The Product Development Section Presents

Underwriting Issues & Innovation Seminar
August 1-2, 2016 | Chicago Marriott O’Hare | Chicago, IL

Medical Topics

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Presenters:
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Mortality trends with Alzheimer's disease

Dr. Brian Ivanovic
Agenda

Alzheimer’s disease (AD) overview
• MCI vs. AD
• Making a diagnosis
• Genetics of AD
• Current treatment efficacy

Mortality considerations
• Survival, relative mortality and life expectancy
• AD as an increasingly important cause of morbidity and mortality in the elderly

Treatments in development
• Success rate of drug trials over the past 15 years
• Moving towards disease modifying therapies for AD

Summary
AD Overview
MCI vs. AD

MCI: an intermediate stage moving from normal cognition to dementia.

• present in 16-20% of individuals over age 60
• it can lead to AD or other types of dementia
• diagnosed when there is evidence of cognitive decline not causing a loss of independent functioning
• associated with a ~10-15% pa progression to dementia

Roberts et al., Clin Geriatr Med. 2013 November; 29(4)
AD medical history findings

History consistent with progressive cognitive decline that is corroborated thru objective cognitive assessment.

• cognitive impairment needs to include at least 2 of the following
  – impaired acquisition of new information
  – impaired reasoning
  – inability to recognize objects/faces
  – impaired language
  – changes in personality/behavior

Medical evaluation should also include testing to rule out potentially reversible causes of cognitive dysfunction (hypothyroidism, vit D deficiency) and other conditions that may have overlapping symptoms with dementia (like depression, hydrocephalus, hematoma, tumor).

McKhan et al, Alzheimer’s Dement. 2011 May ; 7(3): 263–269
Dementia screening

Screening instruments

- commonly used in physicians office: Mini-Cog or Mini-Mental State Examination (MMSE)
- commonly used by insurers\(^1\)
  Delayed word recall
  Clock-Drawing Test
- a combination of the delayed word recall and clock drawing has greater sensitivity than the individual tests

<table>
<thead>
<tr>
<th>Dementia screens(^2)</th>
<th>Cutoff</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Test times</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini-Cog (3 item word memory + clock)</td>
<td>&lt;3</td>
<td>76%</td>
<td>89%</td>
<td>2-4 min</td>
</tr>
<tr>
<td>3-Item Recall</td>
<td></td>
<td>54%</td>
<td>96%</td>
<td>2 min</td>
</tr>
<tr>
<td>Clock Drawing</td>
<td></td>
<td>59%</td>
<td>90%</td>
<td>1-2 min</td>
</tr>
<tr>
<td>MMSE</td>
<td>23/24</td>
<td>71%</td>
<td>94%</td>
<td>5-12 min</td>
</tr>
<tr>
<td></td>
<td>24/25</td>
<td>79%</td>
<td>88%</td>
<td>5-12 min</td>
</tr>
<tr>
<td>Standard neuropsych battery</td>
<td></td>
<td>75%</td>
<td>90%</td>
<td>&gt;30 min</td>
</tr>
</tbody>
</table>

1. Report on the Survey of Older Age Mortality and other Assumptions, SOA 2013
Fluid tests for dementia

CSF
• spinal fluid assays for tau protein

Blood
• mitogen-activated protein kinase (MAPK)\(^1\)
  MAPKAPK5 protein found to be lower in the blood of individuals who had cognitive decline over the next 10 years in twin studies
• IRS-1 blood protein which has a role in insulin signaling in the brain\(^2\)
  those with AD appear to have higher amounts of an inactive form of IRS-1 and lower amounts of the active form compared to non AD individuals
• microRNA’s\(^2\)
  those with AD appear to have differences in 3 microRNA’s compared to non AD individuals

1. Kiddle et al., Transl Psych 2015 (5)
2. www.alzheimers.net
AD imaging

MRI

• the hippocampus is a region of the brain involved in learning and memory and is one of the first areas affected by AD

• hippocampal volume loss is associated with worsening scores on cognitive assessments

