Personalized Medicine for Geriatric Care: Are We There Yet?

2013 Geriatric Update
Meharry Consortium Geriatric Education Center
Personalized Medicine in the News


- “…personalized medicine, a fledgling clinical field that is not only saving lives but could save the health care system billions of dollars in prescription drug costs and reduced hospital readmission rates.” [http://www.bizjournals.com/nashville/print-edition/2012/09/28/vanderbilts-personalized-in.html?page=all]

Questions about Personalized Medicine

- We hear about personalized medicine for cancer treatment and heart medications. What about personalized medicine for geriatrics: are we there yet?

- Can personalized medicine answer the following questions:
  - Who will get sick?
  - Which geriatric patients respond best to various treatments?
  - Which geriatric patients are at risk of adverse reactions?
Inter-Professional Panel

Moderator: Charles P. Mouton, MD, MS
Senior Vice President for Health Affairs & Dean, School of Medicine, Meharry Medical College
Meharry Consortium Geriatric Education Center, Director/Principal Investigator

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Vanderbilt University School of Medicine

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Center for Human Genetics Research
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Disclosures

Moderator: Charles P. Mouton, MD, MS
Disclosure: None

Josh Denny, MD, MS
Disclosure:
Grants, Contracts: NIH: NLM, NHGRI, NIGMS, NCI, NCATS, Reynolds Foundation (Geriatrics Education), National Board of Medical Examiners

Tricia Thornton-Wells, PhD
Disclosure:
Grants, Contracts: Vanderbilt Kennedy Center, Vanderbilt Brain Institute, and Vanderbilt Institute for Clinical & Translational Research
Objectives

- Identify opportunities for healthcare providers to use unique patient-specific information to assist with diagnosis and prevention in geriatric patients.
- Assess the diagnostic value of genetic testing and biomarkers for different geriatric patient presentations.
Personalized Medicine for Geriatric Care: Are We There Yet?

Josh Denny, MD, MS
Associate Professor of Biomedical Informatics and Medicine
Vanderbilt University

2013 Geriatric Update
Meharry Consortium Geriatric Education Center
Case: A 57yo female with chest pain

First admission for angina, receives stent

Recath, stent
"Plavix x 1 year minimum. ASA life long."

In-stent thrombosis, restent

Angina, Cath, more stents

In-stent thrombosis, restent

9th admission, 5th intervention, 9th stent placed

January

April

December

clopidogrel started
One perception of genomic medicine
People have different disease risk, genetics may help predict this.
How do we get here?

Some requirements:
1. We know what genetic variants mean
2. We know what variant a patient has
3. That data is available when you need it
4. What to do is clear

Francis Collins
NIH Director, NEJM 9/16/2009
SNPs (single nucleotide polymorphism)

- Can be substitution, insertion, or deletion
- Most SNPs don’t mean little, some carry risk of disease, very few cause disease
- Early onset Alzheimer’s, cystic fibrosis, some cancers (BRCA1/2)
Early 21st century disease genetics: a new locus for early MI at chr9p21

Genome-wide association study = GWAS

$P = 10^{-10}$

Samani et al 2007
Discovery and Application using the EHR

In-house developed, web-based EHR with CPOE, patient portal, messaging, etc.

VanderbiltBioVU

De-identified resource for genomics and pharmacogenomics discovery
BioVU Key implementation steps

<table>
<thead>
<tr>
<th>Year</th>
<th>Focus groups</th>
<th>Patient mail survey</th>
<th>Communications materials</th>
<th>CAB established</th>
<th>Opt out caller survey</th>
<th>Pre-launch awareness generation</th>
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<tr>
<th>Year</th>
<th>Logistics/process mapping</th>
<th>Sample acceptance validation</th>
<th>De-Identification effectiveness</th>
<th>Proof of Concept</th>
<th>Form implementation</th>
<th>Pilot testing</th>
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<tr>
<th>Year</th>
<th>Protocol development</th>
<th>IRB review and modifications</th>
<th>Ethics review and modifications</th>
<th>Legal review and modifications</th>
<th>Final IRB approval</th>
<th>OHRP confirmation</th>
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Sample accrual begins
Demonstration project
Patient research, live setting

