Update in Internal Medicine for the *Outpatientalist*: 2015

George D. Comerci, Jr., MD, FACP
Professor of Internal Medicine
Division of General Internal Medicine
Project ECHO Pain and Headache Clinic
Pain Consultation and Treatment Center
Disclosures

I have no disclosures to report
Objectives

- Precision Medicine
- Cholesterol: new treatments
- *Borrelia miyamotoi*: a new tick-borne illness
- Prevention of Stroke in Afib with Device therapy
- Prevention of Alzheimer's Disease
- New Drugs/New Uses for old drugs
Case 1: Mr. JH

JH is a 40 y/o man with complex regional pain syndrome (CRPS 1) due to a GSW to his left upper thigh. He is on a complex regimen of neuropathic pain medications, has a spinal cord stimulator and is one 300 MME of oxycodone. You would like to rotate him to methadone given it’s NMDA (neuropathic pain) receptor blocking attributes. You are concerned about methadone’s extremely variable half life as you contemplate this change. What tools are available to aid you in your decision making?
Precision Medicine

Utilization of all tools at our disposal to improve the care of the individual patient by recognizing variations that distinguish them from others:
Precision Medicine

- Classification, diagnosis and treatment of disease being redefined by advances in:
  - Genetic
  - Biomarker
  - Phenotypic
  - Psychosocial
  - Imaging
  - Informatics
  - Pharmacology, proteomics, metabolomics, etc.
# Examples of Conditions in Which Precision Medicine Has Been Used.

<table>
<thead>
<tr>
<th>Medical Field</th>
<th>Disease</th>
<th>Biomarker</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>Chronic myeloid leukemia</td>
<td>BCR-ABL</td>
<td>Imatinib[^4]</td>
</tr>
<tr>
<td></td>
<td>Lung cancer</td>
<td>EML4-ALK</td>
<td>Crizotinib[^1]</td>
</tr>
<tr>
<td>Hematology</td>
<td>Thrombosis</td>
<td>Factor V Leiden</td>
<td>Avoid prothrombotic drugs[^5]</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>HIV/AIDS</td>
<td>CD4+ T cells, HIV viral load</td>
<td>Highly active antiretroviral therapy[^6]</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>Coronary artery disease</td>
<td>CYP2C19</td>
<td>Clopidogrel[^7]</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>Cystic fibrosis</td>
<td>G551D</td>
<td>Ivacaftor[^8]</td>
</tr>
<tr>
<td>Renal disease</td>
<td>Transplant rejection</td>
<td>Urinary gene signature</td>
<td>Antirejection drugs[^9]</td>
</tr>
<tr>
<td>Hepatology</td>
<td>Hepatitis C</td>
<td>Hepatitis C viral load</td>
<td>Direct-acting antiviral agents[^10]</td>
</tr>
<tr>
<td>Endocrine disease</td>
<td>Multiple endocrine neoplasia type 2</td>
<td>RET</td>
<td>Prophylactic thyroidectomy[^11]</td>
</tr>
<tr>
<td>Metabolic disease</td>
<td>Hyperlipidemia</td>
<td>LDL cholesterol</td>
<td>Statins[^12]</td>
</tr>
<tr>
<td>Neurology</td>
<td>Autoimmune encephalitis</td>
<td>CXCL13</td>
<td>Immunotherapy[^13]</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>Alcohol-use disorder</td>
<td>GRIK1</td>
<td>Topiramate[^14]</td>
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<tr>
<td>Pharmacogenomics</td>
<td>Smoking cessation</td>
<td>CYP2A6</td>
<td>Varenicline[^15]</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>Leber’s congenital amaurosis</td>
<td>RPE65</td>
<td>Gene therapy[^16]</td>
</tr>
</tbody>
</table>

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Precision Medicine Initiative

- $215 million in 2016 (if Congress approves)
- $130 million: NIH to develop a national research cohort of 1 million people
- $70 million: NCI to further efforts to identify molecular basis of cancer
Variant Histogram from Mendelian Disease Testing of 15,000 Probands.