• structural MRI’s can be used for one time quantification of hippocampal volume or serial quantification of volume loss
AD imaging

Tests for β-amyloid deposition in the brain using positron emission tomography (PET) scans

- Pittsburgh Compound B (PIB) is a radiolabeled compound that binds to β-amyloid
- People with AD who have more β-amyloid in their brains take up more PIB compared to cognitively healthy older people
- PET scans can be used to initially establish the level of β-amyloid found in the brain and correlate changes in cognitive decline with subset changes on PET scans

AD imaging

Tests for neuronal degeneration

• fluorodeoxyglucose (FDG) is a radiolabeled compound that can detect regional glucose metabolism at the cellular level
  – used in the brain with PET imaging FDG uptake is a marker of reduced neuronal activity.
  – AD patients show imaging deficits in particular areas of the brain

AD genetics

Early onset AD (<5% of total AD patients)

- occurs in people age 30-60

- caused by a number of different single gene mutations on chromosomes 1, 14 and 21 leading to abnormal proteins (amyloid and presenilin) to be formed

- those abnormal proteins play a role in the breakdown of another protein called APP which results in amyloid plaque formation

Other genetically mediated AD: genome wide association studies

- next generation genetic sequencing (NGS) allows for study of the entire human genome

- as of 2015 researchers had identified about 33 regions of interest in the human genome that might increase a persons risk of AD to some degree

AD genetics

APOE and AD

• A gene on chromosome 19 codes for apolipoprotein E (ApoE)

• 3 types (alleles) epsilon2, 3 and 4 (E2, E3, E4)

• An individual's genotype is made up of 2 alleles leading to 6 possible combos E2/E2, E2/E3, E2/E4, E3/E3, E3/E4, and E4/4

• E2 is associated with better clearance of beta-amyloid and reduced risk of AD

• E4 is associated with increased risk of AD and found in about 20% of the population (Risk in women > than in men)

Only 40% of individuals with AD have one or two E4 alleles, indicating that the presence of E4 is not required for AD to develop.

Relative risk of AD depending on APOE genotype

http://alzdiscovery.org
AD treatment options

Current treatments do not cure AD or materially alter its progression.

- Cholinesterase inhibitors: potentiate acetylcholine synaptic transmission. Donepezil (Aricept) is in this treatment category. Others in this category included rivastigimne (Exelon), galantamine (Razadyne) and tacrine (Cognex) which was discontinued in the US in 2013.

- N-methy-D-aspartate (NMDA) glutamate receptor blockers. In AD excess glutamate can be released from damaged cells, leading to overexposure to calcium furthering cell damage. This drug helps slow this process. Menantine (Namenda) is in this treatment category.

- Therapies aimed at behavioral and psychiatric symptoms (agitation, mood disorders, psychosis). Antidepressants, antipsychotics and other drugs are in this treatment category.

- Therapies aimed at control of cardiovascular risk factors in case vascular dementia is a contributing factor.

Menchola, et al., J of Fam Practice 2015 64:1
Mortality considerations
Treatment effects on excess mortality associated with AD

Two studies of individuals age 75+ with dementia separated in time by approximately 12 years.

A majority of dementia cases are AD so we can assume increased pharmalogic treatment for AD is likely in the latter cohort.

Absolute 5yr survival measures slightly higher for the latter dementia group, however when survival compared to timeframe matched groups with no dementia the relative hazard of mortality due to dementia was basically the same.

KP=Kungsholmen Project: (n=1700, age 75+
SNAC-K = Swedish National study on Aging and care in Kungsholmen (n=1575, age 75+

Mortality HR (relative to timeframe matched groups with no dementia)

<p>| | |</p>
<table>
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<tbody>
<tr>
<td>KP</td>
<td>2.42 (2.03-2.87)</td>
</tr>
<tr>
<td>SNAC-K</td>
<td>2.47 (2.03-3)</td>
</tr>
</tbody>
</table>

Qiu C et. al., Neurology 2013;80:1888–94
Compared to cohorts without dementia, mortality is elevated 2 to 3 fold in those with AD. In terms of differences in the observed hazard of mortality the studies shown have differences in cohorts followed (incident only vs. prevalent + incident) length of follow-up, and represent studies published over the last 15 years.
Life expectancy differentials

The 75<sup>th</sup> to 25<sup>th</sup> interquartile range of life expectancy (LE) after diagnosis with AD compared to LE in the US pop. The horizontal marker represents the 50<sup>th</sup> percentile of LE.

