

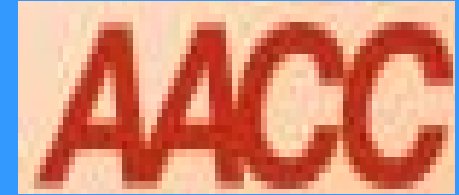
Health Personalized



Presentation to:

**Clinical Applications
of Pharmacogenetics**

*Case Reports on the Practice
of Personalized Medicine*



Pharmacogenomics Case Studies in Psychiatry and Neurology

Gualberto Rúaño, M.D., Ph.D.
President and Chief Executive Officer, Genomas
Director of Genetics Research, Hartford Hospital

The Program

Introduction

Gualberto Rúaño, M.D., Ph.D.
Genomas, Inc.
Hartford Hospital
Hartford, CT

Somatic Complications of Psychotropic Medications in a Patient with Multiple CYP2 Drug Metabolism

Gualberto Rúaño, M.D., Ph.D.
Genomas, Inc.
Hartford, CT

Translation of Basic Research into Clinical Practice: Psychiatry at the Forefront of Translational Medicine

Julio Licinio, M.D.
Miller School of Medicine
University of Miami
Miami, FL

Clinical Relevance of CYP450 Genotyping: Case studies on drug metabolizer status

Jose de Leon, M.D.
Eastern State Hospital
University of Kentucky School of Medicine
Lexington, KY

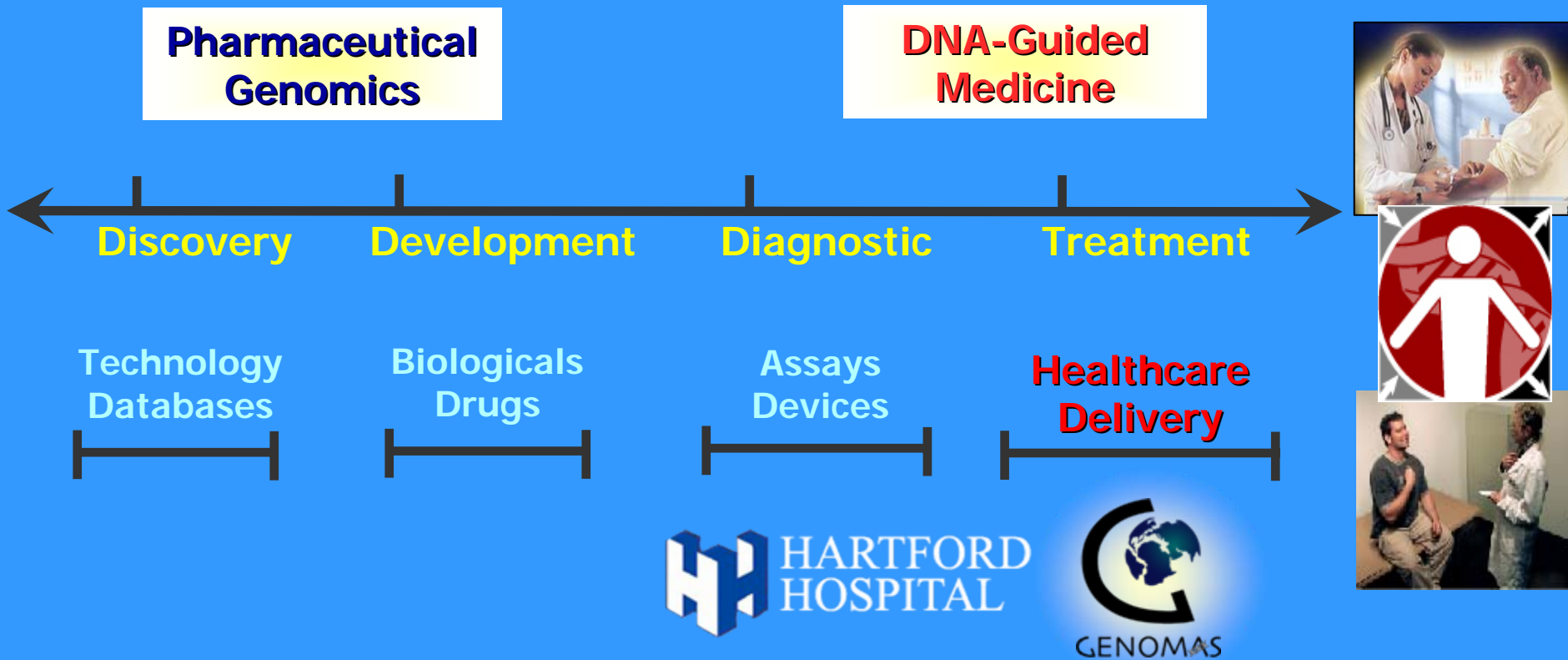
The Case of the Not-So-Regional Anesthetic