83% of patients have variants that are rare or of uncertain clinical significance (5776 variants)

17% of patients have pathogenic or “likely pathogenic” variants seen ≥10 times (63 variants)

- Variants of uncertain significance (71%)
- Pathogenic or “likely pathogenic” variants (29%)

“Million Person Cohort”
Whole-genome sequencing designed to discover genes and their variants associated with disease

- Tier One:
  - genes /variants with evidence for clinical validity and utility to provide actionable information

- Tier Two
  - genes /variants with evidence for clinical validity but without evidence of utility to support recommendation for medical action

- Tier Three
  - genes /variants without evidence for clinical validity or utility to support recommendation for medical action
Clinical Genome Resource (ClinGen).

ClinGen

Launched in 2013 and supported by the National Institutes of Health, ClinGen is intended to be an authoritative central resource that defines the clinical relevance of genomic variants for use in precision medicine and research.

Critical Questions of the Program

- Is this gene associated with a disease?  
  *Clinical validity*
- Is this variant causative?  
  *Pathogenicity*
- Is this information actionable?  
  *Clinical usefulness*

Building a Genomic Knowledge Base

ClinVar and Other Resources

ClinGen is developing several resources for the community. The first is ClinVar, which is a database at the National Center for Biotechnology Information that archives information submitted about variants with medical relevance. It is an integral part of ClinGen and serves as its public portal for the deposition and retrieval of variants and the interpretation of their clinical significance.

Improved Patient Care through Genomic Medicine
Implementation of Precision Medicine.

- Genetic makeup
- Unique medical history
- Exposome
- Population-based guidelines for screening and prevention
- Specific diagnostic tests that are based on unique risks of the individual patient
- Decision support from health system
- Unique interventions that are based on the results of precision diagnostics
- Use of clinical research to inform best practices

- Informatics
- Health system
- Systems approach to population health
- Most effective health care for the individual patient and the population

<table>
<thead>
<tr>
<th>GENE</th>
<th>GENOTYPE</th>
<th>PREDICTED PHENOTYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2B6</td>
<td>*1/*6</td>
<td>Intermediate Metabolizer (IM)</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>*2/*2</td>
<td>Intermediate Metabolizer (IM)</td>
</tr>
<tr>
<td>CYP3A4/CYP3A5</td>
<td>*1/*1; *1/*3</td>
<td>Extensive Metabolizer (EM)</td>
</tr>
<tr>
<td>MTHFR</td>
<td>C/T (C677T);</td>
<td>Greatly Reduced Activity (GRA)</td>
</tr>
<tr>
<td></td>
<td>A/C (A1298C)</td>
<td></td>
</tr>
<tr>
<td>OPRM1</td>
<td>A/G</td>
<td>Reduced Expressor (RE)</td>
</tr>
<tr>
<td>COMT</td>
<td>A/G</td>
<td>Normal Activity (NA)</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>*1/*1</td>
<td>Extensive (Normal) Metabolizer (EM)</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>*1/*4</td>
<td>Extensive (Normal) Metabolizer (EM)</td>
</tr>
<tr>
<td>DRD2</td>
<td>INS/INS</td>
<td>Normal Responder (NR)</td>
</tr>
<tr>
<td>HLA-B*15:02</td>
<td>NEGATIVE</td>
<td>Typical Risk of Hypersensitivity (TR)</td>
</tr>
<tr>
<td>HTR2C</td>
<td>C/C</td>
<td>Normal Expressor (NE) a</td>
</tr>
<tr>
<td>UGT2B15</td>
<td>*1/*1</td>
<td>Extensive (Normal) Metabolizer (EM)</td>
</tr>
</tbody>
</table>
# MEDICATION SELECTION GUIDE (based on potential genetic impact)

