The Personal Touch
Status and Future Outlook of Personalized Medicine in the Clinical Lab

Matt Silverman, PhD
Background

- BS, MS, PhD in Chemical Engineering at UCLA
- MS research: biofuels production, metabolism, genetic engineering
- PhD: cancer imaging and metabolism
- Teaching at SFSU with CLS Program for 5 years
- 55-60 CLS graduates/year
Outline

• What is personalized medicine?
  o Omics and new testing

• Patient involvement
  o How much is too much?

• Demonstrating lab value
  o How do we show that new testing is useful?
Country Doctor Ernest Ceriani Making House Call on Foot in Small Town: W. Eugene Smith 1948
Edward Jenner - 1796
Clinical Trial

Toxic Side Effects

No Effect

Responds to Treatment

Why?
Estimated 13 billion tests performed in the US/year

3-5% of healthcare spending
Shift from quantity of treatment/testing to quality of results

• Over $200 billion/year spent on unnecessary tests and procedures

• High volume of lab testing makes it a prime target for improving efficiency, despite the low contribution to total healthcare costs

• 16-25% test overutilization

• 34-56% test underutilization
2011 Audit at Southampton General Hospital

- Looked at 40 patients admitted with a diagnosis of epistaxis
- 28 of those C-reactive protein test done
- Only 3 actually had a valid clinical reason to test
More than 90% of test price data came from commercial labs; 1% came from hospitals.
Collecting more hospital data will be essential for keeping reimbursement rates at sustainable levels.
## COLA ANALYSIS

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
<th>Value to diagnosis &amp; treatment</th>
<th>2017 National Limit Amount</th>
<th>2018 Amount with 10% cap</th>
<th>Weighted Median</th>
<th>Percentage of Cut over 3 years</th>
<th>Number of Tests 2016 (in Millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>83036</td>
<td>A1C Test</td>
<td>Treatment of chronic diabetes</td>
<td>$13.32</td>
<td>$11.99</td>
<td>$8.50</td>
<td>-36.7%</td>
<td>19.1</td>
</tr>
<tr>
<td>85025</td>
<td>Complete CBC with auto differential</td>
<td>Diagnosis of infection, anemia etc.</td>
<td>$10.66</td>
<td>$9.59</td>
<td>$6.88</td>
<td>-35.46%</td>
<td>41</td>
</tr>
<tr>
<td>80053</td>
<td>Comprehensive Metabolic panel</td>
<td>Check major organ function</td>
<td>$14.49</td>
<td>$13.04</td>
<td>$9.08</td>
<td>-37.34%</td>
<td>41</td>
</tr>
<tr>
<td>84443</td>
<td>Thyroid Test</td>
<td>Monitoring thyroid function and medication</td>
<td>$23.05</td>
<td>$20.75</td>
<td>$14.87</td>
<td>-35.49%</td>
<td>21.3</td>
</tr>
<tr>
<td>85610</td>
<td>Prothrombin Time</td>
<td>Monitoring patients on Coumadin and coagulation disorders</td>
<td>$5.39</td>
<td>$4.85</td>
<td>$4.29</td>
<td>-20%</td>
<td>19.1</td>
</tr>
<tr>
<td>83880</td>
<td>Assay of natriuretic peptide</td>
<td>Testing for heart failure</td>
<td>$46.56</td>
<td>$41.90</td>
<td>$39.26</td>
<td>-15.68%</td>
<td>1.4</td>
</tr>
</tbody>
</table>
Quantity to Quality Shift

• What are the cheapest tests we can do that deliver the greatest amount of information?

• Disease state
  o 100% sensitivity and 100% specificity

• Response to treatment
  o Switch from 60% to either 0% or 100%

• Prognosis

• Risk factors
  o Genetic, epigenetic, environmental, lifestyle, and more
DIKW Framework

• Data: Reliably identify abnormalities in lab results
• Information: Derive new knowledge from patterns
• Knowledge: Apply medical knowledge to determine clinical significance
• Wisdom: Clinical significance → improve outcome
Personal Medicine - Knowledge Gap

- 4/10 consumers aware of personalized medicine
- 11% of patients have discussed personalized treatment options with doctors
- Many doctors don’t feel properly equipped to address
- What happens now that patients have unprecedented access to their medical information?
What exactly is “Personal”?