Neil Sandson, M.D.
Sheppard and Enoch Hospital
Baltimore, MD

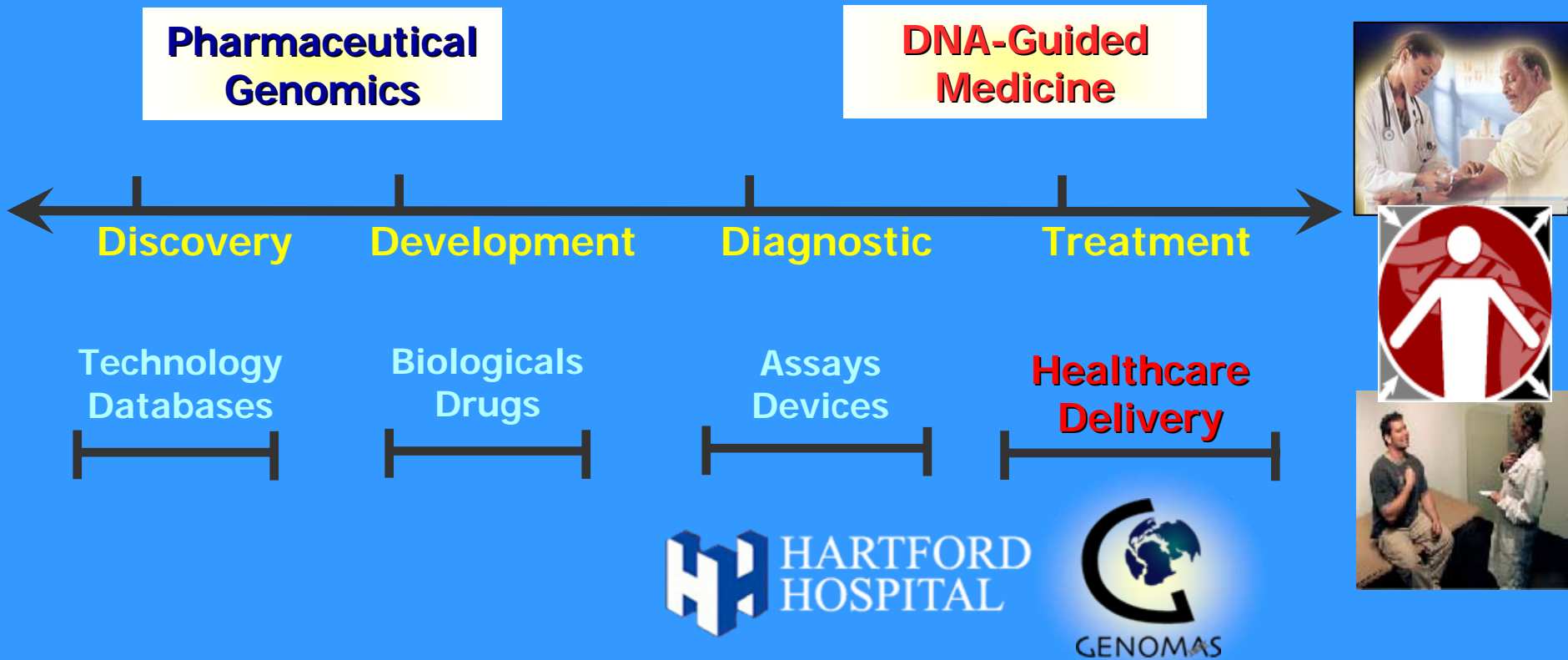
Scenarios for psychiatric application of pharmacogenetics and pharmacogenomics

Anil Malhotra, M.D.
The Zucker Hillside Hospital
Long Island Jewish Medical Center
Long Island, NY

Institute of Living, Hartford Hospital *Genomas Partners for DNA-Guided Medicine*



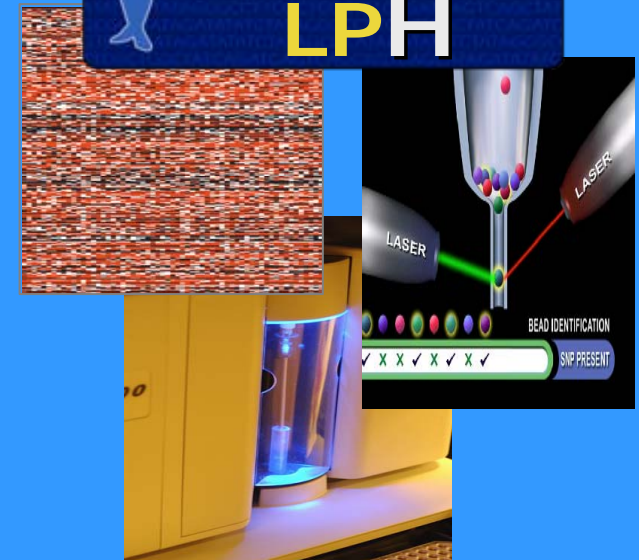
Institute of Living, Hartford Hospital *Genomas Partners for DNA-Guided Medicine*



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**

**LABORATORY OF
PERSONALIZED HEALTH**



**In operation since October 2005
Cytochrome P450 DNA Typing
*HILomet CYP 2D6, 2C9, 2C19***

**50 doctors served
300 patients referred
900 DNA Typing tests**

Case: Connecticut Medicine, in press
Patient referred to IOL and LPH

**Somatic Complications of
Psychotropic Medications in a Patient with
Multiple CYP2 Drug Metabolism Deficiencies**

C. Lee Blair, M.D.

Godfrey Pearlson, M.D.

John W. Goethe, M.D.

Harold I. Schwartz, M.D.