Community / Patient

Methods/ Feasibility

Regulatory, Legal, Ethics

Live Operations Phase I
Vanderbilt BioVU: an Opt-Out DNA Biobank

Extracting DNA from leftover blood samples

I also understand that if I check the box shown below:

- DNA Research: Leftover blood from tests, treatment, or surgery may also be used for DNA research through the Vanderbilt BioVU Program. If I do not want my leftover blood to go to the Vanderbilt BioVU Program for DNA research, I must check the box below. If I have questions or want further information on BioVU, I may call 866-436-4710.

Please click "Next" and write your name on the next screen.

Next
One way hash:

~2 million records

The Synthetic Derivative: can be updated
The Synthetic Derivative: can be updated

~2 million records
How can we use the EMR for research?
The Electronic Medical Record as a platform for research

Electronic Medical Record

- Clinical Notes
- Physician Orders
- Billing codes
- Patient and Staff Messaging
- Labs, Radiology, Test Results

De-identification

Synthetic Derivative

~ 2 million records

Discarded blood samples from routine testing

If eligible, extract DNA

VanderbiltBioVU

De-identified DNA repository

- 155k samples
- 17k pediatric
- >28k with dense genetic data
Hypothyroidism algorithm

**Case medications**
- levothyroxine, synthroid, levoxyl unithroid, armour thyroid, desicated thyroid, cytome, triostat, liothyrone, synthetic triiodothyronine, liotrix, thyrolar

**Pregnancy exclusion ICD 9 codes**
Any pregnancy billing code or lab test if all Case Definition codes, labs, or medications fall within 6 months before pregnancy to one year after pregnancy.

**Exclusion keywords**
- optiray, radiocontrast, iodine, omnipaque, visipaque, hypaque, ioversol, diatrizoate, iodixanol, isovue, iopamidol, conray, iothalamate, renografin, sinografin, cystografin, conray, iodipamide

**ICD-9 codes for hypothyroidism**
- 244, 244.8, 244.9, 245, 245.2, 245.8, 245.9

**Abnormal lab values**
- TSH > 5 OR FT4 < 0.5

**ICD-9 codes for secondary causes of hypothyroidism**
- 244.0, 244.1, 244.2, 244.3

**ICD-9 codes for post surgical or post radiation hypothyroidism**
- 193*, 242.0, 242.1, 242.2, 242.3, 242.9, 244.0, 244.1, 244.2, 244.3, 258*

**CPT codes for post radiation hypothyroidism**
- 77261, 77262, 77263, 77280, 77285, 77290, 77295, 77299, 77300, 77301, 77305, 77310, etc.

**Exclusion keywords**
- multiple endocrine neoplasia, MEN I, MEN II, thyroid cancer, thyroid carcinoma

**Thyroid-altering medications**
- Phenytoin, Dilantin, Infatabs, Dilantin Kapseals, Dilantin-125, Phenytek, Amiodarone Pacerone, Cordarone, Lithium, Eskalith, Lithobid, Methimazole, Tapazole, Northyx, Propythiouracil, PTU

**Case Definition**
All three conditions required:
- ICD-9 code for hypothyroidism OR abnormal TSH/FT4
- Thyroid replacement medication use
- Require at least 2 instances of either medication or lab with at least 3 months between the first and last instance of medication and lab

**Case Exclusions**
Exclude if the following information occurs at any time in the record:
- Secondary causes of hypothyroidism
- Post surgical or post radiation hypothyroidism
- Other thyroid diseases
- Thyroid altering medication

**Case Exclusions**
Time dependent case exclusions:
- Recent pregnancy TSH/FT4
- Recent contrast exposure

Conway et al. AMIA 2010.
Hypothyroidism GWAS

FOXE1

Denny et al., Am J Hum Genet 2011
GWAS of QRS Duration

SCN5A/SCN10A

Ritchie et al., Circulation 2013
“PheWAS” - Phenome-wide association study

Genotype of interest (e.g., SCN10A) → Electronic Medical Record → Phenotype mapping → ~1,600 Clinical phenotypes (& controls)

Compare with genetic loci

Vanderbilt BioVU

Denny et al. Bioinformatics. 2010
PheWAS of rs6795970 (SCN10A) (associated with longer QRS duration in normal hearts)

N=13617 subjects

Ritchie et al., Circulation 2013
What happens in the “heart healthy” population?