- ICD-10-CM Codes
  - T20.12 –
  - Z14.01 –
  - Y93.66 –

Is the goal to get more detail or just to make it harder to get reimbursed for tests?
Definitions: Omics

• Entirety of relationships and actions at molecular level
• Genomics
• Epigenomics
• Lipidomics
• Proteomics
• Metabolomics
• Microbiomics
• Transcriptomics
• Foodomics…
Genomics

• >3 billion base pairs
• 20-30k genes coding for ~3 proteins each on average
• Matching drug therapy to particular genetic makeup: Pharmacogenomics
• Matching particular genotypes to disease risk
• Can be misleading
  o 5-fold increase in risk from 0.01% to 0.05%
  o Over 3 billion potential variables: signal vs noise problem
Epigenomics

Epigenetic changes to the chromatin may result from:
- Development (in utero, childhood)
- Environmental chemicals
- Drugs/Pharmaceuticals
- Aging
- Diet

Epigenetic changes may result in:
- Cancer
- Autoimmune disease
- Mental disorders
- Diabetes

Histones are proteins around which DNA winds for compaction and gene regulation.
DNA methylation and chemical modification of histone tails alter the spacing of nucleosomes and change gene expression.
Proteomics

- Post-translational modifications
  - Phosphorylation
  - Ubiquitination
  - Methylation
  - Acetylation
  - Glycosylation
- Varies over cell type and time
- Immunoassays
- Mass spec
Theranostics

- Combination of diagnostics and therapy

Me-4FDG  2-FDG  Me-4FDG  2-FDG
Inhibition of SGLT activity

color
+dapa
Genomics: Guiding Risk and Therapy
## Family Risk Factor: 1\textsuperscript{st} Degree Relative

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 diabetes</td>
<td>2.3–2.8</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>4.5</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>2–2.6</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>1.6–2</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1.7–2.5</td>
</tr>
</tbody>
</table>

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# Health Risk Assessments

**Framingham coronary heart disease model**

**Gail model breast-cancer risk assessment**
### 1.1%  
10-year risk of heart disease or stroke

- On the basis of your age alone, the USPSTF guidelines suggest there is insufficient evidence you will benefit from starting aspirin for heart disease and stroke risk reduction.
- On the basis of your calculated risk for heart disease or stroke less than 7.5%, the ACC/AHA guidelines suggest you have no indication to be on a statin.
- Based on your age, your blood pressure is well-controlled.

<table>
<thead>
<tr>
<th>Demography</th>
<th>Cholesterol</th>
<th>Blood pressure</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: 40</td>
<td>Total: 180</td>
<td>Systolic: 120</td>
<td>Diabetes: no</td>
</tr>
<tr>
<td>Gender: male</td>
<td>HDL: 40</td>
<td>Diastolic: 80</td>
<td>Smoking: no</td>
</tr>
<tr>
<td>Race: not African-American</td>
<td></td>
<td></td>
<td>On medication: no</td>
</tr>
</tbody>
</table>

### 73.7%  
10-year risk of heart disease or stroke

- On the basis of your age and calculated risk for heart disease or stroke over 10%, the USPSTF guidelines suggest you discuss starting aspirin with your doctor.
- On the basis of your age, your calculated risk for heart disease or stroke over 7.5%, and diabetes, the ACC/AHA guidelines suggest you should be on a high intensity statin.
- Based on your age and race, your blood pressure is poorly-controlled, and you should initiate lifestyle interventions and consider starting a thiazide diuretic, ACEI/ARB, or calcium channel blocker.

<table>
<thead>
<tr>
<th>Demography</th>
<th>Cholesterol</th>
<th>Blood pressure</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: 65</td>
<td>Total: 260</td>
<td>Systolic: 170</td>
<td>Diabetes: yes</td>
</tr>
<tr>
<td>Gender: male</td>
<td>HDL: 25</td>
<td>Diastolic: 130</td>
<td>Smoking: yes</td>
</tr>
<tr>
<td>Race: not African-American</td>
<td></td>
<td></td>
<td>On medication: yes</td>
</tr>
</tbody>
</table>
## Type 2 diabetes Genetic Risk Factors

<table>
<thead>
<tr>
<th>Region/gene</th>
<th>Chromosome</th>
<th>Approximate effect size</th>
<th>Disease mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPARG</td>
<td>3p25</td>
<td>1.19</td>
<td>Insulin resistance</td>
</tr>
<tr>
<td>KCNJ11</td>
<td>11p15.1</td>
<td>1.14</td>
<td>β-cell dysfunction</td>
</tr>
<tr>
<td>TCF7L2</td>
<td>10q25.3</td>
<td>1.45</td>
<td>β-cell dysfunction</td>
</tr>
<tr>
<td>SLC30A8</td>
<td>8q24.11</td>
<td>1.15</td>
<td>β-cell dysfunction</td>
</tr>
<tr>
<td>HHEX</td>
<td>10q23.33</td>
<td>1.15</td>
<td>Reduced β-cell mass</td>
</tr>
<tr>
<td>CDKN2A/CDKN2B</td>
<td>9p21</td>
<td>1.20</td>
<td>Reduced β-cell mass</td>
</tr>
</tbody>
</table>

Malandrino et al.
Genomics

- Estrogen Receptor in Breast Cancer
  - Tamoxifen Treatment, regulated by CYP2D6 and CYP3A4

- High Levels of HER-2/neu or ERBB2 in Breast Cancer
  - Trastuzumab Treatment

- BRCA risk for breast and ovarian cancer
  - 60% with mutation develop breast cancer
  - Only 1% has mutation
  - Myriad had patent on gene until 2013
Colon Cancer