AD lowers LE, with the largest absolute differences observed at younger ages.

At older ages AD is the 5th leading cause of death.

Given the current trajectory of declines in cerebrovascular disease death rates AD may become the 4th leading cause of death in older age groups in the near future.

By age band AD represents at least 1% of the overall death rate at ages 65-74, 3.7% at ages 75-84 and 6.8% at ages 85+.
Potential future AD burden

The aging population has an ongoing risk for development of AD

- larger numbers of individuals living to older age means more individuals developing dementias including AD

- Weuve et al estimated 600,000 individuals with AD dying in 2010 based on incidence and mortality information from the Chicago Health and Aging project (CHAP). Wevue emphasizes that: "our estimates are counts of deaths among people with AD rather than counts of deaths pathogenically attributed to AD"

- extrapolating to the year 2050 1.6 million individuals who die will have developed AD representing 43% of all older adult deaths

Weuve J, et al 2014
AD treatments in development
Why only 5 drugs currently?

The high cost of drug development and high failure rate has driven many larger pharmaceutical companies to close parts of their own neuroscience research areas, increasing collaborative work and investments with academics and small biotech companies.

If promising drug candidates in downstream development phases emerge those biotech companies can be purchased by mergers & acquisitions.

- 413 AD trials between 2002 to 2012
  - 36% investigated drugs that were hoped to improve cognition
  - 53% investigated agents that were hoped to be disease modifying
    - small molecules
    - immunotherapies

- Overall success rate 0.4% (>99% failure rate)
Monoclonal antibody treatment of β amyloid plaques:

Solanezumab

• in a subgroup analysis of pts with **mild AD** a slower rate of cognitive decline compared to the control group with mild AD was noted. Results from a Phase III trial of 2100 pts with mild AD and confirmed brain amyloid begun in 2013 and will run thru October of 2016

Aducanumab

• phase 1b trial results (n=160) demonstrated a dose response reduction in amyloid plaque via PET scan at 26 and 52 weeks. Treatment was also associated with a slower rate of cognitive decline

• two Phase III trials are enrolling patients currently (n=2700) with these studies running thru 2022 at a cost of $1 billion

Sevigny J et al., Neurodegenerative Diseases, March 2015
Cummings et al., Alzheimer’s Research 6:37 2014
Metabolic enhancement for neurodegeneration:

- reversal of memory loss was achieved in a small (n=10) trial of patients using a complex 36 point personalized program involving changes in diet, brain stimulation, exercise, sleep patterns, pharmaceuticals, vitamins and multiple additional steps that can affect brain chemistry

- “Patients who had discontinued work were able to return to work and those struggling at work were able to improve their performance” MRI evidence confirmed a reversal of hippocampal volume loss in one 66yo male who had been diagnosed with MCI

- none of the pts in the series met criteria for MCI or AD post treatment

- discontinuation of the protocol (n=1) resulted in regression
Prions as the putative cause of neurodegenerative diseases including AD

• prions are pathogenic agents that can induce abnormal folding of proteins
  - Creutzfeldt-Jakob Disease, Kuru and Fatal Familial Insomnia are examples of prion neurologic diseases in humans

• under this theory propagating, mis-folded (Amyloid & Tau) proteins are felt to be cause of AD
  - therapies would be designed to target these specific propagating strains
  - ~5-10 years out from clinical trials
Neural stem cell (NSC) based therapies

- multipotent NSC can differentiate into a variety of cell types, including neurons, and astrocytes and may be useful for cell replacement therapy
  - animal model research: mice
    - transplanted NSC’s differentiate into mature cell types within the brain and improve learning and memory
    - transplanted NSC’s have also been used as a vehicle to deliver therapeutic agents to decrease β-amyloid levels (fibroblast delivered neprilysin)