<table>
<thead>
<tr>
<th></th>
<th>LOW GENETIC IMPACT</th>
<th>MODERATE GENETIC IMPACT</th>
<th>HIGH GENETIC IMPACT</th>
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<tbody>
<tr>
<td><strong>NSAIDs</strong></td>
<td></td>
<td></td>
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<tr>
<td>Fenoprofen (Nalfon®)</td>
<td>N/A</td>
<td></td>
<td>Celecoxib (Celebrex®) CYP2C9</td>
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<tr>
<td>Ketoprofen (Orudis®)</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meloxicam (Mobic®)</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nabumetone (Relafen®)</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulindac (Clinoril®)</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Opioids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butorphanol (Stadol®)</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocodone (Vicodin®)</td>
<td>CYP2D6</td>
<td></td>
<td></td>
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<tr>
<td>Hydromorphone (Dilaudid®)</td>
<td>N/A</td>
<td></td>
<td></td>
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<tr>
<td>Meperidine (Demerol®)</td>
<td>N/A</td>
<td></td>
<td></td>
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<tr>
<td>Oxycodone (Oxycontin®)</td>
<td>CYP2D6</td>
<td></td>
<td></td>
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<tr>
<td>Oxymorphone (Opana Er®)</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tapentadol (Nucynta®)</td>
<td>N/A</td>
<td></td>
<td></td>
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<tr>
<td>Tramadol (Ultram® Er)</td>
<td>CYP2D6</td>
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<tr>
<td><strong>Platelet Inhibitors</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Aspirin/extended-Release</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dipyridamole (Aggrenox®)</td>
<td>CYP2C19</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clopidogrel (Plavix®)</strong></td>
<td>CYP2C19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dipyridamole (Persantine®)</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prasugrel (Effient®)</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Case 2: Mr. AR

AR is a 64 y/o man who suffered an uncomplicated STEMI. Prior to the event he was not on a statin given an “acceptable” LDL of 110mg/dL. He was placed on atorvastatin 80mg daily with a reduction of his LDL to 70mg/dL at 4 months post event. At a follow up visit, AR asks you if there is any benefit to lowering the LDL further to minimize his risk of another event.
Statin vs. LDL Hypotheses

• **Statin Hypothesis:**
  the beneficial effect of statins is due as much to it’s LDL lowering effect as from it’s pleiotropic effects

• **LDL Hypothesis:**
  the beneficial effect of statins is due entirely to the effect on LDL lowering
When added to statin therapy, can addition of a non-statin drug lower the risk of CV events?

**Methods:**
- Patients with an ACS with LDL cholesterols of 50-100mg/dL on lipid lowering therapy or 50-125 mg/dL not on therapy
- 18,144 patients were randomized to simvastatin (40-80mg/d) or simvastatin (40mg) + ezitimibe (10mg)
- 42% dropout rate primarily due to statin side effects.
Endpoints:
- Any cardiovascular event or stroke

Results
- Average LDL-C at baseline = 93.8 mg/dL
- Average LDL-C at one year post randomization
  - 69.9 mg/dL in simvastatin monotherapy group
  - 53.2 mg/dL in the simvastatin- ezetimibe group
    a 24% reduction
- Decreased total cholesterol, TGs, CRP and ApoB
At 7 years 32.7% of the patient in the simvastatin group and 34.7% in the simvastatin monotherapy group had experienced an index CV event- a 2% reduction (p=0.016)

Benefit particularly pronounced in diabetics and the elderly (75 years or older)

No difference between groups in safety endpoint
Kaplan–Meier Curves for the Primary Efficacy End Point.

Hazard ratio, 0.936 (95% CI, 0.89–0.99)  
$P=0.016$

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Simvastatin–ezetimibe</th>
<th>Simvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at Risk</td>
<td>9067</td>
<td>9077</td>
</tr>
<tr>
<td>1 year</td>
<td>7371</td>
<td>7455</td>
</tr>
<tr>
<td>2 years</td>
<td>6801</td>
<td>6799</td>
</tr>
<tr>
<td>3 years</td>
<td>6375</td>
<td>6327</td>
</tr>
<tr>
<td>4 years</td>
<td>5839</td>
<td>5729</td>
</tr>
<tr>
<td>5 years</td>
<td>4284</td>
<td>4206</td>
</tr>
<tr>
<td>6 years</td>
<td>3301</td>
<td>3284</td>
</tr>
<tr>
<td>7 years</td>
<td>1906</td>
<td>1857</td>
</tr>
</tbody>
</table>
Conclusions