- Homozygous UGT1A1 increased risk for neutropenia with irinotecan
- High EGFR expression more likely to respond to tyrosine kinase inhibitors, mutations in BRAF and KRAS decrease response
- MLH1
- MSH2
- MSH6
- MUTYH
- PTEN
Clinically available molecular tests

<table>
<thead>
<tr>
<th>Time point in clinical decision making</th>
<th>Test</th>
<th>Indication</th>
<th>Test</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk/susceptibility</td>
<td>BRCA1, BRCA2</td>
<td>Breast</td>
<td>KIF6, 9p21</td>
<td>CAD</td>
</tr>
<tr>
<td></td>
<td>HNPCC, MLH1, MSH2</td>
<td>Colon</td>
<td>Familion® 5-gene profile</td>
<td>LQTS</td>
</tr>
<tr>
<td></td>
<td>TP53, PTEN</td>
<td>Sarcomas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening</td>
<td>HPV genotypes</td>
<td>Cervical</td>
<td>Corus™ CAD</td>
<td>CAD</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Lymphochip</td>
<td>Lymphoma</td>
<td>Corus CAD</td>
<td>CAD</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Oncotype DX® (21-gene assay)</td>
<td>Breast</td>
<td>TnI, BNP, CRP</td>
<td>ACS</td>
</tr>
<tr>
<td></td>
<td>MammaPrint® (70-gene assay)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Her2/neu, ER, PR</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Chan, I et al.
# Clinically available molecular tests

<table>
<thead>
<tr>
<th>Time point in clinical decision making</th>
<th>Cancer</th>
<th>Cardiovascular disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test</td>
<td>Indication</td>
</tr>
<tr>
<td>Pharmacogenomics</td>
<td>Her2/neu</td>
<td>Herceptin</td>
</tr>
<tr>
<td></td>
<td>UGT1A1</td>
<td>Irinotecan</td>
</tr>
<tr>
<td></td>
<td>KRAS</td>
<td>Cetuximab</td>
</tr>
<tr>
<td></td>
<td>EGFR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amplichip®; DMET™ CYP2D6/CYP2C19</td>
<td></td>
</tr>
<tr>
<td>Monitoring</td>
<td>CTCs</td>
<td>Tumor recurrence or progression</td>
</tr>
<tr>
<td>Disease area</td>
<td>Host genotype</td>
<td>Treatment</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>---------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Optimizing drug efficacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic hepatitis C</td>
<td>IL28B</td>
<td>Pegylated interferon alpha, Ribavirin</td>
</tr>
<tr>
<td>Breast cancer, other tumors</td>
<td></td>
<td>Antracyclines, poly(adenosine diphosphate-ribose) polymerase inhibition</td>
</tr>
<tr>
<td>Preventing drug toxicities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV type 1</td>
<td>(HLA)-B*5701</td>
<td>Abacavir</td>
</tr>
<tr>
<td>Rheumatic and inflammatory bowel disorders</td>
<td>Thiopurine methyl transferase genotypes</td>
<td>Azathioprine</td>
</tr>
<tr>
<td></td>
<td>HLA-B*58:01</td>
<td>Allopurinol</td>
</tr>
<tr>
<td>Gastrointestinal cancers</td>
<td>Dehydropyrimidine dehydrogenase deficiency</td>
<td>5-fluorouracil</td>
</tr>
<tr>
<td></td>
<td>UGT1A1 polymorphism</td>
<td>Irinotecan</td>
</tr>
</tbody>
</table>
Pathogen Genomes

• *Haemophilus influenza* genome sequenced in 1995
• Since then, over 1000 bacterial and 3000 viral genomes sequenced
• Compare pathogenic and nonpathogenic strains
• Identify vaccine targets
Clinical Decision Support

- Computerized alerts
- Reminders
- Clinical guidelines
- Patient date reports
- Documentation templates
- Diagnostic support
- Clinical workflow tools
- Difficult and complicated to implement and keep updated
Clinical Decision Support

• Goals:
  o Best knowledge available when needed
  o High adoption and effective use
  o Continuous improvement

• Adjust for the massive amount of information

• Are robots going to run the hospital?
Implementing Genomics in Practice (IGNITE)

The IGNITE Consortium was created to enhance the use of genomic medicine by supporting the development of methods for incorporating genomic information into clinical care and exploration of the methods for effective implementation, diffusion and sustainability in diverse clinical settings.
eMERGE is a national network organized and funded by the National Human Genome Research Institute (NHGRI) that combines DNA biorepositories with electronic medical record (EMR) systems for large scale, high-throughput genetic research in support of implementing genomic medicine.

CAGACAGTATTG
TAAATTCGCGGT
GAAATGATCATC

POPULAR TOOLS (CLICK ON A BUTTON BELOW)

PheKB
A knowledgebase for discovering phenotypes from genomic and biological databases.

MyResults.org
An informational tool for educating patients about genetic test results.

SPHINX
A data exploration tool for genetics-related drug response and pathway investigations.