Examined the n=5272 “heart healthy” population

Followed for development of atrial fibrillation based on genotype

HR=1.49 per G allele
p=0.001

Ritchie et al., Circulation 2013
Alzheimer’s disease GWAS using EMRs
Pharmacogenetics: Explanation of drug outcomes via genetics
GWAS for a rare adverse drug effect
Flucloxacillin-induced liver injury

- HLA variants
- 51 cases
- 282 population controls

Daly et al., Nat Genetics 2009
Variable drug response is common; Genetics may predict this too.
WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

See full prescribing information for complete boxed warning.

• Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)
• Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)
• Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)
• Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)
Use of EMR data to predict drug response

clopidogrel failure=MI, stroke, revascularization, death following MI or PCI
n=225 cases, 468 controls

Delaney et al. *Clin Pharm Ther.* 2012
Warfarin Pharmacogenetics
Using genetics to predict effective dose

<table>
<thead>
<tr>
<th>SNP (Gene)</th>
<th>Beta</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1057910 (CYP2C9*3)</td>
<td>0.83</td>
<td>2.70x10^{-26}</td>
</tr>
<tr>
<td>rs9934438 (VKORC1)</td>
<td>0.87</td>
<td>4.48x10^{-61}</td>
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</table>
Medication initiation:
warfarin

1 month  3 months  6 months  9 months  12 months

Medication initiation:
simvastatin

1 month  3 months  6 months  9 months  12 months

Medication initiation:
azathioprine

1 month  3 months  6 months  9 months  12 months

Medication initiation:
tacrolimus

1 month  3 months  6 months  9 months  12 months

Medication initiation:
abacavir

1 month  3 months  6 months  9 months  12 months

2. The SEARCH Collaborative Group, NEJM 2008
3. Higgs et al, Pharmacogenomics 2010
5. Mallal et al, NEJM 2008
FDA’s role

- FDA began including pharmacogenomic (PGx) effects in labels in 2007
- Now includes >100 medications

<table>
<thead>
<tr>
<th>Gene</th>
<th>Drug Metabolism Pathways</th>
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<tbody>
<tr>
<td>TPMT</td>
<td>azathioprine</td>
</tr>
<tr>
<td>UGT1A1</td>
<td>irinotecan, nilotinib</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>atomoxetine, fluoxetine, paroxetine</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>proton pump inhibitors</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>celecoxib, warfarin</td>
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<tr>
<td>N-acetyl transferase</td>
<td>rifampin, isoniazid, pyrazinamide</td>
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<tr>
<td>DPD</td>
<td>capecitabine</td>
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<table>
<thead>
<tr>
<th>Gene</th>
<th>Other Germline Variants</th>
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<tbody>
<tr>
<td>VKORC1</td>
<td>warfarin</td>
</tr>
<tr>
<td>HLA-B*1501</td>
<td>carbamazepine</td>
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<tr>
<td>HLA-B*5701</td>
<td>abacavir</td>
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<tr>
<td>CCR5</td>
<td>maraviroc</td>
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<tr>
<td>Familial hypercholesterolemia</td>
<td>atorvastatin</td>
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<tr>
<td>G6PD deficiency</td>
<td>rasburicase, primaquine</td>
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<tr>
<td>Protein C deficiency</td>
<td>warfarin</td>
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<tr>
<td>urea cycle disorder</td>
<td>valproate</td>
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http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm
A Case for Prospective Genotyping

52,942 Vanderbilt “Medical Home” patients followed for up to 5 years....

