Precision Medicine Symposium

PGx Beyond Drug Metabolizing enzymes, An Integrative Physiology Approach

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“There are approximately 75,000 genetic tests on the market, with about ten new tests entering the market daily.”

Percentages of spending on genetic testing in six clinical domains, by quarter, 2014–16

Of the 75K available tests, 86% of the genetic tests were single-gene tests. The remaining tests were panel tests, including 9,311 multi-analyte assays with algorithmic analyses, 85 noninvasive prenatal tests (NIPT), 122 whole exome sequencing tests (WES), and 873 whole genome (WGS) analysis tests.  

Percentages of spending on types of genetic testing, by quarter, 2014–16

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Hypertension as a risk factor

Figure 6: Deaths attributed to 19 leading risk factors, by country income level, 2004.

- High blood pressure
- Tobacco use
- High blood glucose
- Physical inactivity
- Overweight and obesity
- High cholesterol
- Unsafe sex
- Alcohol use
- Childhood underweight
- Indoor smoke from solid fuels
- Unsafe water, sanitation, hygiene
- Low fruit and vegetable intake
- Suboptimal breastfeeding
- Urban outdoor air pollution
- Occupational risks
- Vitamin A deficiency
- Zinc deficiency
- Unsafe health-care injections
- Iron deficiency

Mortality in thousands (total: 58.8 million)
Underserved Populations

Results:
There was a significantly (p < 0.001 for each) greater percentage of blacks and Hispanics between 18-39 years, higher rates of diabetes, less CKD, nearly a 2-fold higher poverty-to-income ratio, and baseline mean sBP and mean dBP were about 3/2 mm Hg higher. During the study period, all three racial groups (whites, blacks, and Hispanics) experienced a substantial increase in hypertension treatment and control. The overall treatment rates were 73.9%, 70.8%, and 60.7%. Hypertension control rates with JNC 7 were 42.9%, 36.9%, and 31.2% for whites, blacks, and Hispanics, respectively (p < 0.001), and a >10% better control was noted in JNC 8 for each group. When stratified by insurance status, blacks (odds ratio [OR], 0.74 for insured and 0.59 for uninsured) and Hispanics (OR, 0.74 for insured and 0.58 for uninsured) persistently had lower rates of hypertension control compared with whites. Unlike black patients, Hispanics received less intensive antihypertensive therapy (OR for combination therapy, 0.77). Racial disparities also persisted in subgroups stratified by age (≥60 and <60 years of age) and presence of comorbidities, but worsened among patients <60 years of age.

Conclusions:
Black and Hispanic patients have poorer hypertension control compared with whites, and these differences are more pronounced in younger and uninsured patients. While black patients received more intensive antihypertensive therapy, Hispanics were undertreated. Future studies should further explore all aspects of these disparities to improve cardiovascular outcomes.
Underserved Populations

- Hispanic/Latino populations possess a complex genetic structure that reflects recent admixture among and potentially ancient substructure within Native American, European, and West African source populations.

- Our results suggest future genome-wide association scans in Hispanic/Latino populations may require correction for local genomic ancestry at a subcontinental scale when associating differences in the genome with disease risk, progression, and drug efficacy, as well as for admixture mapping.

http://www.pnas.org/content/107/Supplement_2/8954
Physiology & Genetics of Blood Pressure:

• **Heart:** Your genes impact how hard the heart beats and heart rate (beta blockers used to treat)

• **Kidney:** Your genes impact sodium reabsorption (diuretics used to treat)

• **Vessels:** Your genes impact vascular constriction and sodium reabsorption (vasodilators used to treat)
The Problem with Standard of Care

Drugs are layered: Each Increase in # of Medications = 85% increase in nonadherence
In large and well-controlled studies there is an increase in BP in some patients with most types of therapy.