RECENT PUBLICATIONS

eMERGE Consortium. Electronic address: ag


**Popular Tools** (Click on a button below)

- **PheKB**
  A knowledgebase for discovering phenotypes from electronic medical records

- **MyResults.org**
  An informational tool for educating patients about genetic test results

- **SPHINX**
  A data exploration tool for genetics-related drug response hypothesis generation

- **CDS_KB**
  A knowledgebase of clinical decision support that drives precision medicine

- **emerge Model Consent Language**

- **PheWAS catalog**
Launch of the collaborative project PEVOdata funded in ERA PerMed’s first JTC2018

For the launch of the European project PEVO\textsuperscript{data} for Personalised Medicine (PM), Prof Christophe Le Tourneau, head of the Department of Drug Development and Innovation (D\textsuperscript{3}i) at Curie Institute and project coordinator, hold a press conference on June 25\textsuperscript{th}, 2019 in Paris (France). PEVO\textsuperscript{data} is funded by ERA PerMed for a period of 3 years in the first Joint Transnational Call (JTC) 2018 with a total budget of €1.54 million.
Established in 2005 by the Office of Public Health Genomics at the Centers for Disease Control and Prevention
In 2014, eight out of 41 new drug therapies approved by FDA were “personalized”
Predicting drug response

60% OF THE TIME

IT WORKS EVERY TIME
Cytochrome P450 2D6 (CYP2D6)

• 74 variants reported
  o Reduced functionality
  o No functionality

• Copy number variants
  o Increased activity
    • Dextromethorphan – cough suppressant, morphinan class
    • Risperidone – mental disorders, atypical antipsychotics class
    • Codeine – pain medication, opioid
    • Haloperidol – mental disorders, antipsychotic
Massive complexity of gene-drug interactions

- Traditional model of listing side-effects won’t suffice
- How many journal articles does it take?
- How do we categorize patients?
  - Genotype?
  - Side-effects?
  - Response rate?
Legal issues

• How much of the drug approval process changes?
• Patient confidentiality
• Direct-to-consumer advertising

Consult with your doctor if you have CYP2D6 variants 4, 13, 35, 52, or 73
Social/Financial issues

- Stigmatization of certain genotypes
- Insurance pre-existing conditions
- Who pays?
- $10,000 for genome sequence
- Patients are empowered for a more active role
- Genetic Information Nondiscrimination Act
  - 2008 law protecting against discrimination based on genetic information
  - Affects job and health coverage
  - Not life insurance or disability insurance
What counts as an “orphan drug”?

• Rare disease or condition (<200,000 people)
• What happens when genetics and disease together are rare?
• Genetics and environmental factors can work together to make smaller patient sub-populations
Metabolomics: Old Tests, New Style
Metabolomics in Drug Response

- Aspirin acts as an antiplatelet agent
- Prevention of CVD
- Reduce risk of cardiovascular death, but ineffective in ~25% of high risk patients

<table>
<thead>
<tr>
<th>Platelet Aggregation</th>
<th>Good Responders (N=40)</th>
<th>Poor Responders (N=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Aspirin</td>
<td>13.3±1.9</td>
<td>14.2±1.9</td>
</tr>
<tr>
<td>After Aspirin</td>
<td>5.7±1.9</td>
<td>14.2±1.9</td>
</tr>
</tbody>
</table>
## Metabolomics in Aspirin Response

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Before Aspirin</th>
<th>After Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salicylic acid</td>
<td>0.1±0.4</td>
<td>1.8±0.8</td>
</tr>
<tr>
<td>Salicyluric acid</td>
<td>0.5±0.2</td>
<td>1.4±0.9</td>
</tr>
<tr>
<td>Azelaic acid</td>
<td>1.3±0.9</td>
<td>0.6±0.4</td>
</tr>
<tr>
<td>D-Ribose</td>
<td>1.3±1.1</td>
<td>0.6±0.7</td>
</tr>
<tr>
<td>L-Aspartic acid</td>
<td>1.2±0.3</td>
<td>0.7±0.2</td>
</tr>
<tr>
<td>Inosine</td>
<td>0.7±0.7</td>
<td>1.2±0.8</td>
</tr>
<tr>
<td>Guanosine</td>
<td>0.7±0.5</td>
<td>1.2±0.7</td>
</tr>
<tr>
<td>Adenosine-5-monophosphate</td>
<td>0.8±0.2</td>
<td>1.1±0.6</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>1.1±0.5</td>
<td>0.8±0.6</td>
</tr>
<tr>
<td>Palmitoleic acid</td>
<td>1.1±0.7</td>
<td>0.8±0.8</td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>1.1±0.4</td>
<td>0.8±0.6</td>
</tr>
<tr>
<td>Hypoxanthine</td>
<td>1.1±0.6</td>
<td>0.8±0.5</td>
</tr>
<tr>
<td>Shikimic acid</td>
<td>1.1±0.4</td>
<td>0.8±0.3</td>
</tr>
<tr>
<td>Xanthine</td>
<td>1.1±0.4</td>
<td>0.8±0.4</td>
</tr>
<tr>
<td>Arachidonic acid</td>
<td>1±0.3</td>
<td>0.9±0.4</td>
</tr>
<tr>
<td>3-Phosphoglyceric acid</td>
<td>1.1±0.4</td>
<td>0.8±0.2</td>
</tr>
<tr>
<td>Adenosine</td>
<td>0.8±0.7</td>
<td>1.1±0.9</td>
</tr>
<tr>
<td>2,5-Furandicarboxylic acid</td>
<td>0.9±0.4</td>
<td>1±0.5</td>
</tr>
</tbody>
</table>
Yerges-Armstrong, L. et al.
Simvastatin