Case History: Symptoms

Patient referred to IOL and LPH

A 54-year Caucasian woman with a history of:

persistent malaise

headache

muscle tension

jaw clenching

hypervigilance

severe anxiety

The patient's difficulties had developed six years ago:

- **improper installation, heating system leaked volatile fuels**
- **escalating fear, frustration, increasingly symptomatic**

She had become:

- **increasingly preoccupied with her somatic condition**
- **had stopped working as a well paid professional**
- **had withdrawn from many of her usual activities**
- **had spent a large amount of time and effort on medical care**

Case History: 18 Psychotropic Drugs

Adverse Drug Reactions and Side Effects

ANTI-DEPRESSANTS

Sertraline (*Zoloft*®)
Paroxetine (*Paxil*®)
Escitalopram (*Lexapro*®)
Venlafaxine (*Effexor*® XR)
Citalopram (*Celexa*®)
Mirtazapine (*Remeron*®)
Nortriptyline (*Pamelor*®)

ANTI-CONVULSANTS

Gabapentin (*Neurontin*®)
Oxcarbazepine (*Trileptal*®)
Topiramate (*Topamax*®)

metallic taste
dry mouth
nausea
vomiting
diarrhea
flatulence
sweating
“crawling” feel
insomnia
akathisia
twitching
parasthesias
“fogginess”
WEIGHT GAIN

ANXIO-LYTICS

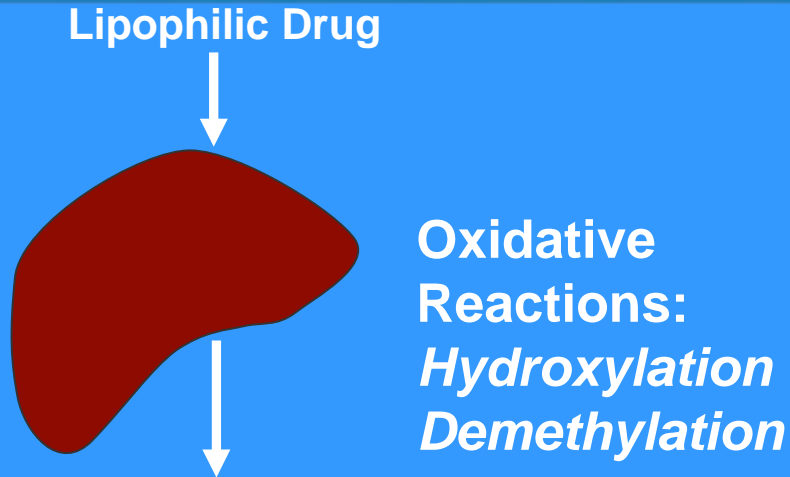
Buspirone (*Buspar*®)
Clonazepam (*Klonopin*®)
Diazepam (*Valium*®)
Lorazepam (*Ativan*®)
Flurazepam (*Dalmane*®)

ANTI-PSYCHOTICS

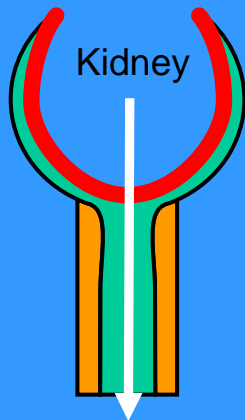
Olanzapine (*Zyprexa*®)
Quetiapine (*Seroquel*®)
Risperidone (*Risperdal*®)