How many patients received drug(s) that have a recognized pharmacogenetic story?

Estimated number of severe adverse events mitigated: 383... or ~12-18 ADEs for the average PCP over 5 years

What is the role of known PGx meds in the geriatric population?

<table>
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<tr>
<th>&gt;=65yo analyzed with outpatient visit after 2007</th>
<th>44,960</th>
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<tbody>
<tr>
<td>With exposure to:</td>
<td></td>
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<tr>
<td>clopidgorel</td>
<td>8040</td>
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<tr>
<td>warfarin</td>
<td>8720</td>
</tr>
<tr>
<td>simvastatin</td>
<td>16,050</td>
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<tr>
<td>tacrolimus</td>
<td>550</td>
</tr>
<tr>
<td>thiopurines (azathioprine, 6-MP)</td>
<td>800</td>
</tr>
<tr>
<td>With any of the above</td>
<td>23,160</td>
</tr>
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“Here's my sequence…”

New Yorker, 2000
PREDICT: Pharmacogenomic Resource for Enhanced Decisions In Care and Treatment

- Multiplexed genotyping with Illumina ADME chip
- Prospective identification of those at risk to receive candidate medications
- Coupled with EMR-based Decision Support
PREDICT: Genotype many variants at once

CYP2C19
- clopidogrel
- Poor metabolizer

CYP2C19
- clopidogrel
- Rapid metabolizer

CYP2C9
- warfarin
dose/bleeds

CYP2C9
- warfarin
dose/bleeds

VKORC1
- warfarin
dose/bleeds

CYP2D6
- tamoxifen,
antidepressants,
codeine
- Poor metabolizer

SLCO1B1
- simvastatin
- Myopathy

PREDICT platform tests 184 variants in 34 drug-related genes
Identifying Patients for PREDICT Genotyping

1. “Just-in-time”
   - All patients scheduled for catheterization in cardiac cath lab

2. Provider Judgment
   - Physician recognizes potential need for genetic information in prescribing

3. Prospective Identification
   - Genomic information is deposited in patient records preemptively, prior to its being needed in care
**CYP2C19** genotypes in 12,521 PREDICT patients (9/2010-4/2013)

- 2.7% homozygous
- 18.9% heterozygous
- 12.2% non-actionable variant
- 66.1% no common variant
Multiplex testing for pharmacogenetic variants

- 0 variants: 17%
- 1 variant: 48%
- 2 variants: 29%
- 3 variants: 6%
- 4 variants: 0.3%

Risk Variants:
- CYP2C19 *2-*8
- SLOC1B1 *5
- CYP2C9 / VKORC1
- TPMT *2-*3
- CYP3A5*3

Total n=12,521

99.8% of African Americans had actionable variants
## Drug Genome Interactions in the Patient Summary

### Adverse and Allergic Drug Reactions
- **(01/05/12 09:34)**
  - SUFLA (nausea)

### Drug Genome Interactions
- **(01/05/12 13:04)**
  - Simvastatin sensitivity: INTERMEDIATE MYOPATHY RISK, MINOR ALLELE HETEROZYGOUS (C:T) - gene: SLCO1B1 - gene result: *1B HET,*5 HET
clopidogrel sensitivity: INTERMEDIATE METABOLIZER, REDUCED ANTI-PLATELET EFFECT - gene: CYP2C19 - gene result: *1/*2

### Medications
- **prepare to print**
- **print and give pt.**
- **Show Hts of medications**

- **DrugHerb Interactions**
  - (01/05/12 14:29)
  - Mycoceplolate metofl 500 mg Tab (Also Known As CeliCept) 1 tablet by mouth twice a day
  - Omeprazole 20 mg orally once daily
  - Aspirin 81mg by mouth once daily
  - [81mg by mouth daily -- Comments: $1mg orally once daily, in the morning]
  - Bupropion HCl SR (wellbutrin) 150 mg orally once daily
  - Multivitamin 1 tab orally once daily
  - Dapsone prophylaxis (on hold 10/27/11)
  - Valcyte prophylaxis (on hold 10/27/11)
  - Colace 1 gelcap twice daily
  - Testosterone one shot bi-weekly
  - Zytrac 10mg by mouth once daily as needed
  - Ramapune 1 mg Tab 5 tablets by mouth daily
  - Prednisone 5 mg Tab 1 tablet by mouth daily
  - Pravastatin 20 mg Tab (Also Known As Pravachol) 1 tablet by mouth daily