- Statins used for reducing CVD risk and reducing cholesterol
- Effectiveness of a given statin ranges from less than 5% to greater than 60%
Simvastatin

Kaddurah-Daouk, R. et al.
## Metabolomics in Drug Response

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Drug Efficacy</th>
<th>Method</th>
<th>Key Metabolite</th>
<th>Increased in plasma of</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Antiplatelet aggregation</td>
<td>GC-MS-based untargeted</td>
<td>inosine</td>
<td>poor-responders at post-treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MS-based targeted</td>
<td>serotonin</td>
<td>poor-responders at both baseline and post-treatment</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Reducing LDL-cholesterol</td>
<td>GC/MS-based untargeted</td>
<td>LCA, TLCA, GLCA, COPR</td>
<td>good-responders at baseline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GC/TOFMS-based untargeted</td>
<td>xanthine, 2-hydroxyvaleric acid, succinic acid, stearic acid</td>
<td>good-responders at baseline</td>
</tr>
<tr>
<td>Drugs</td>
<td>Drug Efficacy</td>
<td>Method</td>
<td>Key Metabolite</td>
<td>Increased in plasma of</td>
</tr>
<tr>
<td>----------------</td>
<td>-----------------------------------</td>
<td>-------------------------------</td>
<td>---------------------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Acamprosate</td>
<td>treating Alcohol Use Disorders</td>
<td>UPLC-MS/MS-based untargeted</td>
<td>glutamate</td>
<td>good-responders at baseline</td>
</tr>
<tr>
<td>Atenolol</td>
<td>lower blood pressure</td>
<td>GC-TOFMS-based untargeted</td>
<td>5-methoxytryptamine</td>
<td>good-responders at baseline</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>lower blood pressure</td>
<td>GC-TOFMS-based untargeted</td>
<td>arachidonic acid, unknown metabolite (223548)</td>
<td>poor-responders at baseline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>unknown metabolite (223548)</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>Anti-depressant</td>
<td>GC-TOFMS-based untargeted</td>
<td>5-methoxytryptamine</td>
<td>good-responders at baseline</td>
</tr>
<tr>
<td>L-carnitine</td>
<td>treating sepsis</td>
<td>NMR-based untargeted</td>
<td>acetyl carnitine/carnitine</td>
<td>poor-responders at baseline</td>
</tr>
</tbody>
</table>
Metabolomics and Disease Susceptibility

- Onset of type 2 diabetes vs initial presentation of hyperglycemia
- Study: 2422 normoglycemic individuals followed for 12 years, 201 developed diabetes
- 61 metabolites measured
Risk adjusting for age, sex, BMI, fasting glucose, and parental history

<table>
<thead>
<tr>
<th></th>
<th>3 amino acids</th>
<th>5 amino acids</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Isoleucine, Phenylalanine, Tyrosine</td>
<td>Isoleucine, Phenylalanine, Tyrosine, Leucine, Valine</td>
</tr>
<tr>
<td>Per SD (score)</td>
<td>1.36 (1.08-1.70)</td>
<td>1.38 (1.09-1.74)</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>0.008</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>1st quartile</strong></td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td><strong>2nd quartile</strong></td>
<td>1.42 (0.73-2.73)</td>
<td>1.48 (0.76-2.89)</td>
</tr>
<tr>
<td><strong>3rd quartile</strong></td>
<td>1.93 (1.00-3.71)</td>
<td>2.16 (1.11-4.20)</td>
</tr>
<tr>
<td><strong>4th quartile</strong></td>
<td>2.01 (1.02-3.99)</td>
<td>2.23 (1.12-4.42)</td>
</tr>
<tr>
<td><strong>P for trend</strong></td>
<td>0.03</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Wang, T. et al.
Metabolomics

• Typical analytical methods
  o Nuclear Magnetic Resonance (NMR)
    ▪ Higher specificity/accuracy, higher start-up cost, lower sensitivity
  o Gas Chromatography-Mass Spectrometry (GC-MS)
    ▪ Good sensitivity, metabolite identification available from commercial databases and software, labor intensive sample preparation, difficult to ID novel compounds
  o Liquid Chromatography-Mass Spectrometry (LC-MS)
    ▪ Higher sensitivity, wider metabolite detection, more difficult to ID
## Rising benefit of Mass Spec