DNA-Guided Drug Therapy

HILomet CYP: Traffic Light for Drugs



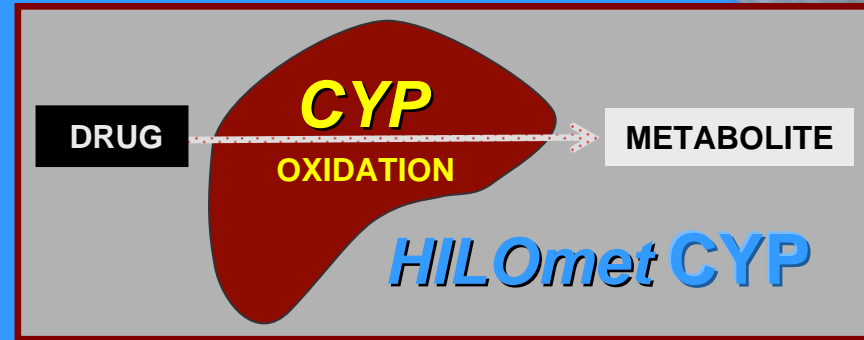
Hydrophilic Drug Metabolite



Excretion

CYTOCHROME P450

CYP2C9
CYP2C19
CYP2D6



TRAFFIC LIGHT FOR DRUGS



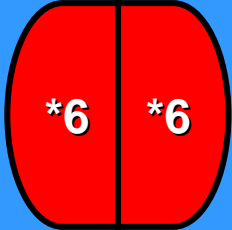
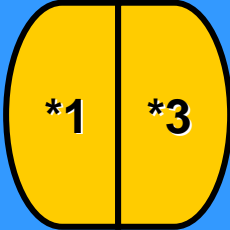
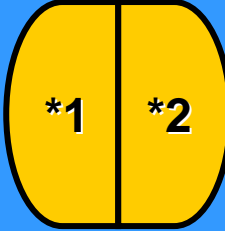
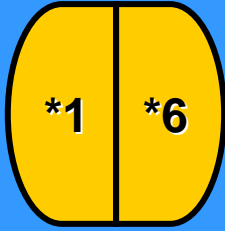
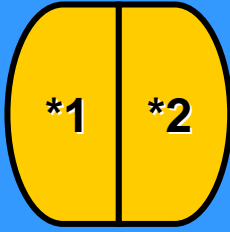
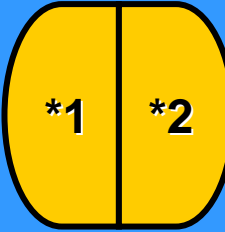
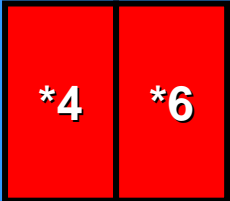

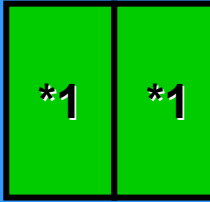
STOP
Drug Contraindicated
Low Metabolic capacity

CAUTION
Drug Interactions
Med Metabolic Capacity

GO
Drug Indicated
High Metabolic Capacity

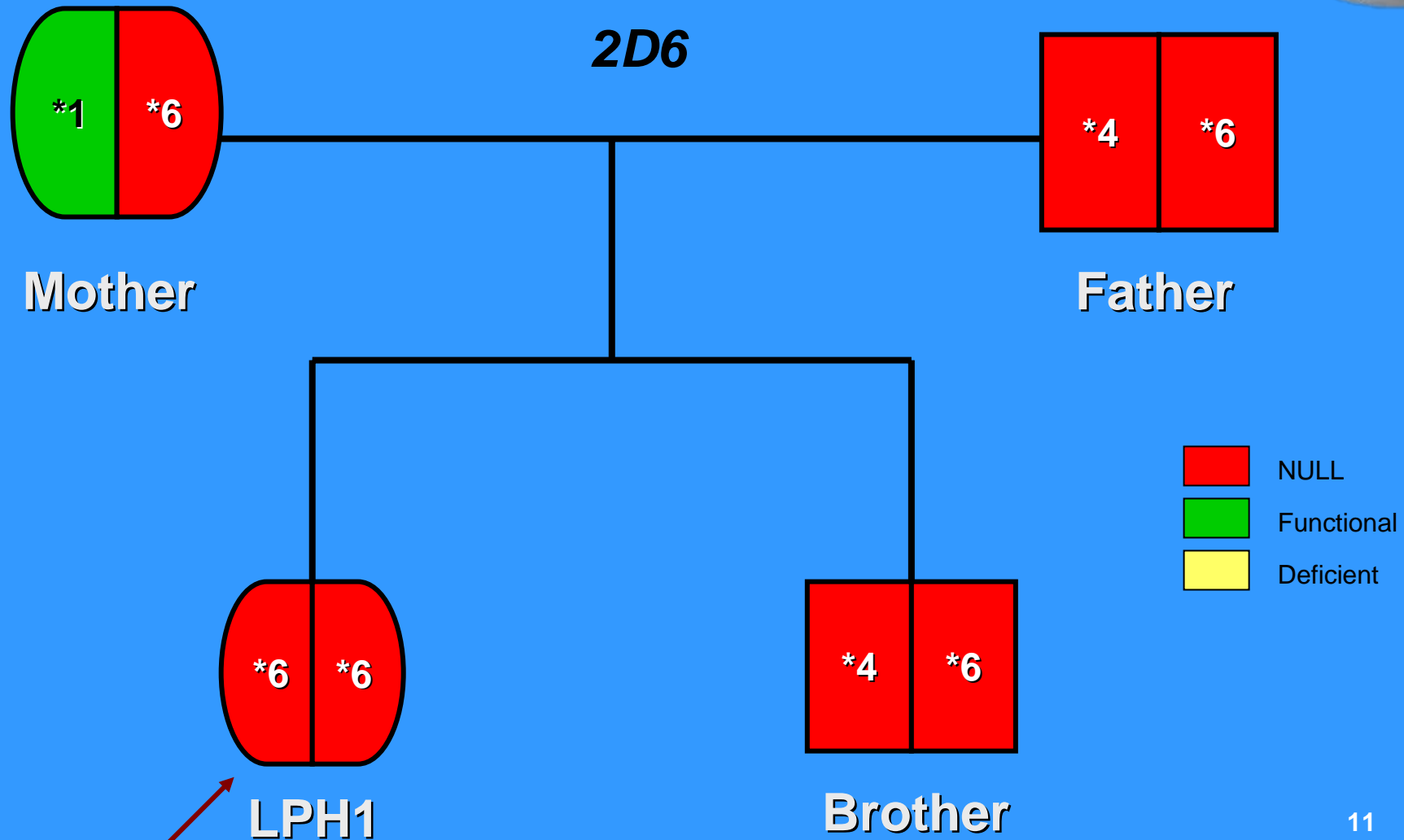
Case History: DNA Typing Results

Multi-gene drug metabolism deficiencies

	2D6	2C9	2C19
Patient			
Mother			
Father			

Case History: DNA Typing Results

Pedigree Analysis: Inherited DNA Types



Case History: 18 Psychotropic Drugs

DNA-Guided Drug Selection

ANTI-DEPRESSANTS

Sertraline (*Zoloft*®)
Paroxetine (*Paxil*®)
Escitalopram (*Lexapro*®)
Venlafaxine (*Effexor*® XR)
Citalopram (*Celexa*®)
Mirtazapine (*Remeron*®)
Nortriptyline (*Pamelor*®)