- donor cell rejection
  - donor cells will have to be human leukocyte antigen haplotype matched and recipients will require some level of immunosuppression to prevent rejection of transplanted cells

- human studies
  - clinical trials will take years to demonstrate success for cell therapies in halting or reversing disease progression
Summary
Alzheimer’s disease

Burden of disease implications
• based on age specific incidence rates and with increased numbers of people living to advanced age as many as 40% of older adults could develop AD

Diagnosis
• currently via med history + neuropsych testing and imaging
• research on a dementia/AD blood test continues

Treatments
• current treatments do not halt or reverse damage to the brain
• as progress is made on new treatments the likely impact will be for individuals to survive longer

COD implications
• with continued declines in older age cardiovascular and cerebrovascular disease death rates Alzheimer’s disease is likely to become the 4th leading cause of death in those age 65+

Combined with increased numbers developing AD this has negative implications on LTC costs
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The Longer Life Foundation and Precision Medicine

Dr. Philip Smalley MD FRCPC

Managing Director of the Longer Life Foundation and Senior Vice President and Global Chief Medical Officer RGA International

Underwriting Issues and Innovation Seminar

August 2nd 2016
Agenda

- Insurance sponsored research Foundations
- What is the Longer Life Foundation?
- Benefits of Foundations to the Insurance Industry
- Funded research including Precision Medicine
- Possible use of Precision Medicine in the insurance industry
# Insurance Company Foundations / Partnerships

<table>
<thead>
<tr>
<th>Foundation Name/Partnership</th>
<th>URL</th>
<th>Backing Insurance Company</th>
<th>Partners</th>
</tr>
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<tbody>
<tr>
<td>AXA Research Fund</td>
<td><a href="https://www.axa-research.org/">https://www.axa-research.org/</a></td>
<td>AXA</td>
<td>None</td>
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<td>Swiss Re Foundation</td>
<td><a href="http://www.swissrefoundation.org/">http://www.swissrefoundation.org/</a></td>
<td>Swiss Re</td>
<td>Medical Network EMN, Institute of Palliative Medicine, Alzheimer’s Society, Ashoka, Harvard School of Public Health, Swiss Innovation Park, University of Zurich</td>
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<tr>
<td>Longer Life Foundation: A RGA / Washington University Partnership</td>
<td><a href="http://www.longerlife.org">www.longerlife.org</a></td>
<td>RGA</td>
<td>Washington University, St. Louis</td>
</tr>
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For more information, visit the respective websites provided in the table.
The Longer Life Foundation is...

A partnership

Mission:
- Improve quantity and quality of life
- Enhance accuracy of disease prognostication
Benefits of the Foundation

- Improve morbidity and mortality
- Find new ways to assess risk
- Access to network of world-class academics / CMO webcasts
- Sponsorship of events and lectures
- Enhanced public awareness
- Good public relations
Successes / Results

- 92 research grants 1998 - 2016
- Longevity Research Program for 8 years
  - Caloric Restriction anti-aging research and identifying novel biomarkers of longevity
- Longer Life Center
  - Cultivates research along the LLF mission
  - Leads to larger studies
    - $4.4M into > 10 times the amount funded
- 109 publications in peer-reviewed journals
Scope of Investigations

- Ageing
- Alzheimer’s Disease
- Cancer
- Cardiovascular disease
- Biomarkers and genomics

- Obesity
- Diabetes
- Comorbidity
- Infection risk
What is Precision Medicine?