### Health Maintenance
- **Immunizations**
  - PPD-03-12-11
  - Influenza vaccine (10/20/2011)

### Nutrition
- **(01/05/12 09:34)**
  - *Regular diet*
  - *Appetite is good*
  - *No complaints of nausea, vomiting, diarrhea, constipation or acid reflux at this time*
Clinical Decision Support within E-Prescribing

Drug-Genome Advisor
Intermediate Metabolizer - clopidogrel (Plavix) - Rare Risk Allele
Substitution recommended due to increased cardiovascular risks

If not otherwise contraindicated:
- Prescribe prasugrel (Effient) 10 mg daily
  - Prasugrel should not be given to patients:
    - history of stroke or transient ischemic attack
    - >= 75 years of age [Current patient age: 51]
    - with body weight < 60 kg [Current patient weight: 59.0 kg as of 10/12/2012]
- Prescribe ticagrelor (Brilinta) 90 mg twice daily
  - Ticagrelor should not be given to patients:
    - history of severe hepatic impairment
    - intracranial bleed
- Continue with clopidogrel (Plavix) prescription
  - Primary override reason:
    - Contraindicated for prasugrel or ticagrelor
    - Potential side effects
    - Provider/Patient opts for clopidogrel
    - Cost

This patient has been tested for CYP2C19 variants which has identified the presence of one copy of a rare risk allele which is associated with intermediate metabolism of clopidogrel. Intermediate metabolizers treated with clopidogrel at normal doses are associated with higher rates of stent thrombosis and other cardiovascular events. The Vanderbilt P&T Committee recommends that prasugrel or ticagrelor replace clopidogrel for poor metabolizers unless contraindicated. If not feasible, maintain standard dose of clopidogrel. The guidelines above were developed based on the outcome studies of patients who received a drug-eluting stent into a coronary artery. However, there is not a national consensus on drug/dose guidance particularly associated with the population possessing extremely rare genetic variants.
Decision Support for Warfarin Initial Dose

Warfarin Recommended Initial Dosing
This patient has been tested for CYP2C9 and VKORC1 genetic variants that can affect a patient's warfarin dosing requirements. The following dosing algorithm uses genetic and other patient information to estimate a weekly warfarin dose. This dosing recommendation ONLY applies to NEW starts of warfarin. If the patient has previously taken a stable dose of warfarin, please disregard this dosing recommendation.

- Age: 25
- Weight (kg): 86.2
- Height (cm): 188.0
- Genetic Variants: vkorc1 a/g; cyp2c9 *3/*3;
  - Is the patient currently taking amiodarone? No
  - Is the patient currently taking an inducer (phenytoin, rifampin, carbamazepine)? Yes

Recommended WEEKLY starting dose of warfarin: 20.9 mg/week
The DAILY equivalent of this recommended starting dose is 3.0 mg/day.
Help me decide the tablet size and number of tablets per day

The advisor appears in the black box and shows the Recommended initial WEEKLY & DAILY dose

Links to clinical evidence and dosing table.
PREDICT helps match patient with proper drug

BY: KATHY WHITNEY

10/28/2010 - Had Scyble Van Cleve, a spry 83-year-old from Brentwood, had her heart procedure done a month ago instead of one week ago, she would have been prescribed the standard dose of clopidogrel, a blood thinner used to prevent blood clots from forming around her coronary stents.

Scyble Van Cleve, right, is the first patient at Vanderbilt to benefit from a new program that puts genetic information in the patient’s medical records to help physicians like John McPherson, M.D., choose the drug and dose that will benefit them the most. (photo by Susan Urmy)
Our case: What personalizing medicine really means

57yo with admitted for angina, receives stent

January

Recath, stent
“Plavix x 1 year minimum.
ASA life long.”