- This study strongly suggests that lowering LDL-C beyond the guideline level of 70 mg/dL reduces the rate of cardiovascular events and supports the LDL hypothesis.
Case 3: Mr. RV

RV is a 49 y/o AA male with chronic HTN, poorly controlled DM and strong family history of CAD. His Framingham Risk Score is 22%. He is very reluctant to take a statin as he is worried about the side effects on the muscles, but relents after doing a coronary CT scan which discloses a score of 888 (624 LAD, 100 CX and 164 RCA). He develops severe myalgias on atorvastatin, simvastatin and pravastatin and stops the meds stating “I told you so”. What are your options for primary prevention at this point?
Do statins cause myalgias?

- Adverse events perceived to be caused by statins most commonly include myalgias, weakness with or without elevations of CK
- True statin myopathy is defined by an increase in CK to 10 x the upper limit of normal.
## Muscle Adverse Events Reported in Randomized, Double-Blind, Placebo-Controlled Cardiovascular Outcome Trials of Statins

<table>
<thead>
<tr>
<th>Trial</th>
<th>Total No.</th>
<th>Agent</th>
<th>Dose, mg</th>
<th>Duration, y</th>
<th>Myalgia, %</th>
<th>Any Muscle Symptoms, %</th>
<th>Myopathy, %</th>
<th>Rhabdomyolysis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Statin</td>
<td>Placebo</td>
<td>Statin</td>
<td>Placebo</td>
<td>Statin</td>
<td>Placebo</td>
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<tr>
<td>4S</td>
<td>4444</td>
<td>Simvastatin</td>
<td>20-40</td>
<td>5.4</td>
<td>3.7</td>
<td>3.2</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>WOSCOPS</td>
<td>6595</td>
<td>Pravastatin</td>
<td>40</td>
<td>4.9</td>
<td>3.5</td>
<td>3.7</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>HPS</td>
<td>20 536</td>
<td>Simvastatin</td>
<td>40</td>
<td>4.9</td>
<td>NR</td>
<td>NR</td>
<td>32.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>33.2&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>PROSPER</td>
<td>5804</td>
<td>Pravastatin</td>
<td>40</td>
<td>3.2</td>
<td>1.2</td>
<td>1.1</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>CARDS</td>
<td>2838</td>
<td>Atorvastatin</td>
<td>10</td>
<td>3.9</td>
<td>4.0</td>
<td>4.8</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>ASPEN</td>
<td>2410</td>
<td>Atorvastatin</td>
<td>10</td>
<td>4.0</td>
<td>3.0</td>
<td>1.6</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>SPARCL</td>
<td>4731</td>
<td>Atorvastatin</td>
<td>80</td>
<td>4.9</td>
<td>5.5</td>
<td>6.0</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>JUPITER</td>
<td>17 802</td>
<td>Rosuvastatin</td>
<td>20</td>
<td>1.9</td>
<td>7.9</td>
<td>6.9</td>
<td>16.0</td>
<td>15.4</td>
</tr>
</tbody>
</table>

**Table Title:** Muscle Adverse Events Reported in Randomized, Double-Blind, Placebo-Controlled Cardiovascular Outcome Trials of Statins<sup>a</sup>

- **Abbreviation:** NR, not reported.
- **Data source:** From the publications cited by the Cholesterol Treatment Trialists’ Collaboration, with the addition of 4S (Pedersen TR, Berg K, Cook TJ, et al.).
- **Safety and tolerability of cholesterol lowering with simvastatin during 5 years in the Scandinavian Simvastatin Survival Study.** Arch Intern Med. 1996;156(18):2085-2092.

<sup>a</sup> Generally defined as unexplained muscle pain or weakness plus creatine kinase level greater than 10 times the upper limit of normal.