ANXIO-LYTICS

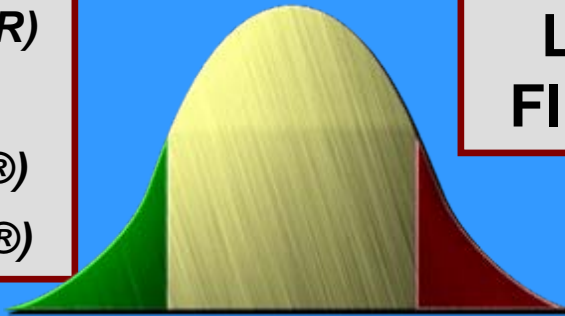
Buspirone (*Buspar*®)
Clonazepam (*Klonopin*®)
Diazepam (*Valium*®)
Lorazepam (*Ativan*®)
Flurazepam (*Dalmane*®)

ANTI-CONVULSANTS

Gabapentin (*Neurontin*®)
Oxcarbazepine (*Trileptal*®)
Topiramate (*Topamax*®)

ANTI-PSYCHOTICS

Olanzapine (*Zyprexa*®)
Quetiapine (*Seroquel*®)
Risperidone (*Risperdal*®)



Case History: 18 Psychotropic Drugs

DNA-Guided Drug Selection

ANTI-DEPRESSANTS

Sertraline (*Zoloft*®)

Paroxetine (*Paxil*®)

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Venlafaxine (*Effexor*® XR)

Citalopram (*Celexa*®)

Mirtazapine (*Remeron*®)

Nortriptyline (*Pamelor*®)



ANXIO-LYTICS

Buspirone (*Buspar*®)

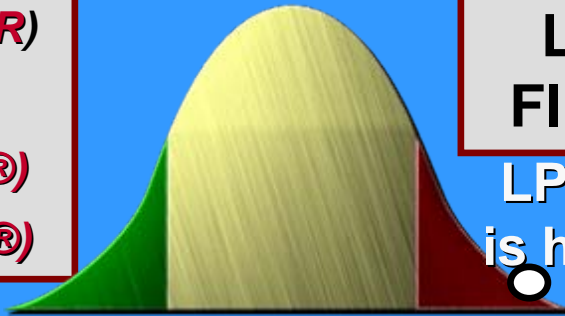
Clonazepam (*Klonopin*®)

Diazepam (*Valium*®)

Lorazepam (*Ativan*®)

Flurazepam (*Dalmane*®)

LPH1
is here



ANTI-CONVULSANTS

Gabapentin (*Neurontin*®)

Oxcarbazepine (*Trileptal*®)

Topiramate (*Topamax*®)

**High
ADR
Risk**

ANTI-PSYCHOTICS

Olanzapine (*Zyprexa*®)

Quetiapine (*Seroquel*®)

Risperidone (*Risperdal*®)

Case History: 18 Psychotropic Drugs

DNA-Guided Drug Selection

ANTI-DEPRESSANTS

Sertraline (*Zoloft*®)

Paroxetine (*Paxil*®)

Escitalopram (*Lexapro*®)

Venlafaxine (*Effexor*® XR)

Citalopram (*Celexa*®)

Mirtazapine (*Remeron*®)

Nortriptyline (*Pamelor*®)



LPH1
is here

ANXIO-LYTICS

Buspirone (*Buspar*®)

Clonazepam (*Klonopin*®)

Diazepam (*Valium*®)

Lorazepam (*Ativan*®)

Flurazepam (*Dalmane*®)

ANTI-CONVULSANTS

Gabapentin (*Neurontin*®)

Oxcarbazepine (*Trileptal*®)

Topiramate (*Topamax*®)