Individualized / Personalized medical care based on patient’s (or the tumour’s) genetics factoring in lifestyle and environment

Leading to:

- More accurate risk stratification optimizing preventative strategies and patient care
- Targeted therapies: Give the right drug, at correct dose, aimed at specific targets
  - 91% cancers/patients have actionable mutations and 10% treatment was altered*

Use of Genetics

- Pharmacogenomics
- Targeted therapies
- Diagnosis  Wang (Cervix Ca)
- Prognosticating known disease  Oh (PVR), Shao (Breast Ca)
- Predictive risk stratification  Boon (Flu), Schaffer (DM Comp)
- Family planning
- CRISPR gene editing?
Doctors are the Third Leading Cause of Death in the U.S.*

<table>
<thead>
<tr>
<th>Deaths per Year**</th>
<th>Cause</th>
</tr>
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<tbody>
<tr>
<td>106,000</td>
<td>Non-error, negative effects of drugs (~17% of hospitalized patients have adverse drug reaction)</td>
</tr>
<tr>
<td>80,000</td>
<td>Infections in hospitals</td>
</tr>
<tr>
<td>20,000</td>
<td>Other errors in hospitals</td>
</tr>
<tr>
<td>12,000</td>
<td>Unnecessary surgery</td>
</tr>
<tr>
<td>7,000</td>
<td>Medication errors in hospitals</td>
</tr>
<tr>
<td>225,000</td>
<td>Total deaths per year from iatrogenic causes</td>
</tr>
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Pharmacogenomics

- Correct type of drug
- Correct dose
- Avoid side effects

https://www.pharmgkb.org/view/drug-labels.do
http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm
Important and growing field.....

- Out of 1200 medications approved by the FDA for use in the US
  - 7% were affected by actionable pharmacogenes

- Out of 4 billion prescriptions in the US
  - 18% were affected by actionable pharmacogenes

- 13 of 45 new drugs approved by FDA in 2015 were ‘personalized medicines’ with gene – drug interaction

Relling MV et al, Nature Oct 2015;526:343

<table>
<thead>
<tr>
<th>Genetic variation</th>
<th>Medications</th>
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<tbody>
<tr>
<td>TPMT</td>
<td>Mercaptopurine, thioguanine, azathioprine</td>
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<tr>
<td>CYP2D6</td>
<td>Codeine, tramadol, tricyclic antidepressants</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Tricyclic antidepressants, clopidogrel, voriconazole</td>
</tr>
<tr>
<td>VKORC1</td>
<td>Warfarin</td>
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<tr>
<td>CYP2C9</td>
<td>Warfarin, phenytoin</td>
</tr>
<tr>
<td>HLA-B</td>
<td>Allopurinol, carbamazepine, abacavir, phenytoin</td>
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<tr>
<td>CFTR</td>
<td>Ivacaftor</td>
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<tr>
<td>DYPD</td>
<td>Fluorouracil, capecitabine, tegafur,</td>
</tr>
<tr>
<td>G6PD</td>
<td>Rasburicase</td>
</tr>
<tr>
<td>UGT1A1</td>
<td>Irinotecan, atazanavir</td>
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<tr>
<td>SLCO1B1</td>
<td>Simvastatin</td>
</tr>
<tr>
<td>IFNL3 (IL28B)</td>
<td>Interferon</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>Tacrolimus</td>
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Abacavir Hypersensitivity

- Abacavir (Ziagen) is an HIV anti-retroviral medication
- 5% - 8% patients get life threatening hypersensitivity reaction
- Associated with major histocompatibility complex class I allele HLA-B*5701
- FDA black box warning stated “Prior to initiating therapy with abacavir, screening for the HLA-B*5701 allele is recommended.”
- Abacavir is contraindicated if HLA-B*5701 positive

Ma JD et al, PLoS Curr. 2010 Dec 7;2:RRN1203
Azathioprine (Imuran) Myelotoxicity

- Immunosuppressant drug
- Enzyme thiopurine methyltransferase (TPMT) inactivates Imuran’s active metabolite 6-mercaptopurine
- 11% of the population has reduced TPMT activity and 0.3% of the population has true deficiency of TPMT
- FDA-approved drug label recommends testing for TPMT genotype or phenotype but still need to follow CBC
- Use lower dose or different drug depending on TPMT testing
Genetic Mutations and Pro-drugs

