DNA-Guided Medicine for Enhancing the Safety of Adolescent Healthcare: Personalizing Prevention of Drug Induced Metabolic Syndrome

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Partnerships for DNA-guided Medicine

Pharmaceutical Genomics

DNA-Guided Medicine

Discovery Development Diagnostic Treatment

Technology Databases

Biologicals Drugs

Algorithms Devices

Healthcare Management

The Hospital of Central Connecticut

Clinical Laboratory Partners, LLC

The Institute of Living
**LPH Laboratory of Personalized Health**

**Clinical Lab, High Complexity DNA Typing**

- Licensed by CT Dept of Public Health (CL-0644)
- CLIA registered (ID # 07D1036625 Clinical Laboratory Improvement Amendments) Centers Medicare and Medicaid (CMS)
- One of the pioneering DNA typing centers

In operation since October 2005
- CYP 2D6+2C9+2C19, VKORC1
- Psych Drugs, Warfarin, Tamoxifen

50 doctors served
- 300 patients referred
- 900 DNA Typing tests
Drivers for Personalized Medicine
The young as a vulnerable population

Simulation Systems

“Crash Test” Dummy
Animal Models

Reality System
People

Product Safety
Drug-Induced Cardio-Metabolic Disease
Variable, Unpredictable, Multi-System

Mechanism
- Pharmacodynamics goes awry
- Effects on energy and endocrine systems
- Unknown mechanism

Medical Need
- Side effect risk is unpredictable
- Maintain effective drugs in the market
- Prophylaxis, preventive treatments

Development Approach
- PhysioGenomics of candidate pathways
- Research based on clinical practice
- Continuous or bimodal side effect distrib.
- Common clinically significant side effects
Personalized Health
Medical Need in Drug Safety and Obesity

PHYZIOTYPE SYSTEMS

DRUG SAFETY
DNA Seatbelts
Safest, most Effective Drug
Suicide risk in depression treatments

OBESITY SYNDROMES
Personalized Prevention of Drug Induced Diabetes
30% psychiatric patients on antipsychotics
DNA-Guided Medicine: Beyond Average

Medical GPS: Genetic Prescription System

20th Century: Public Health

21st Century: Personal Health

Number of People

AVERAGE

INDIVIDUALIZED

Response

You are Here

You are Here

SD

SD
Each person’s DNA is unique. The DNA is inherited from ancestors who adapted best to the challenges posed by their environments. The Legacy of the Genome is the repertoire of these adaptive traits. The optimal use of these traits is the basis of personalized health.
The Legacy of the Genome

Detoxification

Cytochrome P450 Enzymes
• 57 genes known
• Each with multiple alleles

ANCESTRAL
Process plant and environmental toxins

MODERN
Metabolism of 90% current drugs
Background:

**CYP DNA Typing for Drug Safety**

**Lipophilic Drug**

**Oxidative Reactions:**
1. Hydroxylation
2. Demethylation

**Hydrophilic Drug Metabolite**

**Kidney**

**Excretion**

**CYTOCHROME P450**

1. CYP2C9
2. CYP2C19
3. CYP2D6

**Therapeutic Window**

- High/low
- Normal

**Therapeutic response**

**Toxicity**

**Plasma drug concentration/metabolic status**
Atomoxetine (Strattera®)

**CYP2D6 Metabolism**

**Drug class**
Selective norepinephrine reuptake inhibitor

**Indication**
Attention deficit hyperactivity disorder (ADHD)

**Reason for HILOm Typing**
Poor metabolizers may be overdosed with standard dose

**Clinical complications**
Appetite suppression, rebound hyperactivity, insomnia, tremor

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**Package insert**
Laboratory tests are available to identify CYP2D6 poor metabolizers
Atomoxetine (Strattera®)
Medical imperative for CYP genotyping

**Atomoxetine Dosage**

Starting doses children and adolescents

<table>
<thead>
<tr>
<th></th>
<th>&lt;70 kg body weight</th>
<th>&gt;70 kg body weight</th>
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<tbody>
<tr>
<td>EM</td>
<td>1.2 mg/kg/day</td>
<td>80 mg/day</td>
</tr>
<tr>
<td>PM</td>
<td>0.5 mg/kg/day</td>
<td>40 mg/day</td>
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</table>

IN PM STRATTERA should be initiated at and only increased to the usual target dose if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.
### CYP2D6 Genotypes, Phenotypes