**Medium
ADR
Risk**

ANTI-PSYCHOTICS

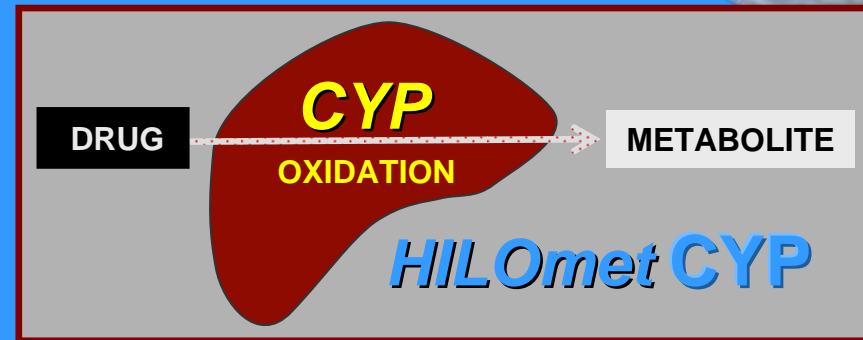
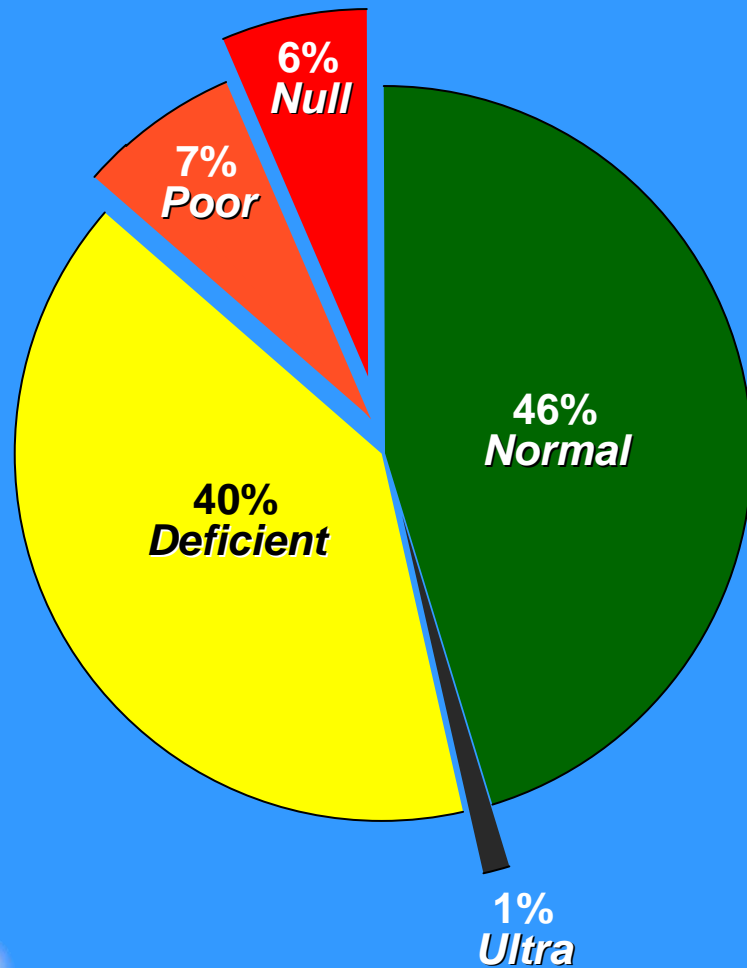
Olanzapine (*Zyprexa*®)

Quetiapine (*Seroquel*®)

Risperidone (*Risperdal*®)