- **Codeine Sensitivity**
  - CYP2D6 metabolizes codeine to morphine
  - Ultra-rapid metabolizers (1% - 2% of patients and 28% of North Africans, Ethiopians, and Arabs; up to 10% in Caucasians; 3% in African Americans, and up to 1% in Hispanics, Chinese, and Japanese)
    - Avoid Codeine to avoid overdose side effects
  - Extensive metabolizers (77% - 92% of patients)
  - Intermediate metabolizers (2% - 11%, Asians > Caucasians)
  - Poor Metabolizers (5% - 10%, EU Caucasians mostly)
    - Use alternative to Codeine as poor response expected

- **Clopidogrel, Tamoxiflen, Galantamine, etc.**

Very slow metabolizer

Warfarin sensitive

0.8% - 10.6% get major bleed in 1st year

Meta-analysis of 11 trials, 2,678 patients:
• 64% less major bleeding
• 14% less adverse events

Gage BF et al, Clin Pharmacol Ther. 2008 Sep;84(3):326-31
Anthracycline-induced Cardiotoxicity

- Commonly used cancer drug (Daunorubicin, Doxorubicin, Epirubicin, etc)
- Sub-clinical cardiotoxicity ~50% of patients, weeks to >10 years after treatment and 5%-16% get clinical heart failure
- Depends on dose (>300 mg/m²) but highly variable
- Genetic predictors
  - Retinoic Acid Receptor Gamma (RARG) variant rs2229774 (Odds ratio = 5.2)
    - Carrier prevalence South Asian 22%, African 11%, European 6%, Hispanic 5%
  - UDP glucuronosyltransferase variant rs17863783 (Odds ratio = 8.0)
  - SLC28A3) variant rs7853758 is protective (Odds ratio = 0.5)
  - Pharmacogenomic Risk Prediction Tool outputs risk range of 14% to 89%
Targeted Therapies – Chronic Myeloid Leukemia (CML)

- Gleevec (imatinib) (FDA 2001)
  - BCR-ABL tyrosine kinase inhibitor (TKI)
  - Only the cancer cells die
  - CML annual mortality now < 2% per year (was 20% – 25% per year)
  - Costs USD $106,322 per year

- Second generation TKIs (dasatinib, nilotinib)
Late Stage Melanoma Treatment (2011)

- FDA approved vemurafenib (Zelboraf) only if BRAF V600E mutation is present
- About 60% of melanomas have this BRAF mutation
- Median overall survival:
  - 13.6 months [95% CI 12.0–15.2] vemurafenib (Zelboraf) at $10,000 per month vs
  - 9.7 months [7.9–12.8] for dacarbazine at $750 per month

Targeted Cystic Fibrosis Therapies

- Many different mutations
- Leads to lung failure and pancreatic dysfunction, median survival is ~ 40 years
- Treated conservatively with antibiotics and chest physio
- 2 new drugs approved depending on genetic test result
  - Ivacaftor (Kalydeco) (2012)
    - Targeted to G551D mutation (~4.5% of patients)
  - Combination Ivacaftor with Lumacaftor (Orkambi) (2015)
    - Targeted to F508 del mutation (85-90% of patients)
  - 10.6% increase in FEV1, decrease risk of lung exacerbations, improves weight gain
  - Cost USD $250,000+ per year

Quon BS et al, BMJ 2016;352:i859
Insurance Use of Precision Medicine

- Genetic testing is being used:
  - Employee group benefits
  - Wellness Programs?

- Other possible uses of Precision Medicine?
  - Decrease claims?
  - Sales tool to attract healthier applicants and decrease lapses?
  - Dynamically underwritten product / impaired life product
    - Can this new technology change behaviour long term? *
    - Mortality credit?

* Hollands GJ et al, BMJ. 2016 Mar 15;352:i1102
Summary

- Insurance company sponsored research Foundations play important role in public health
- Precision medicine is already being used and growing fast
- One size does not fit all!
- Improves disease outcomes and decreases drug side effects
- Leading to more accurate prognostication
- Cautious optimism for possible uses in insurance but needs a combined multi-disciplinary approach and more research
Thank you !!

psmalley@rgare.com