## Side Effect Profile per Drug Class

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Common</th>
<th>Less Common</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective β-blocker (METOPROLOL SUCCINATE EXTENDED-RELEASE TABLETS)</td>
<td>Tiredness and dizziness (10%), Depression (5%), Pruritus or rash (5%)</td>
<td>Shortness of breath and bradycardia (3%), Wheezing (bronchospasm) and dyspnea (1%), Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema;</td>
<td>Peyronie’s disease (&lt;0.001%)</td>
</tr>
<tr>
<td>Non-selective β-blocker (LABETALOL HYDROCHLORIDE)</td>
<td>Dizziness (11%), Nausea (6%), Fatigue (5%)</td>
<td>Dyspepsia (3%), Nasal stuffiness (3%), Headache (2%), Dyspnea (2%), Vertigo (2%), Ejaculation failure (2%), Impotence (1%), Taste distortion (1%), Edema (1%), Vomiting (&lt;1%), Diarrhea (&lt;1%), Paresthesia (&lt;1%), Increased sweating (&lt;1%)</td>
<td></td>
</tr>
<tr>
<td>CA+ channel blocker (VERAPAMIL HYDROCHLORIDE TABLET, EXTENDED RELEASE)</td>
<td>Contipation (7.3%)</td>
<td>Dizziness (3.3%), Nausea (2.7%), Hypotension (2.5%), Headache (2.2%), Edema (1.9%), CHF/Pulmonary Edema (1.8%), Fatigue (1.7%), Dyspnea (1.4%), Bradycardia (1.4%), AV Block-1°, 2°, and 3° (1.2%), Rash</td>
<td>Flushing (0.6%)</td>
</tr>
<tr>
<td>Thiazide and thiazide-like diuretic (INDAPAMIDE)</td>
<td>Headache Dizziness Fatigue, weakness, loss of energy, lethargy, tiredness, or malaise, muscle cramps or spasm, or numbness of the extremities Nervousness, tension, anxiety, irritability, or agitation (≥5%)</td>
<td>Hypokalemia Lightheadedness Drowsiness Vertigo Insomnia Depression Blurred Vision Constipation Nausea Vomiting Diarrhea Gastric irritation Abdominal pain or cramps Anorexia Orthostatic hypotension Premature ventricular contractions Irregular heart beat Palpitations Frequency of urination Nocturia Polyuria Rash Hives Pruritus Vasculitis Impotence or reduced libido Rhinorrhea</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor (LISINOPRIL)</td>
<td>Headache (5.7%), Dizziness (5.4%), Cough (3.5%),</td>
<td>Diarrhea (2.7%), Fatigue (2.5%), Upper Respiratory Infection (2.1%), Asthenia (1.3%), Orthostatic Effects (1.2%), Hypotension (1.2%), Vomiting (1.1%), Common</td>
<td>Dyspepsia (0.9%), Paresthesia (0.8%), Decreased Libido (0.4%), Nasal Congestion (0.4%), Influenza (0.3%), Vertigo (0.2%)</td>
</tr>
<tr>
<td>Angiotensin-II receptor blocker ((LOSARTAN POTASSIUM)</td>
<td>Upper Respiratory Infection (8%)</td>
<td>Dizziness (3%), Back Pain (2%), Nasal Congestion (2%), Muscle cram (1%), Leg Pain (1%), Sinusitis (1%)</td>
<td></td>
</tr>
</tbody>
</table>

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Variant Selection

1. **Initial SNP Selection**
   - 14 SNPs based on MAF & functionality

2. **Pilot Trial**
   - N=100 trial to test individual genotypes

3. **Panel Refined**
   - Removed 2 SNPs, added 5. 17 SNP panel tested
   - Based on delta BP and strength of evidence.

4. **SNP Weighting**
   - Organ systems weighted against one another. If Fx threshold not met, individual SNPs and haplotypes are considered.