**16 alleles**

- **white** = Functional
- **yellow** = Deficient
- **red** = Null
- **blue** = Ultra

<table>
<thead>
<tr>
<th>Allele</th>
<th>Change</th>
<th>Metabolizer phenotype</th>
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<tbody>
<tr>
<td>*1</td>
<td>Reference</td>
<td>Normal</td>
</tr>
<tr>
<td>*2</td>
<td>Arg 296 C</td>
<td>Normal</td>
</tr>
<tr>
<td>*2A</td>
<td>Promoter</td>
<td>Ultra</td>
</tr>
<tr>
<td>*3</td>
<td>Frameshift</td>
<td>Null</td>
</tr>
<tr>
<td>*4</td>
<td>Splicing defect</td>
<td>Null</td>
</tr>
<tr>
<td>*5</td>
<td>Gene deletion</td>
<td>Null</td>
</tr>
<tr>
<td>*6</td>
<td>Frameshift</td>
<td>Null</td>
</tr>
<tr>
<td>*7</td>
<td>His 324 Pro</td>
<td>Null</td>
</tr>
<tr>
<td>*8</td>
<td>Truncation</td>
<td>Null</td>
</tr>
<tr>
<td>*9</td>
<td>Lys 281 del</td>
<td>Deficient</td>
</tr>
<tr>
<td>*10</td>
<td>Pro 34 Ser</td>
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<td>*11</td>
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<tr>
<td>*12</td>
<td>Gly 42 Arg</td>
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<tr>
<td>*17</td>
<td>Thr 107 Ile</td>
<td>Deficient</td>
</tr>
<tr>
<td>Duplication *2A</td>
<td>Gene duplication</td>
<td>Ultra</td>
</tr>
<tr>
<td>Duplication *4</td>
<td>Gene duplication</td>
<td>Null</td>
</tr>
</tbody>
</table>
CYP2D6 DNA Typing Survey

Allele Carrier Frequencies

- **Antidepressants**
  - Amitriptyline (Elavil®)
  - Mirtazapine (Remeron®)
  - Fluvoxamine (Luvox®)
  - Duloxetine (Cymbalta®)
  - Venlafaxine (Effexor® XR)
  - Paroxetine (Paxil®)

- **Antipsychotics**
  - Haloperidol (Haldol®)
  - Aripiprazole (Abilify®)
  - Risperidone (Risperdal®)

- **ADHD**
  - Atomoxetine (Strattera®)
  - Dextroamphetamine (Adderall®)

- **Pain**
  - Codeine

Ruano, Thompson, Wu et al

*Personalized Medicine 2006*
The Legacy of the Genome

**Energy and Nutrition**

- **Multiple Pathways**
  - Hundreds of genes
  - <1% variability

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**ANCESTRAL**

Thrifty genes, extract and conserve energy from food sources

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**MODERN**

Food- and Drug-induced obesity and diabetes
Obesity and Metabolic Syndrome
Medical Need in Personalized Healthcare

47 million people with Metabolic Syndrome in U.S.
Precursor to Diabetes and Cardiovascular Disease

Obesity and Diabetes

- Waist
  - M >102cm
  - F >88cm

- GLU
  - >110 mg/dL

Cardiovascular Disease

- HDL
  - M<40 mg/dL
  - F<50 mg/dL

- TG
  - >150 mg/dL

- BP
  - >130 / 85 mm Hg

National Cholesterol Education Program, Adult Treatment Panel III
National Heart, Lung and Blood Institute, JAMA 285:2486-97 (2001)
Psychotropics: Common Side Effects

**DiMS: Diabetic Metabolic Syndromes**

**DiMS Clinical Manifestations**
- Weight gain
- Increased waist size
- High Triglycerides
- Elevated blood glucose
- Diabetes

**Current Diagnostics**
- Body type changes
- Lipid + Glucose Profiles
- Confounders: mental status, compliance, lifestyle

**Product**

*DiMS PhyzioType*

predicts patient’s antipsychotic specific risk of weight gain and pre-diabetic syndromes

$1.8 MM SBIR Grants
NIMH / NIH

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**FOR IMMEDIATE RELEASE**
July 24, 2007

GENOMAS AWARDED $1.4 MILLION NIH SBIR GRANT TO DEVELOP DNA-GUIDED SYSTEM FOR MANAGEMENT OF PSYCHOTROPIC THERAPY

*Product Predicts, Compares Metabolic Side Effects of Antipsychotics for Each Patient*
PhysioGenomics Technology