<sup>b</sup> Generally defined as myopathy with severe elevations in creatine kinase levels 40 times the upper limit of normal and/or renal impairment or myoglobinuria.

<sup>c</sup> HPS included direct questioning about muscle symptoms at each visit.
Alternatives to statin therapy for cholesterol lowering

Ezetimibe
Nicotinic Acid
Bile Acid Sequestrants
Fibrates

…..
Proprotein Convertase Subtilisin /Kexin Type 9 PCSK9 Inhibitors


• Pro-protein convertase subtilisin/ kexin type 9 (PCSK9)
  ▪ A 692-amino acid protein that binds surface low-density lipoprotein (LDL) receptor (LDLR)
  ▪ With endocytosis this results in its lysosomal degradation
  ▪ loss-of-function mutations of PCSK9 result in increased surface LDLR and improved LDL-C clearance

- Meta analysis of 24 studies: 10, 159 patients
- Adults with hypercholesterolemia
- Treated with: alirocumab and evolocumab
- Primary endpoints:
  - All cause mortality and CV mortality
- Secondary endpoints:
  - MI, creatinine and serious events
Myocardial infarction (top) and unstable angina (bottom).

See the legend for Figure 1 for abbreviation expansions.
Case 4: Ms. CG

CG is a 55 y/o lady with IHSS, HTN, epilepsy and paroxysmal atrial fibrillation. Her CHAD-2 score is 3. She was started on warfarin and has maintained a therapeutic INR. In May she was admitted with a LGI bleed from diverticulosis and in June with a massive UGI bleed from an anastomotic ulcer at the site of her Rou en Y (for bariatric surgery) anastomosis. What treatment options does she have to prevent a CVA?
Percutaneous left atrial appendage closure closure vs warfarin for atrial fibrillation: a randomized clinical trial.


• The PROTECT AF trial
• 707 patients with non-valvular AF and CHADS2 score of 1 or more
• Left atrial appendage (LAA) closure device vs warfarin
• 4 year follow-up
Figure 1. LAA Ostium by 3-Dimensional TEE and Watchman Device (A) Shown is the Watchman filter device; notice the 10 equally-spaced struts, each with a small anchoring time. (B) Third-generation Watchman device with spherical shape (small arrows). These 2 i...


The Clinical Impact of Incomplete Left Atrial Appendage Closure With the Watchman Device in Patients With Atrial Fibrillation : A PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) Substudy


http://dx.doi.org/10.1016/j.jacc.2011.11.028
• Percutaneous device met criteria for non-inferiority and superiority:
  – stroke, systemic embolism and cardiovascular death
  – safety
From: **Percutaneous Left Atrial Appendage Closure vs Warfarin for Atrial Fibrillation: A Randomized Clinical Trial**


**Figure Legend:**

Kaplan-Meier Curves for Ischemic Stroke, Cardiovascular Mortality, and All-Cause Mortality. HR indicates hazard ratio; RR, rate ratio.
Case 5: Ms. MJ

• MJ is a 24 y/o student at UCSF who, while visiting her parents after a week of camping at Big Sur, developed insidious onset of a severe generalized HA and neck pain over the course of 3 days. She was brought by her mother to her PCP for evaluation when she began complaining of fevers and chills. She was admitted to the hospital after an LP in the ER disclosed pleocytosis. An astute houseofficer proposed that a dark field microscopy be done on her CSF.
Morphologic Features of Spirochetes Detected in Cerebrospinal Fluid.
Tick-Borne Diseases
(* Ixodes sp.)