5. **Algorithm Build**

6. **Large Trial**
   - N=400

7. **Machine Learning**
   - Tests additional SNPs, adjusts weighting
Impact on Therapy with Functional Genetics: Difference b/t functional and non-functional genotypes on target drug
Variant Sorting and Weighting

<table>
<thead>
<tr>
<th>GENE</th>
<th>RESULT</th>
<th>CARDIAC</th>
<th>RENAL</th>
<th>VASCULAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>Homozygous, Non-Functional Gene</td>
<td>![Checkmark]</td>
<td>![Cross]</td>
<td></td>
</tr>
<tr>
<td>ADRB1_49</td>
<td>Homozygous, Functional Gene</td>
<td>![Checkmark]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADRB1_389</td>
<td>Heterozygous, Functional Gene</td>
<td>![Checkmark]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADRB2_16</td>
<td>Homozygous, Functional Gene</td>
<td>![Checkmark]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADRB2_27</td>
<td>Heterozygous, Functional Gene</td>
<td>![Checkmark]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WNK1 (1)</td>
<td>Homozygous, Functional Gene</td>
<td>![Checkmark]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WNK1 (2)</td>
<td>Homozygous, Functional Gene</td>
<td>![Checkmark]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WNK1 (3)</td>
<td>Homozygous, Functional Gene</td>
<td>![Checkmark]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLC12A3</td>
<td>Homozygous, Non-Functional Gene</td>
<td>![Cross]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCNN1A</td>
<td>Heterozygous, Functional Gene</td>
<td>![Checkmark]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha Adducin</td>
<td>Homozygous, Functional Gene</td>
<td>![Checkmark]</td>
<td></td>
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</tbody>
</table>

**Selective β-blocker**

**Non-selective β-blocker**

**Thiazide or Thiazide-like diuretic**

**ACE-inhibitor**

**Angiotensin-II receptor blocker**

- **Checkmark** Likely to respond
- **Intermediate responder**
- **Cross** Not likely to respond

Not likely to respond

Likely to respond
Using AI to build better algorithms

**Problem – The data is big:**

- Complex Genetic profiles
- Interconnected physiology of organ systems
- Multiple drugs / Variable responses
- Multiple gene/gene interactions

**Solution – Use AI to solve for complexity:**

- Use Random Forest to build multiple algorithms
- Use clinical trial data as training set
- Compete AI’s against each other and use tuning to create most predictive
Random Forest Classifier

The Result:

• 110 trees each assigned a random set of 6 genes

• Algorithm generated that produces a confidence score for drug response
Current Clinical Data and Research Studies
## Clinical Trials

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</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
<td>Retrospective</td>
<td>Prospective</td>
<td>Retrospective</td>
<td>Prospective</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Chart Review/Genotyped</td>
<td>Random/Controlled/Blinded</td>
<td>Chart Review/Genotyped</td>
<td>Reduced time to control, lower absolute BP, fewer meds, Adherence</td>
</tr>
<tr>
<td><strong>Subjects (n=)</strong></td>
<td>100</td>
<td>130</td>
<td>700</td>
<td>Up to 1000</td>
</tr>
<tr>
<td><strong>Completed</strong></td>
<td>2015</td>
<td>2017</td>
<td>2018</td>
<td>Recruiting 2020</td>
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</table>
Publications

**Article**

**Relationship between a Weighted Multi-Gene Algorithm and Blood Pressure Control in Hypertension**

Pamela K. Phelps 1,*, Eli F. Kelley 2,*, Danielle M. Walla 3, Jennifer K. Ross 1, Jerad J. Simmons 1, Emma K. Bulock 1, Audrie Ayres 1, Monica K. Akre 3,*, Ryan Sprissler 3,4, Thomas P. Olson 3,5 and Eric M. Snyder 3,*

**The Effect of Genetically Guided Mathematical Prediction and the Blood Pressure Response to Pharmacotherapy in Hypertension Patients**

Eli F. Kelley 1,*, Thomas P Olson 3,3, Timothy B Curry 2,3, Ryan Sprissler 4 and Eric M Snyder 2

1School of Kinesiology, University of Minnesota, Minneapolis, MN, USA. 2Genetics, Inc, Rochester, MN, USA. 3College of Medicine and Science, Mayo Clinic, Rochester, MN, USA. 4Department of Genetics, University of Arizona Genomics Core, Tucson, AZ, USA.