April

In-stent thrombosis, restent

In-stent thrombosis, restent

Cath, more stents

December

9th admission, 5th intervention,
9th stent
PREDICT: CYP2C19*2/*2

Switched to prasugrel

clopidogrel started
Personalized medicine – not a new idea

The good physician treats the disease; the great physician treats the patient who has the disease.

Sir William Osler
The Teams

**Informatics**
- Josh Peterson
- Hua Xu
- Brad Malin
- Dan Masys
- Lisa Bastarache
- Robert Carroll
- Wei-Qi Wei
- Carmelo Blanquie\n- Genie McPeek Hinz
- Anne Eyler

**BioVU/SD**
- Melissa Basford
- Jill Pulley
- Erica Bowton
- Jay Cowan
- Sunny Wang
- Jenny Madison
- Sue Bradeen

**Medicine**
- Dan Roden
- Russ Wilke
- Ellen Clayton
- Jessica Delaney
- Sara Van Driest
- Jonathan Mosley
- Andrea Ramirez
- Peter Weeke

**Biostatistics**
- Jonathan Schildcrout
- Yaping Shi

**Center for Human Genetics Research**
- Tricia Thornton-Wells
- Dana Crawford
- Todd Edwards

**eMERGE Network**
- Children’s hospital of Philadelphia
- Boston Children’s/Cincinnati Children’s Hospitals
- Northwestern
- Marshfield Clinic
- Mayo Clinic
- Group Health/UW
- Mount Sinai
- Geisinger

**Funding**
- VICTR/NCATS
- NHGRI
- NIGMS
- NLM
- NCI
Personalized Medicine in Alzheimer’s Disease: Are We There Yet?

Tricia A. Thornton-Wells, Ph.D.
Center for Human Genetics Research
Vanderbilt University

2013 Geriatric Update
Meharry Consortium Geriatric Education Center
Can we prevent or delay Alzheimer’s disease?

Shaw et al., 2007
Why personalized medicine for patients with Alzheimer’s disease (AD)?

- Using the ‘right’ medicine from the start
- NOT using a medicine that will not work (and will have adverse side effects)
- Prevention / delay of symptoms in preclinical patients with brain pathology or high genetic risk
Why personalized medicine for patients with Alzheimer’s disease (AD)?

- Prevalence differs by ancestry / race / ethnicity

- Etiology (genetic and environmental factors) likely differ by ancestry / race / ethnicity also

- Treatments should match etiology
Why not?

- Prediction is limited; genetic factors only explain ~60% of disease risk

- Most known genetic factors have been discovered in Caucasians so there is limited generalizability to other groups

- Currently FDA approved treatments for AD mitigate symptoms and do not address underlying disease physiology
What will / needs to change in the near future?

- New Clinical Trials are focused on disease pathology and progression (Amyloid immunotherapy / vaccination)
- Less expensive, less invasive technologies for early disease detection & monitoring (MRI; blood biomarkers)
- More complete understanding of genetic risk across entire genome
Direct to Consumer (DTC) Genetic Testing

Get to know you. Health and ancestry start here.

- Reports on 240+ health conditions and traits
- Discover your lineage, find relatives and more
- Get updates on your DNA as science advances

23andMe DNA Spit Kit
order now $99

What your DNA says about you.
Find out things like if your body metabolizes caffeine quickly, or if you're at a higher risk for diabetes. The more you know about your DNA, the more you know about yourself.

Carrier status

Health risks

Drug response
Disease Prediction is Hard

Fig. 1. Relative disease risk assigned by 3 DTC services for a series of diseases evaluated by all 3 services. Values in parentheses indicate the number of SNPs analyzed (3^a, results for 2 of 5 SNPs were unavailable, i.e., no base calls).

