Genomas: Health Personalized

Pharmaceutical Genomics

DNA Guided Medicine

Discovery  Development  Diagnostic  Treatment

Technology Databases  Biologicals Drugs  Assays Devices

Healthcare Delivery

LABORATORY OF PERSONALIZED HEALTH
## DNA Guided Medicine and Drug Safety

*From average to individualized responses*

### Population Medicine

<table>
<thead>
<tr>
<th>Catastrophic Events</th>
<th>1 in 10,000 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Average response</td>
<td></td>
</tr>
<tr>
<td>Clinical Trials</td>
<td></td>
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<tr>
<td>Market withdrawals</td>
<td></td>
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</table>

### DNA Guided Medicine

<table>
<thead>
<tr>
<th>Clinical side effects</th>
<th>20% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic markers</td>
<td></td>
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<tr>
<td>Individual response</td>
<td></td>
</tr>
<tr>
<td>Post market surveillance</td>
<td></td>
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<tr>
<td>Seatbelts for drugs</td>
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</tbody>
</table>
Product: HILOMet System
Precision Treatment Guided by your DNA

Drug A

You’re here

Side Effect Risk
LOW

Drug B

You’re here

Side Effect Risk
AVERAGE

Drug C

You’re here

Side Effect Risk
HIGH
LPH Laboratory of Personalized Health
Clinical Lab, High Complexity DNA Testing

- Licensed by CT Dept. of Public Health (CL-0644)
- CLIA registered (ID # 07D1036625 Clinical Laboratory Improvement Amendments)
  Centers for Medicare and Medicaid (CMS)

PRODUCTS

- HILOmect System:
  4 tests for drug safety
  CYP2D6, CYP2C9, CYP2C19, WARFARIN
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.
**Xenobiotic Systems:** p450 system, 57 genes known, each with multiple alleles

- **Ancestral:** Process plant and environmental toxins,
- **Modern:** Metabolism of 90% current drugs
HILOmet System for Drug Safety

Lipophilic Drug

Oxidative Reactions: Hydroxylation Demethylation

Hydrophilic Drug Metabolite

CYTOCHROME P450
CYP2C9
CYP2C19
CYP2D6

Kidney

Excretion

Therapeutic Window

Toxicity

Therapeutic response

Low/Fast Normal/normal High/slow

Plasma drug concentration/metabolic status
**Adverse Drug Reactions**

- 100,000 deaths per year
- 17% of hospital admissions
- $182 billion cost per year

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**Metabolizer Types**

- **Deficient Metabolizer**: Drug interactions risk
- **Poor Metabolizer**: Adverse event risk
- **Null Metabolizer**: Serious toxicity

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**Average Drug Dose**

50% Population at Risk
5% at Extreme Risk
High carrier prevalence of deficient and null alleles of CYP2 genes in a major USA hospital: implications for personalized drug safety

Many drugs are metabolized by highly polymorphic cytochrome P450 (CYP) enzymes. Among these enzymes, members of the CYP2 family coded by the CYP2D6, CYP2C9 and CYP2C19 genes are best amenable to the precise prediction of an individual’s innate capacity to metabolize drugs by DNA typing of inherited null and deficient alleles. We determined the frequency of these alleles and the prevalence of their carriers in a New England, USA, tertiary care center to assess underlying population genetic features for the practice of personalized medicine. We determined that 54, 25 and 27% are carriers of at least one deficient or null allele for the CYP2D6, CYP2C9 and CYP2C19 genes, respectively. Furthermore, 6% of individuals are carriers of two null alleles for CYP2D6 and are predicted to have no biochemical activity for this isoenzyme. These results support the implementation of DNA typing of CYP2 genes to diagnose adverse drug reactions and to prevent a substantial number of patients being prescribed drugs they cannot adequately metabolize.
# Genotypes and Phenotypes

## Alleles genotyped at LPH

<table>
<thead>
<tr>
<th>Alleles</th>
<th>Amino Acid Change</th>
<th>Nucleotide Change</th>
<th>Metabolizer Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1</td>
<td>Reference</td>
<td>Reference</td>
<td>WILD-TYPE</td>
</tr>
<tr>
<td>*3</td>
<td>Frameshift</td>
<td>2549-A Del</td>
<td>NULL</td>
</tr>
<tr>
<td>*4</td>
<td>Splicing defect</td>
<td>G-1846-A SNP</td>
<td>NULL</td>
</tr>
<tr>
<td>*5</td>
<td>No protein</td>
<td>Deletion of gene</td>
<td>NULL</td>
</tr>
<tr>
<td>*9</td>
<td>Lys 281del</td>
<td>2613-15 AGA Del</td>
<td>DEFICIENT</td>
</tr>
<tr>
<td>*10</td>
<td>Pro-34-Ser</td>
<td>C-100-T SNP</td>
<td>DEFICIENT</td>
</tr>
<tr>
<td>*17</td>
<td>Thr-107-Ile</td>
<td>C-1023-T SNP</td>
<td>DEFICIENT</td>
</tr>
<tr>
<td>Duplication</td>
<td>Reference</td>
<td>Tandem genes</td>
<td>ULTRA</td>
</tr>
</tbody>
</table>
CYP2D6 DNA Typing Survey
Allele Carrier Frequencies

- Gene duplication: 6%
- Non-carriers: 46%
- Single carriers: 40%
- Double carriers:
  - Two Deficient alleles: 2%
  - Null + Deficient alleles: 5%
  - Two Null alleles: 1%
CYP2D6 DNA Typing Survey