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Typical Ranges</th>
<th>Architect (Abbott)</th>
<th>LIAISON (DiaSorin)</th>
<th>iSYS (IDS)</th>
<th>Elecsys (Roche)</th>
<th>Centaur (Siemens)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D3</td>
<td>18-29 nM</td>
<td>0.3%</td>
<td>&lt;1%</td>
<td>2.7%</td>
<td>5%</td>
<td>0.3%</td>
</tr>
<tr>
<td>D2</td>
<td></td>
<td>0.1%</td>
<td>&lt;1%</td>
<td>2.7%</td>
<td>6%</td>
<td>0.2%</td>
</tr>
<tr>
<td>25(OH)D3</td>
<td>8-165 nM</td>
<td>105%</td>
<td>100%</td>
<td>100%</td>
<td>98%</td>
<td>106%</td>
</tr>
<tr>
<td>25(OH)D2</td>
<td>&lt;7 nM</td>
<td><strong>52%</strong></td>
<td>104%</td>
<td>100%</td>
<td>81%</td>
<td>97%</td>
</tr>
<tr>
<td>1,25(OH)2D3</td>
<td>48-168 pM</td>
<td>13%</td>
<td>17%</td>
<td>nd</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>1,25(OH)2D2</td>
<td>nd</td>
<td></td>
<td>40%</td>
<td>nd</td>
<td>6%</td>
<td>1%</td>
</tr>
<tr>
<td>24R,25(OH)2D3</td>
<td>&lt;30 nM</td>
<td>112%</td>
<td>nd</td>
<td>&gt;100%</td>
<td>121%</td>
<td>nd</td>
</tr>
<tr>
<td>3-epi-25(OH)D3</td>
<td>&lt;22 nM</td>
<td>3%</td>
<td>&lt;1%</td>
<td>nd</td>
<td>93%</td>
<td>1%</td>
</tr>
</tbody>
</table>
Mass Spec in Vitamin D – Diet/Environment Matters
Metabonomics of Newborn Screening Dried Blood Spot Samples: A Novel Approach in the Screening and Diagnostics of Inborn Errors of Metabolism

Extraction → Single-stage HR-MS → Diagnosis

- Healthy (500)
- MCADD (21)
- PKU (21)
- CLD (21)
- HCY (6)
- CLD (4)
Mass Spec and Proteomics

Seibert, V et al.
Adverse Drug Reactions in the US

- 6.7% adverse drug reactions
- 0.3% fatal reactions
- ~100,000 deaths per year
- 5% of hospital admissions ~ 2 million
- Increase in $2500/patient
  - Warfarin complications ~$11,000 per patient
- Total $4 billion in cost
Saved by Personalized Medicine

• Between 1976 and 2005, 28 drugs withdrawn in US
  o Hepatotoxicity
  o Nephotoxicity
  o Rhabdomylosis
  o Physicians ignoring recommended guidelines
Saved by Personalized Medicine

• Example: Perhexilene, effective in treating angina, but unacceptable hepatotoxicity
  o Withdrawn in US, but not Australia or New Zealand
  o Use was linked to pre-treatment phenotyping and therapeutic drug monitoring

• Example: Natalizumab for MS
  o Withdrawn in US due to reactivation of JC virus (progressive multifocal leukoencephalopathy)
  o Available in Europe – testing for seropositivity for JC antibodies
Following the $

• Introduction of new testing needs to show cost/benefit

• $100 test, reducing risk of $10,000 ADR from 50% to 30% for 100 patients
  - Test cost: $10,000
  - ADR costs: $500,000 → $300,000; $200k savings
  - Test pays for itself even if just one patient affected

• Take advantage of the low contribution of testing to total medical costs
Data Collection- The Electronic Medical Record

- Massive database
- Age
- Gender
- Ethnicity
- Medical History
- Prescription Information
- Lab Results
- Comorbidities
Patient access to personal health data

- 27% of hospitals allowed patients to access EHRs in 2012
- 93% in 2016
- Become expected
Patient interaction

- Feedback from doctor
- Patient can update demographic info
  - 80% doctors think patients should be able to update demographic info
  - ~50% think patients should be able to update test results…

https://www.carecloud.com/continuum/patient-access-to-ehrs-how-much-is-too-much/
A dangerous patient

• A patient with WebMD can be a very troublesome thing

• Patients altering medical records
  o Getting access to drugs/treatment they shouldn’t have
  o Missed diagnosis
  o Lack of understanding
Volume To Value
Make Every Test Count
Advances in Testing Algorithms

• Decrease turnaround time
• Lower cost
• Improve accuracy
• Minimize the work needed to get the most accurate results
When Cutoffs Are Complicated

Not always a clear division between normal and abnormal

Multiple tests needed to identify patient status
Laboratory Screening Tests for Suspected Multiple Myeloma

Begin testing with:
- SMOGA / Monoclonal Gammopathy Screen, Serum
- OR
- MPSS / Monoclonal Protein Study, Serum
- FLCP / Immunoglobulin Free Light Chains, Serum
to establish baseline information

If any of the following are detected:
- Monoclonal IgG
- Monoclonal IgA
- Monoclonal IgD
- Monoclonal kappa free light chain
- Monoclonal lambda free light chain