- Lyme Disease*
- Anaplasmosis*
- Babesiosis*
- Ehrlichioses
- Relapsing Fever
- Colorado Tick Fever
- Rickettsial Disease (RMSF)
and now…..*Borrelia miyamotoi*

- First identified in Japan (1994) and identified as a pathogen in Russia (2011)
- In New England prevalence in deer ticks is 1-5%. In California 0.7%
- PCR for glycerophosphodiester phosphodiesterase antigen (GlpQ) insensitive for acute testing but reliable in convalescent sera
- Coexistence of other tick-borne infections is frequent
- Doxycycline is preferred initial treatment
From: Borrelia miyamotoi Disease in the Northeastern United States: A Case Series


**Table 1. Clinical Features of the 51 Case Patients**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range), y</td>
<td>55 (12-82)</td>
</tr>
<tr>
<td>Male</td>
<td>29 (57)</td>
</tr>
<tr>
<td>Fever/chills</td>
<td>49 (96)</td>
</tr>
<tr>
<td>Headache†</td>
<td>49 (96)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>42 (84)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>39 (76)</td>
</tr>
<tr>
<td>Malaise/fatigue</td>
<td>42 (82)</td>
</tr>
<tr>
<td>Rash</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Gastrointestinal symptoms‡</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Cardiac/respiratory symptoms§</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Neurologic symptoms</td>
<td></td>
</tr>
</tbody>
</table>

BMD = *Borrelia miyamotoi* disease.

* Number (percentage) unless otherwise indicated.
† Severe in most patients.
‡ Nausea, abdominal pain, diarrhea, and anorexia.
§ Dyspnea.
|| Dizziness, confusion, and vertigo.
Early diagnosis of Alzheimer’s Disease

Jansen, et al. JAMA.2015;313:1924

- Assessed the presence of amyloid pathology in normal patients, subjective cognitive impairment and mild cognitive impairment
- Related to age, education and APOE status
- Amyloid PET scanning
- CSF amyloid
From: Prevalence of Cerebral Amyloid Pathology in Persons Without Dementia: A Meta-analysis


Figure L:

Association of Age With Prevalence Estimates of Amyloid Positivity According to Cognitive Status and Apolipoprotein E (APOE) Genotype

The model for the analyses in panels A and B included age, cognitive status, APOE-ε4 status, an interaction between age and cognitive status, and an interaction between age and APOE-ε4 status as predictors. The models for the analyses in panels C and D included age, cognitive status, APOE genotype, an interaction between age and cognitive status, an interaction between age and APOE genotype, and an interaction between cognitive status and APOE genotype as predictors. In panel C, none of the 10 participants with ε2ε2 were amyloid positive, and no 95% confidence interval is provided for this group. In panel D, data of participants with ε2ε2 are not shown because of the small sample size (n = 5). Shading indicates 95% CIs; SCI, subjective cognitive impairment; MCI, mild cognitive impairment.
• Apolipoprotein APOE e4 carriers and non-carriers with mild to moderate Alzheimer disease dementia.
• Treated with Bapineuzumab by IV infusion every 13 weeks for 78 weeks
• PET imaging results demonstrated a significant reduction of amyloid accumulation
• No clinical benefit was observed
New Meds:
Suvorexant: (Belsomra™)

• First-in-class orally active orexin-1 and orexin-2 antagonist
• Orexin A and B are neuropeptides produced in lateral hypothalamus
• Linked to circadian rhythms and wakefulness
• 10 mg within 30 mins of retiring
• Caution with CYP 3A inhibitors (antifungals, clarithromycin and many antivirals)
New Meds:
Flibanserin: (Addyi ™)

- **Female Hypoactive sexual desire disorder:** characterized by low sexual desire that causes marked distress or interpersonal difficulty and **not** due to a coexisting medical or psychiatric condition, problems within the relationship, or the effects of a medication or other drug substance
- **Mixed 5-HT$_{1A}$ Agonist/5-HT$_{2A}$ Antagonist**
- **Black Box:** contraindicated
  - Alcohol usage
  - CYP-3A4 inhibitors
  - Hepatic impairment
- **100mg at bedtime**
In Summary.....

• Precision Medicine Initiative
• New development in the treatment of hypercholesterolemia
• Left Atrial Appendage closure device for prevention of stroke
• A new tick borne illness: Borrelia miyamotoi
• A novel treatment of Alzheimers disease
• Suvorexant for sleep and fibanserin for female hypoactive sexual disorder