Allele Carrier Frequencies

- Pain
  - Codeine
  - Cancer
  - Tamoxifen (Nolvadex®)

- Beta Blockers
  - Propranolol (Inderal®)
  - Metoprolol (Lopressor®)

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

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

- ADHD
  - Atomoxetine (Strattera®)
## Alleles genotyped at LPH

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<td>*1</td>
<td>Reference</td>
<td>Reference</td>
<td>WILD-TYPE</td>
</tr>
<tr>
<td>*2</td>
<td>Arg -144 -Cys</td>
<td>C -430 -T SNP</td>
<td>DEFICIENT</td>
</tr>
<tr>
<td>*3</td>
<td>Ile -359 -Leu</td>
<td>A -1075 -C SNP</td>
<td>DEFICIENT</td>
</tr>
</tbody>
</table>
CYP2C9 DNA Typing Survey
Allele Carrier Frequencies

- 75% Non-carriers
- 22% Single carriers
- 3% Double carriers (Two Deficient alleles)
CYP2C9 DNA Typing Survey
Allele Carrier Frequencies

Thromboembolism
Warfarin (Coumadin®)

Angiotensin II Blockers
Losartan (Cozaar®)
Irbesartan (Avapro®)

Glitazones
Rosiglitazone (Avandia®)
Pioglitazone (Actos®)

Sulfonylureas
Glipizide (Glucotrol®)
Glimepiride (Amaryl®)

NSAIDs
Ibuprofen (Advil®)
Naproxen (Naprosyn®)

Antidepressants
Fluoxetine (Prozac®)
Sertraline (Zoloft®)
**Alleles genotyped at LPH**

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<td>WILD-TYPE</td>
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<tr>
<td>*2</td>
<td>Splicing defect</td>
<td>G-681-A SNP</td>
<td>NULL</td>
</tr>
<tr>
<td>*3</td>
<td>Stop codon</td>
<td>G-636-A SNP</td>
<td>NULL</td>
</tr>
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CYP2C19 DNA Typing Survey
Allele Carrier Frequencies

- Non-carriers: 73%
- Single carriers: 27%
CYP2C19 DNA Typing Survey
Allele Carrier Frequencies, 121 patients at HH

27%

Proton Pump Inhibitors
Omeprazole (Prilosec®)
Lansoprazol (Prevacid®)
Esomeprazole (Nexium®)

Anti-epileptics
Phenytoin (Dilantin®)
Diazepam (Valium®)

Antidepressants
Escitalopram (Lexapro®)
Citalopram (Celexa®)
HILOmét Warfarin
DNA-Guided Warfarin Management

HILOmét Warfarin is a clinically accurate test for analyzing DNA variants relevant to warfarin dosing and prevention of bleeding.

DNA Typing of 7 VKORC1 + 5 CYP2C9
DNA Typing Predicts 33-50% of variability in warfarin dosing
DNA Typing + clinical covariates explains 60% of variability in warfarin dosing.
Immediate Need for Personalized Medicine

Association Between CYP 2C9 Genetic Variants and Anticoagulation-related Outcomes During Warfarin Therapy

*JAMA 2002, Higashi et al 287:1690*

**CYP 2C9*2 and CYP 2C9*3 are associated with excessive anticoagulation and bleeding**

Polymorphisms and the Pocketbook: Cost Effectiveness of CYP 2C19 Genotyping in the Eradication of *Helicobacter pylori* Infection Associated with Duodenal Ulcer


**Omeprazole treatment for H.p. infection based on CYP 2C19 genotyping decreases expenses for health plans**
Physicians Provide Personalized Drug Prescription

- Patient requires warfarin or any of several drugs metabolized by Cytochrome p450
- Doctor orders HILQmet test
- Blood sample sent to LPH (Laboratory of Personalized Health) for DNA analysis
- Doctor receives HILQmet report from LPH
- HILQmet test is reimbursed by insurance
**HILOmét System for Drug Safety**

**DNA Guided Medicine**

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**Drugs:** C, F, K, M, Z

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**Joe**

- **Z**
- **C**
- **K**

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**Mary**

- **C**
- **K**
- **M**

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What is your risk of drug side effects?
**Side Effect diagnosis**

- Patient has taken a prescribed drug and manifested side effects
- *HILOmet* tests used to diagnose likely cause of side effect based on individualized risk
- Allows doctor to clarify etiology of symptoms versus confounding factors (mental status, physical activity, polypharmacy)

**Side Effect prevention**

- *HILOmet* tests allow doctor to prescribe drugs according to patient’s individualized risk
- **IF SIDE EFFECT RISK IS LOW:**
  - Prescribe drug w. safeguard
- **IF SIDE EFFECT RISK IS HIGH:**
  - Reduce drug dose
  - Switch to other drugs
  - Proactively monitor/treat ADRs
What Are the Implications for Clinical Medicine and Patients?

Available NOW

- **HILOmé 2D6, 2C9, 2C19 DNA Typing** for several drugs used in psychiatry and internal medicine
- **HILOmé Warfarin** to guide dosing
- FDA is driving DNA-based guidelines for prescription of safest drugs

New paradigm for Drug Therapy

*DNA Typing for guiding dosage, selecting drugs and preventing side effects*

*DNA Guided medicine will be expected by patients*