Hypothesis-free Total Genome Analysis

DNA
1 nm

Body
1,000,000,000 nm

1,000,000 SNPs
PhysioGenomics Technology

Novel Platform for DNA-Guided Medicine

Highly parallel search for DNA markers with frequency dependence on phenotype distribution

Localized Regression (LOWESS: LOcally WEighted Scatterplot Smooth)

Ruaño, Holford, Windemuth, Biomedical Engineering Handbook 2006
Holford, Windemuth, Ruaño, Personalized Medicine 2005
PhysioGenomics of DiMS: Olanzapine

Discovery from Side Effect Spectrum: Weight

ApoE
Apolipo-protein E

ApoA4
Apolipo-protein A4

Ruaño, Goethe, de Leon, Molecular Psychiatry 2007
PhysioGenomics of DiMS: 
Risperidone Discovery from Side Effect Spectrum: Weight

**Marker Frequency**

- **LEPR**
  Leptin Receptor

- **NPY5R**
  Neuropeptide Y receptor Y5

*p* = 0.000987805  
\( r^2 = 11.3\% \)

PhyzioType Systems: DiMS
Predicting Weight Side Effect, Patient LPH1

Patient LPH1 on Zyprexa®
- Clinical Symptoms: 8 kg weight gain and abnormal lipids
- Referred to LPH and IOL for DNA typing of drug metabolism status
- PhyzioType Diagnosis: Psychotrophic DiMS

*Risperdal®* is predicted to have the least weight gain for this patient and *Zyprexa®* the most.
Statins: Common Side Effects

**SIM: Statin-Induced Myopathy**

**SIM Clinical Manifestations**
- Myalgia (muscle aches, cramps)
- Weakness, disability
- Statin intolerance
- Myositis
- Neuropathy

**Current Diagnostics**
- Serum tests per drug label: Creatine Kinase CK
- Clinical Symptoms: Myalgias, Cramps
- Confounders: physical activity, polypharmacy, advanced CV disease

**Product**

*SIM PhyzioType* predicts patient’s statin-specific risk of neuro-muscular side effects

$200K Grants
Hartford Hosp
PhysioGenomics of SIM: Myositis

Discovery from Side Effect Spectrum

GFP205

AGTR1
Angiotensin II Receptor I

NOS3
Nitric oxide synthase 3 (endothelial)

Ruaño, Thompson et al, Pharmacogenomics 2005
PhysioGenomics of SIM: Myalgia

Discovery from Side Effect Spectrum

PhyzioType Systems
Medical Device for DNA-Guided Medicine

SNP Ensemble Assays
Biomathematical Algorithms
Physician Interface
Genetic Heterogeneity of USA Hispanics
Comparison with Self-Identified Ethnicity

Africa

Latin America

Europe

Asia
Genomas and UPR
Partners in Medical Education + Training

Medical Technology Internships
Genomas and Hartford Hospital

Hartford, Connecticut
2005-2008

CURRICULUM:
PRACTICUM AND RESEARCH
Pharmacogenetics
Laboratory of Personalized Health
at Genomas
Transplantation
Transplantation Laboratory
at Hartford Hospital

Pharmacogenetics and Physiogenomics:
The Scientific Principles of Personalized Medicine
University of Puerto Rico
Medical Sciences Campus
College of Health Professions
School of Pharmacy
Graduate School of Public Health
School of Medicine

Medical Technology Program with University of Puerto Rico begins at Hartford Hospital and Genomas
The affluent citizens of this Nation enjoy better health than do its minority and poorer citizens. The most striking health disparities involve shorter life expectancy among the poor, as well as higher rates of cancer, birth defects, infant mortality, asthma, diabetes, and cardiovascular disease. Although health care access might account for some of this disparity, the differences in environmental and occupational exposures are also thought to play a role.

What are Cancer Health Disparities? Why do Racial and Ethnic Disparities Exist?

There is no single, simple answer. Racial and ethnic minorities tend to receive lower-quality health care than whites do, even when insurance status, income, age, and severity of conditions are comparable, says a 2002 report of the Institute of Medicine.
PhysioGenomics + Personalized Health
Mechanism Discovery from Clinical Research

Today
DNA-Guided Medicine
Clinical Research
Systems
Prevention
Personalized Health

PhysioGenomics

Before
Reductionist Medicine
Animal + Cell Models
Targets
Drugs
Molecular Medicine

Molecular Biology