All testing is negative but clinician still has high index of suspicion

Monoclonal IgM is detected

Differential diagnosis:
- IgM MGUS
- Waldenstrom macroglobulinemia
- Other lymphoproliferative disorders

Differential diagnosis:
- Multiple myeloma (MM)
- Smoldering multiple myeloma (SMM)
- Monoclonal gammopathy of undetermined significance (MGUS)
- Light chain MGUS
- Primary amyloidosis (AL)

Order the following tests to establish baseline information:
- MPSU / Monoclonal Protein Study, 24 Hour, Urine
- HPWET / Hematopathology Consultation, MML Embed*
- OR
- HPCUT / Hematopathology Consultation, Client Embed*
Thyroid Function Ordering Algorithm

Nonhospitalized patients without known or suspected pituitary disease

Begin evaluation by ordering either the cascade approach
- THSCM / Thyroid Function Cascade, Serum (all appropriate tests are performed automatically) or order each test individually, beginning with
- STSH / Thyroid-Stimulating Hormone-Sensitive (s-TSH), Serum

s-TSH
- Functional sensitivity: 0.01 mIU/L

<0.10 mIU/L*
- Hyperthyroid suspect
- Order Free T4: FRT4 / T4 (Thyroxine), Free, Serum
- If Free T4 is normal
- Order Total T3: T3 / T3 (Triiodothyronine), Total, Serum

0.10–0.29 mIU/L*
- Borderline low TSH
- Order Free T4: FRT4 / T4 (Thyroxine), Free, Serum

0.30–4.2 mIU/L*
- No further testing unless clinically indicated

>4.2 mIU/L*
- Hypothyroid suspect
- Order Free T4 and TPO:
  - FRT4 / T4 (Thyroxine), Free, Serum
  - TPO / Thyroperoxidase (TPO) Antibodies, Serum

*normal range: 0.3–5.5 mIU/L
Deep Vein Thrombosis Algorithm

- Negative Test D-Dimer
  - Negative: DVT Excluded
  - Positive: One week US
- Positive
  - Treat
Proposed New Algorithm

Low prob Test D-Dimer

Negative DVT Excluded

Initial clinical probability assessment

High prob Test D-Dimer and US

Positive US

Wells, P.
Statistics and Diagnostics

- Sensitivity
  - Percentage of sick patients identified

- Specificity
  - Percentage of healthy patients identified

- Positive Predictive Value
  - Percentage of positive patients that are sick

- Negative Predictive Value
  - Percentage of negative patients that are healthy

- Disease Prevalence
  - Percentage of population with the disease
# Calculations

<table>
<thead>
<tr>
<th></th>
<th>Sick</th>
<th>Healthy</th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive</strong></td>
<td>19</td>
<td>1</td>
<td>20</td>
<td>Positive predictive value 95%</td>
</tr>
<tr>
<td>Results</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Negative</strong></td>
<td>6</td>
<td>974</td>
<td>980</td>
<td>Negative predictive value 99.4%</td>
</tr>
<tr>
<td>Results</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>25</td>
<td>975</td>
<td>1000</td>
<td>Disease Prevalence 2.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>76%</td>
<td>99.9%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Ideal cheap screening test with a more expensive confirmatory test(s)

<table>
<thead>
<tr>
<th></th>
<th>Sick</th>
<th>Healthy</th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive</strong></td>
<td>25</td>
<td>10</td>
<td>35</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td></td>
<td></td>
<td></td>
<td>71.4%</td>
</tr>
<tr>
<td><strong>Negative</strong></td>
<td>0</td>
<td>965</td>
<td>965</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td></td>
<td></td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>25</td>
<td>975</td>
<td>1000</td>
<td>Disease Prevalence</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.5%</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>99.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Impact of rare disease
(same sensitivity and specificity)

<table>
<thead>
<tr>
<th></th>
<th>Sick</th>
<th>Healthy</th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Results</td>
<td>2</td>
<td>10</td>
<td>12</td>
<td>Positive predictive value 16.7%</td>
</tr>
<tr>
<td>Negative Results</td>
<td>0</td>
<td>988</td>
<td>988</td>
<td>Negative predictive value 100%</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>998</td>
<td>1000</td>
<td>Disease Prevalence 0.2%</td>
</tr>
</tbody>
</table>

- Sensitivity: 100%
- Specificity: 99.0%
Positive Predicament

• A 16.7% positive predictive value will just be thrown out by a physician

• Screened out 988 of 1000 patients who didn’t need the more expensive, more accurate test

• Example: $10 screen, $100 confirmation
  - $10,000 screen + $1,200 confirmation = $11,200
  - $88,800 savings with same accuracy
The financial and human perspectives

• Cost of each step in the algorithm
• Cost of missed/delayed diagnosis
  o Cost to hospital
  o Risk to patient (life expectancy)
  o Public health risk – contagious disease
• Disease prevalence
• Cost of over diagnosis/treatment
  o Dollar cost
  o Patient time
  o Side effects
  o Global problem: antibiotic resistance?
Mapping out the Value