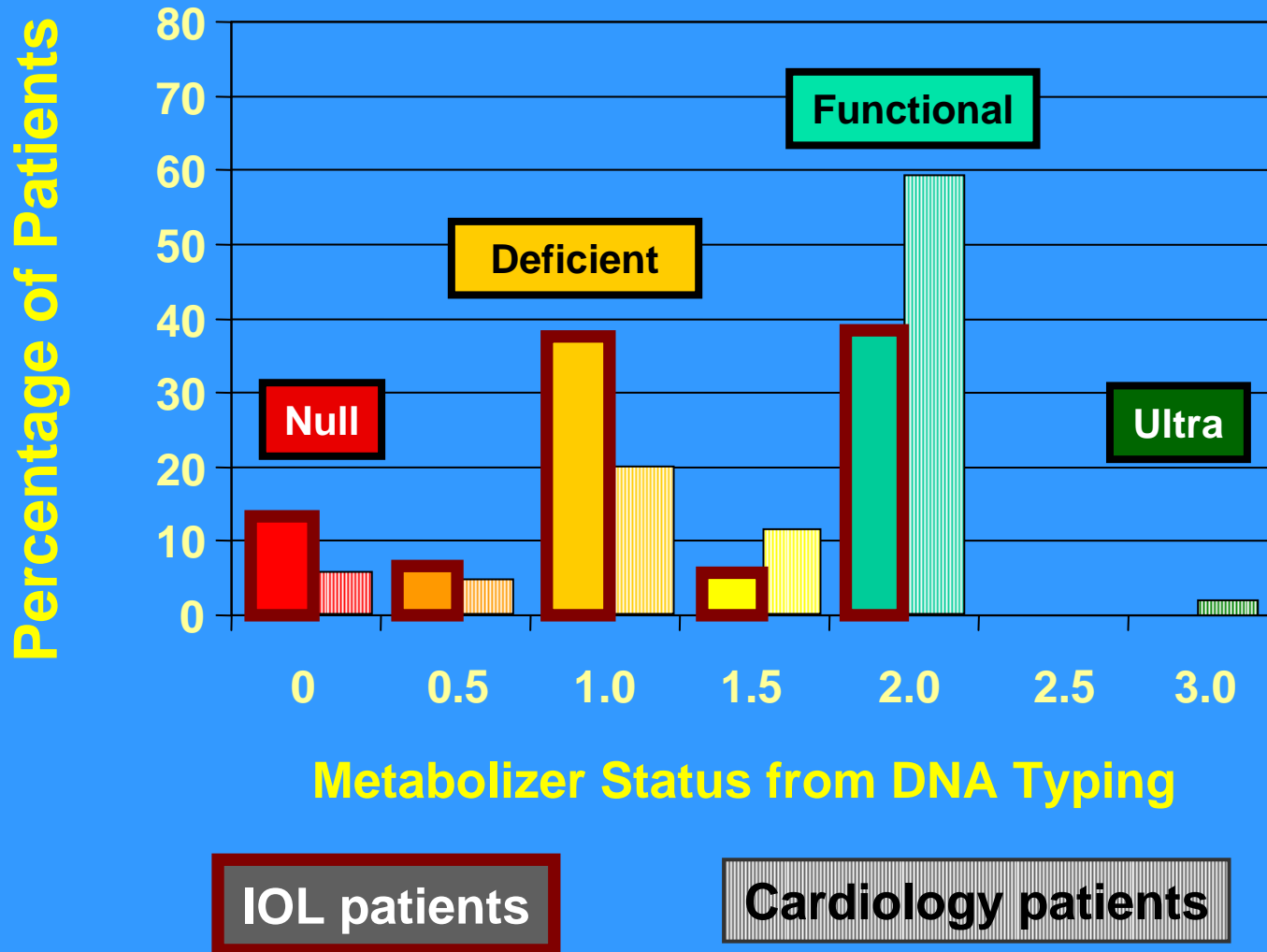
CYP2D6 Survey at Lipid Clinic, Hartford

DNA-Guided Drug Selection



^{RESEARCH}
Personalized Medicine 3: 131-137, 2006
High carrier prevalence of deficient and null alleles of *CYP2* genes in a major USA hospital: implications for personalized drug safety

Clinical DNA Typing at HH and IOL Drug Metabolizer Status CYP2D6



Psychotropic Adverse Drug Reactions

DiMS: Diabetes + Metabolic Syndromes

Clinical Manifestations

- Weight gain
- Increased waist size
- High Triglycerides
- Elevated blood glucose
- Diabetes



Current Diagnostics

- Body type changes
- Lipid+Glucose Profiles
- Confounders: mental status, appetite, poly-pharmacy, compliance

ORIGINAL ARTICLE

Molecular Psychiatry (2007), 1–9
© 2007 Nature Publishing Group All rights reserved 1359-4184/07 \$30.00
www.nature.com/mp



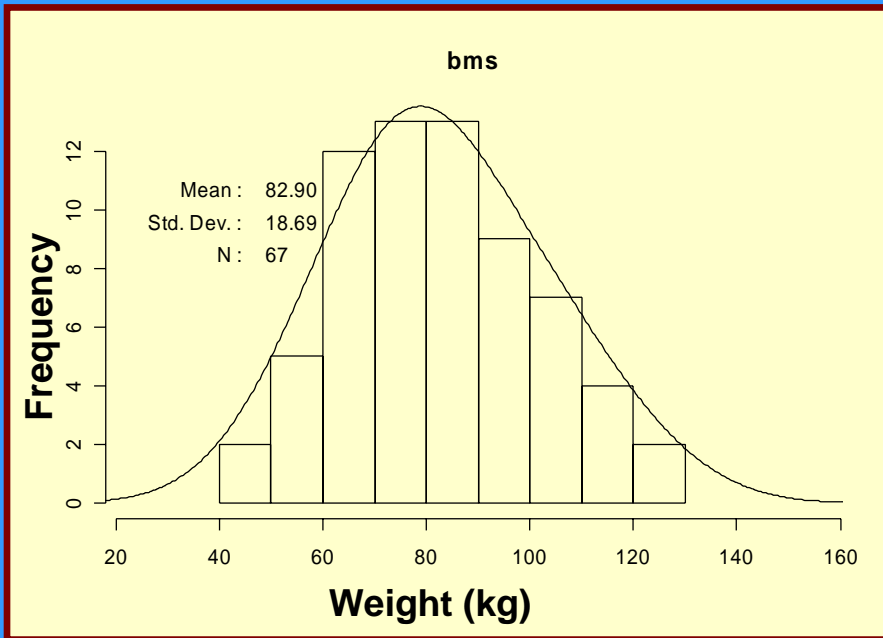
Physiogenomic comparison of weight profiles of olanzapine- and risperidone-treated patients

G Ruaño¹, JW Goethe², C Caley², S Woolley², TR Holford³, M Kocherla¹, A Windemuth¹ and J de Leon⁴

¹Genomas, Inc., Hartford, CT, USA; ²Institute of Living, Hartford Hospital, Hartford, CT, USA; ³Department of Epidemiology

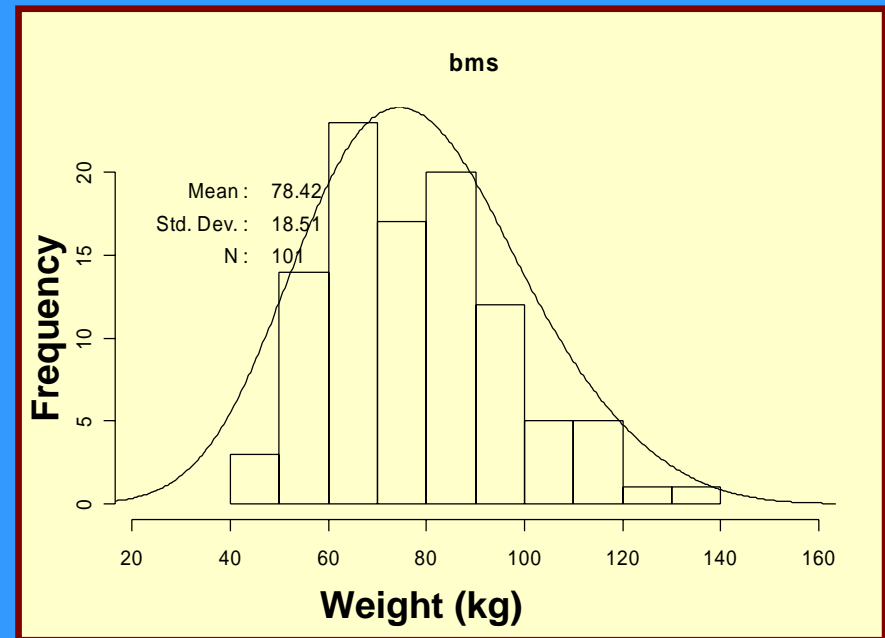
PhysioGenomics of DiMS: Weight *Discovery from Side Effect Spectrum*

