DNA-Guided Tamoxifen Therapy for Breast Cancer
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
Cytochrome P450 DNA Typing HILOmet CYP 2D6, 2C9, 2C19

100 MDs served (9/07)
350 patients referred
1000 DNA Typing tests
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
DNA-Guided Medicine: Beyond Average

Medical GPS: Genetic Prescription System

20th Century: Public Health

21st Century: Personal Health

AVERAGE

INDIVIDUALIZED

You are Here

You are Here

Number of People

Response

Response

SD

SD

You are Here
## Breast Cancer

*Incidences and Morbidity 2006*

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
<th>Both</th>
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<tbody>
<tr>
<td><strong>Estimated New Cases</strong></td>
<td>212,920</td>
<td>1,720</td>
<td>214,640</td>
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<tr>
<td><strong>Estimated Deaths</strong></td>
<td>40,970</td>
<td>460</td>
<td>41,430</td>
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Hormonal Therapies of Breast Cancer

SERMs, Aromatase Inhibitors as Alternatives

Selective Estrogen Receptor Modulators

- Tamoxifen (*Nolvadex*)

- Raloxifene (*Evista*)
  *Osteoporosis. Drug is preventive of breast cancer, but raises the risk of blood clots and fatal strokes.*

Aromatase Inhibitors

- Anastrazole (*Arimidex*)
- Letrozole (*Femara*)
- Exemestane (*Aromasin*)
Tamoxifen Activation to Endoxifen

Primary CYP2D6 Role in Endoxifen Formation

**ProDrug, Inactive**
Requires metabolism by CYP2D6 to endoxifen for anti-estrogenic activity

**Metabolite, Active**
50 times more potent as anti-estrogen than tamoxifen

Tamoxifen in Early Breast Cancer
5-yr Tamoxifen Treatment

Recurrence (%)

Years after randomization

N=10,386

TAMOXIFEN

CONTROL

Early Breast Cancer Trialists’ Collaborative Group EBCTCG
Lancet 365:1687, 2005
## 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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<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>Normal</td>
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<tr>
<td>*3</td>
<td>Frameshift</td>
<td>Null</td>
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<tr>
<td>*4</td>
<td>Splicing defect</td>
<td>Null</td>
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<tr>
<td>*5</td>
<td>Gene deletion</td>
<td>Null</td>
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<td>*6</td>
<td>Frameshift</td>
<td>Null</td>
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<tr>
<td>*7</td>
<td>His 324 Pro</td>
<td>Null</td>
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<td>*8</td>
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<td>*11</td>
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<tr>
<td>*17</td>
<td>Thr 107 Ile</td>
<td>Deficient</td>
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<tr>
<td>Duplication *2A</td>
<td>Gene duplication</td>
<td>Ultra</td>
</tr>
<tr>
<td>Duplication *4</td>
<td>Gene duplication</td>
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</table>
CYP2D6 DNA Typing Survey
Allele Carrier Frequencies

- **40% Deficient**
- **46% Functional**
- **6% Null**
- **7% Poor**
- **1% Ultra**

**Cancer**
Tamoxifen (Nolvadex®)

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

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

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

**Pain**
Codeine

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

Ruano, Thompson, Wu et al
Personalized Medicine 2006
SSRI Inhibition of CYP2D6
Lowered Endoxifen Concentrations

Jin Y et al, J Natl Cancer Inst 97:30, 2005
Relapse-free Survival

CYP2D6 Stratification of Tamoxifen Cohort

Years after randomization

P=0.020

CYP2D6 FUNCTION
NORMAL
DEFICIENT
NULL

Goetz et al J Clin Oncol 23: 9312, 2005
Relapse-free Time
CYP2D6 Stratification of Tamoxifen Cohort

P=0.030

Years after randomization

CYP2D6 FUNCTION
NORMAL
DEFICIENT
NULL

0 2 4 6 8 10 12

Goetz et al J Clin Oncol 23: 9312, 2005
DNA-Guided Adjuvant Hormonal Rx
CYP2D6 Individualized Decision Support

Postmenopausal women
ER positive breast cancer

CYP2D6 Status
- Functional
- Deficient
  - Poor

Consider Alternatives
Aromatase Inhibitors
Raloxifene

Tamoxifen

Functional

Tamoxifen

Tamoxifen
Conclusions

**DNA-Guided Tamoxifen Therapy**

- Endoxifen is an active metabolite of tamoxifen, present in patients at 5-10 x greater concentration than 4-OH-tamoxifen
- *In vitro* studies demonstrate the primary role of CYP2D6 in the formation of endoxifen.
- Potent inhibitors of CYP2D6 reduce endoxifen concentrations in patients taking tamoxifen
- CYP2D6 genotype correlates with endoxifen concentrations in patients taking tamoxifen