Symptomatic Patients
Cost of initial testing

True Positive
False Positive
False Negative
True Negative

Cost of Treatment
Over-treatment
Delay In Diagnosis
Additional Testing

Improved Life Expectancy
Delay In Diagnosis
Public Health Risk
Peace of Mind
Assigning Values For Algorithms

- Sensitivity, Specificity, Disease Prevalence
  - Diabetes – Pretend 15% prevalence
  - FBS – Sensitivity 85%, specificity 95%

<table>
<thead>
<tr>
<th></th>
<th>True Positives</th>
<th>False Positives</th>
<th>False Negatives</th>
<th>True Negatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>15% x 85%</td>
<td>15% x 5%</td>
<td>15% x 15%</td>
<td>85% x 95%</td>
<td>12.75%</td>
</tr>
<tr>
<td></td>
<td>85%</td>
<td>2.25%</td>
<td>80.75%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12.75%</td>
<td>4.25%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

True Positives = 15% prevalence x 85% sensitivity
False Positives = 85% specificity x 5% false positives
False Negatives = 15% prevalence x 15% false negatives
True Negatives = 85% specificity x 95% true negatives
Assigning Values For Algorithms

<table>
<thead>
<tr>
<th>True Positives</th>
<th>False Positives</th>
<th>False Negatives</th>
<th>True Negatives</th>
</tr>
</thead>
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<td>85% x 5%</td>
<td>15% x 15%</td>
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</tr>
<tr>
<td>12.75%</td>
<td>4.25%</td>
<td>2.25%</td>
<td>80.75%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>$ cost treatment</th>
<th>$ cost treatment until corrected</th>
<th>Cost of additional tests</th>
<th>Cost of additional tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years life expectancy increased</td>
<td>Delay in treatment</td>
<td>Peace of mind</td>
<td></td>
</tr>
</tbody>
</table>
Assigning Values For Algorithms

- Infection—Say 45% bacterial, 55% viral
- Patients demand antibiotics: 99% sensitivity?, specificity 15%?

<table>
<thead>
<tr>
<th>True Positives</th>
<th>False Positives</th>
<th>False Negatives</th>
<th>True Negatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>45% x 99%</td>
<td>55% x 85%</td>
<td>45% x 1%</td>
<td>55% x 95%</td>
</tr>
<tr>
<td>44.55%</td>
<td>46.75%</td>
<td>0.45%</td>
<td>8.25%</td>
</tr>
</tbody>
</table>

-Cheap and usually covered by insurance
-Antibiotic resistance adds $1400 to cost

Risk of lawsuit
Assigning Values For Algorithms

- Infection—Say **45%** bacterial, **55%** viral
- Patients demand antibiotics: **99%** sensitivity?, specificity **15%**?

<table>
<thead>
<tr>
<th>True Positives</th>
<th>False Positives</th>
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<td>45% x 99%</td>
<td>55% x 85%</td>
<td>45% x 1%</td>
<td>55% x 95%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>False Negatives</th>
<th>True Negatives</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>44.55%</strong></td>
<td><strong>0.45%</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>46.75%</strong></td>
<td><strong>8.25%</strong></td>
</tr>
</tbody>
</table>

Highlight the danger of antibiotic resistance
100% increase over 13 years

- Cheap and usually covered by insurance
- Antibiotic resistance adds $1400 to cost
- Risk of lawsuit
Diagnostic Gray Zone

- FBS < 100 mg/dL: Normal
- 100 mg/dL < FBS < 125 mg/dL: Pre-diabetes
- FBS > 125: Diabetic

- How could cutoffs work with personalized medicine?
- Keep in mind, blood sugar isn’t the real concern, insulin resistance/deficiency is
Mapping out the Value

Initial FBS Test

- Normal
  - Minimal false neg
- Gray
  - Low cost intervention
- Positive
  - High cost intervention
Gray Zone

- Important to establish baselines for measurements with great inter-individual variability
- Normal for one person may be abnormal for another
A1C and red blood cell life

Assumption: Rate of A1C glycosylation ~average glucose conc
A1C and red blood cell life

Older red blood cells have high glycosylation.
Red blood cell life

• ~120 days

• Very consistent, but varies from person to person
  ○ 115 days vs 125 days

• 7% A1C may not mean as much for someone with 125 day lifespan as it does for someone with 115 day lifespan
Wrap it up

- The trend toward personalized medicine holds opportunity for the clinical lab to leverage low cost and high contributions to clinical decisions.
Wrap it up

- Presentation of value of emerging tests is essential

Results

5% Cost
Wrap it up

• Informed patients can become allies

Results

5% Cost
References

References


References


• Seibert, V., Ebert, M., Buschmann, T. (2005) Advances in clinical cancer proteomics: SELDI-ToF-mass spectrometry and biomarker discovery. BRIEFINGS IN FUNCTIONAL GENOMICS AND PROTEOMICS. Vol 4. NO 1. 16–26
