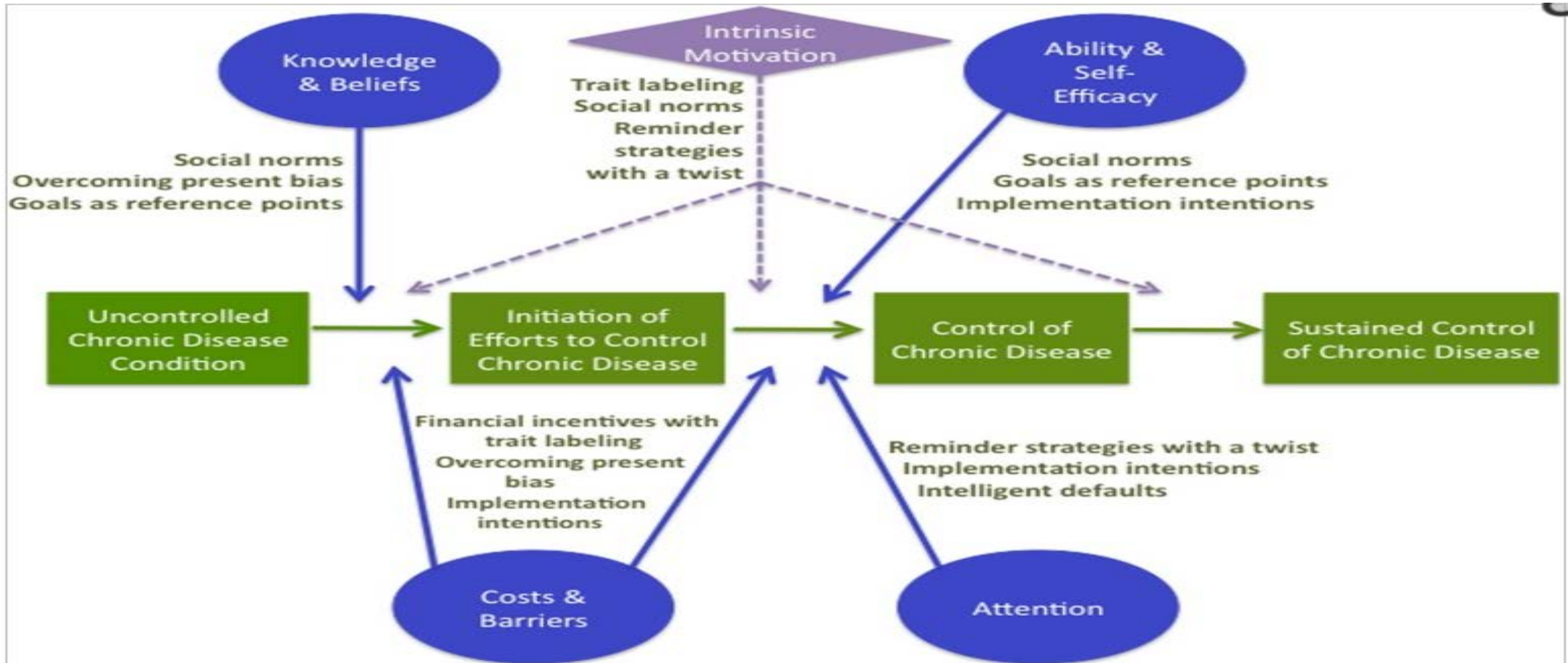
PM

Dose 3 actual:

3

PM

People and Their Choices are Complex!



Intervention Study

- Using apoE genotyping as a tool to promote lifestyle changes
 - Used apoE genotype because has impact on lipid metabolism and cholesterol absorption in CV disease
 - One year study – divided the subjects into 3 groups
 - High risk E4 + (n= 16)
 - Low risk E4 - (n=35)
 - Control Group
- Results:
 - Dietary fat quality improved more in the E4+ group than E4 – group **BUT ONLY FOR A SHORT TIME !!!!**

New Ways to Improve Compliance

Hovering

- What form can the hovering take?
 - Wellness programs
 - Medication adherence reminders
 - Home-based biometrics (longitudinal clinical care), wearable technology, mobile phones, other wireless devices
 - Telemonitoring or mentoring

What Form Will Hovering Take?

Methods to track performance, adherence remotely



Automated Hovering – The Evidence

Diabetes compliance improvement with hovering

■ Results:

- HbA_{1c} after 6 months
 - Control group ~ 9.9% to 9.8%
 - Peer mentor group ~ 9.8% to 8.7%
-
- Mean change in HbA_{1c} level from baseline to 6 months relative to control
 - Peer mentor group –1.07% (95% CI, –1.84% to –0.31%)

Summary

- Detection of geriatric syndromes in underwriting is difficult
 - Dementia, Frailty, Falls all associated with substantial mortality risk but no good way to identify
 - New biomarkers for AD and immunity may help recognize high risk individuals
 - Falls linked to gait and weakness
 - Research ongoing to determine new ways to detect problems in mobility
- Inactivity and smoking are important modifiable risk factors in diseases of the elderly
- Function is one of the most important markers for mortality in this cohort
 - Cognitive and physical function should be evaluated with objective measures
 - New imaging technics and biomarkers may help to detect disease before there are symptoms

Summary

- Anticholinergic medication associated with the development of cognitive impairment, delirium, and death
 - Scoring tool helps clinicians determine proper combination of medications
- Precision medicine will individualize health care
 - Elderly will receive better care because
 - Less drug interactions and side effects – more targeted therapy
 - Lifestyle, nutrition, exercise will be major factors for precision medicine prescriptions
- Hovering is a sophisticated method of watching or monitoring behavior based on medication compliance, lab data
 - Better compliance translates to better outcomes

RGIA