**Hypertension: An Open Access**

**Association of a Multi-Gene Panel with Blood Pressure Medication Success in Patients with Hypertension: A Pilot Study**

Eric M Snyder 1,*, Eli F Kelley 1, Ryan Sprissler 1,3 and Thomas P Olson 1,4

1Genetics, Inc, Rochester, MN 55902, USA. 2School of Kinesiology, University of Minnesota, Minneapolis, MN 55405, USA. 3Department of Genetics, University of Arizona Genomics Core, Tucson, AZ 85721 USA. 4Division of Cardiovascular Diseases, Mayo Clinic, College of Medicine, Rochester, MN 55905, USA. 5Author for correspondence: olson.thomas@mayo.edu

**The importance and challenges of developing a pharmacogenetics test for hypertension**

Eric M Snyder 1,*, Eli F Kelley 1, Ryan Sprissler 1,3 and Thomas P Olson 1,4

1Genetics, Inc, Rochester, MN 55902, USA. 2School of Kinesiology, University of Minnesota, Minneapolis, MN 55405, USA. 3Department of Genetics, University of Arizona Genomics Core, Tucson, AZ 85721 USA. 4Division of Cardiovascular Diseases, Mayo Clinic, College of Medicine, Rochester, MN 55905, USA. 5Author for correspondence: olson.thomas@mayo.edu
Retro study #1 – testing the genotypes

Change in Diastolic Blood Pressure in Patients with Functional Genotypes who are on a B-Blocker vs. Patients Who are Not on a B-Blocker

- Average on B-blocker: ~11.6mmHg
- Average not on B-blocker: ~6.5mmHg

= 40% Reduction in Stroke
= 26% Reduction CV Death
Pilot RCT trial – Inferiority study

- Both arms achieved > 90% control rates at 6 months
- Geneticure arm used slightly few meds to gain control
- SOC arm had many more serious adverse events (SAE)
  - ~70% of SAE occurred in SOC arm
  - Most were due to diuretic side effects
Retro Study #2 – testing the algorithm

Difference in BP from diagnosis to current 1-yr avg if patient is on the FIRST drug recommended by the Geneticure algorithm vs. not

- Avg SBP: 5.8mmHg (21% lower)
- Avg DBP: 3.3mmHg (29% lower)
- Avg MAP: 5.6mmHg (36% lower)

* < p=0.05
Simulation Population and Assumptions

**Standard of Care Population**

- **Un-treated**
  - 5.4%
  - # of visits: 0
  - # of meds: 0
  - AE risk: 4.0%

- **Treated, Un-controlled**
  - 40%
  - # of visits: 5
  - # of meds: 2
  - AE risk: 3.6%

- **Treated, Controlled**
  - 60%
  - # of visits: 5
  - # of meds: 2
  - AE risk: 0.7%

**Multi-Gene Panel Population**

- **Un-treated**
  - 5.4%
  - # of visits: 0
  - # of meds: 0
  - AE risk: 4.0%

- **Treated, Un-controlled**
  - 15%
  - # of visits: 2.5
  - # of meds: 1.5
  - AE risk: 2.9%

- **Treated, Controlled**
  - 85%
  - # of visits: 2.5
  - # of meds: 1.5
  - AE risk: 0.4%

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Health Economics Results

**Standard of Care Population**
- Un-treated: $14,760/person, 5.4%
- Treated, Un-controlled: $15,813/person, 40%
- Treated, Controlled: $3,778/person, 60%
  - Total = $7,970,400,000

**Direct Cost Elements by Treatment Population**
- Categories:
  - Genetic Testing
  - Medications
  - Adverse Events
  - Evaluation and Management
- Volume Scale: $10 billion

**Multi-Gene Panel Population**
- Un-treated: $14,760/person, 5.4%
- Treated, Un-controlled: $13,309/person, 15%
- Treated, Controlled: $2,502/person, 85%
  - Total = $7,970,400,000

**Aggregated Savings**

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>Savings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Un-treated</td>
<td>$40,950,637,200</td>
</tr>
<tr>
<td>Treated, Un-controlled</td>
<td>$1,362,099,016</td>
</tr>
</tbody>
</table>

Values are over a 3-year period.
Thanks for listening