Alzheimer Disease Genetics 2013

- PS1 & PS2: <1%
- 10 “small effect” genes: ~10%
- APOE: ~40%
- APP: < 1%
- Unknown: ~48%
We all inherit 2 forms or copies of the APOE gene

- **ε2**
  - GOOD COPY
  - decreases risk and delays age of onset

- **ε3**
  - NEUTRAL COPY
  - is the most common form

- **ε4**
  - BAD COPY
  - increases risk and lowers age of onset
Alzheimer’s Research Forum

A compendium of published genetic association results

As of Sept 2013:

1395 papers

695 genes
Recent “Small Effect” Genetic Findings

<table>
<thead>
<tr>
<th>Gene</th>
<th>Odds Ratio</th>
<th>Gene</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOE</td>
<td>3.68</td>
<td>PICALM</td>
<td>1.14</td>
</tr>
<tr>
<td>BIN1</td>
<td>1.17</td>
<td>MS4A6A</td>
<td>1.11</td>
</tr>
<tr>
<td>CLU</td>
<td>1.12</td>
<td>CD33</td>
<td>1.12</td>
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<td>ABCA7</td>
<td>1.23</td>
<td>MS4A4E</td>
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<td>CR1</td>
<td>1.15</td>
<td>CD2AP</td>
<td>1.12</td>
</tr>
</tbody>
</table>

Alzgene.org (9/9/2013)
Biology is Complex
No Gene Acts Alone

• Interactions among known AD candidate genes demonstrate complex genetic architecture

• You cannot simply add up the number of “bad” alleles you have and know your risk for AD (even if we knew them all, which we do not).

• Genetic interactions are COMMON and can have substantial effects on disease risk and progression
**By Itself, BIN1 minor allele is “bad”**

**But in persons with the PICALM “protective” A allele, it’s not so bad afterall**

![Graph showing the interaction between BIN1 and PICALM genotypes and their effects on amyloid deposition.](image_url)

**BIN1 A/A genotype**

→ Increases Aβ aggregation

**PICALM A allele**

→ Increases Aβ clearance

**Risk Prediction Must Consider Interaction**

Hohman et al., PLoS ONE (In Press)
By Itself, GSK3β minor allele is neither “bad” nor good

→ In persons with the common APP allele, it’s good
→ In persons with the overactive APP allele, it’s really “bad”

GSK3β A/A genotype
→ Increases cytokines and microglial –mediated Aβ clearance

APP minor allele
→ Increases Aβ production

Risk Prediction Must Consider Interaction

Hohman et al., PLoS ONE (In Press)
**By Itself, RYR3 minor allele isn’t “bad” or good and neither is the CACNA1C minor allele.**

*But together one minor allele exacerbates the effect of the other and vise versa.*

Minor alleles interact to disrupt calcium homeostasis → which increases Aβ deposition → further disrupts calcium homeostasis → ...and so on, in a feed-forward cycle.

*Koran et al., Human Genetics 2013*
By Itself, Phosphorylated Tau is “bad”

But in persons with POT1 A/A genotype, it’s really bad

POT1 A/A genotype
→ Lower levels of the anti-inflammatory marker IL-6R
→ Increased neuroinflammation
→ Increased neuronal cell loss

Hohman et al., Alzheimer’s & Dementia (In Press)
Biology is Complex
No Gene Acts Alone
Disease Prediction is Hard

Fig. 1. Relative disease risk assigned by 3 DTC services for a series of diseases evaluated by all 3 services. Values in parentheses indicate the number of SNPs analyzed (3n, results for 2 of 5 SNPs were unavailable, i.e., no base calls).

Personalized Medicine in Alzheimer’s Disease: Are We There Yet?

No, in fact we have a long way to go.

But we are on our way!
Can we prevent or delay Alzheimer’s disease?

Shaw et al., 2007
What will / needs to change in the near future?

- New Clinical Trials are focused on disease pathology and progression (Amyloid immunotherapy / vaccination)
- Less expensive, less invasive technologies for early disease detection & monitoring (MRI; blood biomarkers)
- More complete understanding of genetic risk across entire genome
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Questions?