Olanzapine



Mean=82.9 kg
SD=18.7 kg
N=67

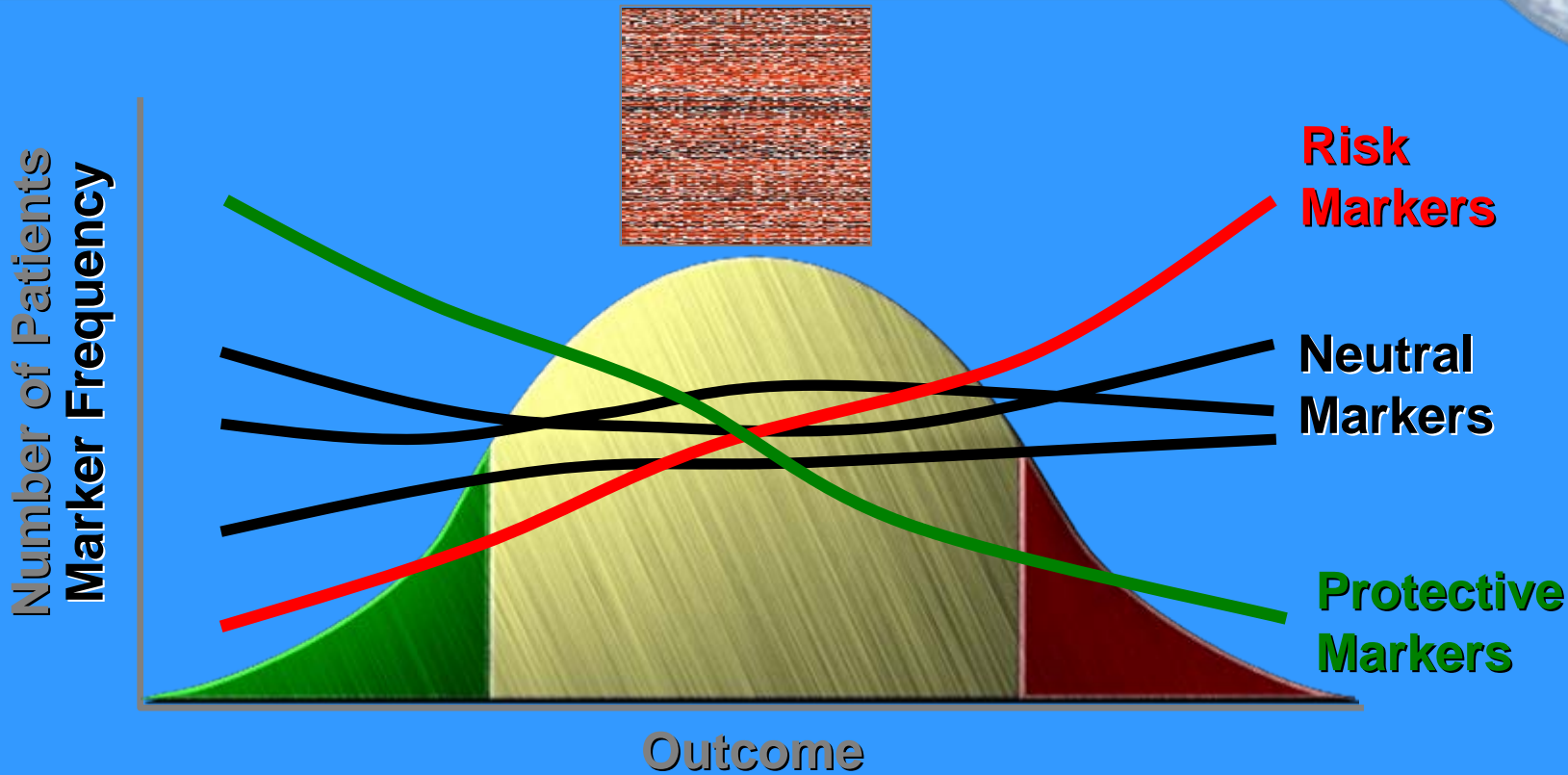
Risperidone



Mean=78.4 kg
SD=18.5 kg
N=101

PhysioGenomics Technology

Proprietary Platform for DNA-Guided Medicine



Highly parallel search for DNA markers with frequency dependence on phenotype distribution
Localized Regression (LOWESS: LOcally WEighted Scatterplot Smooth)

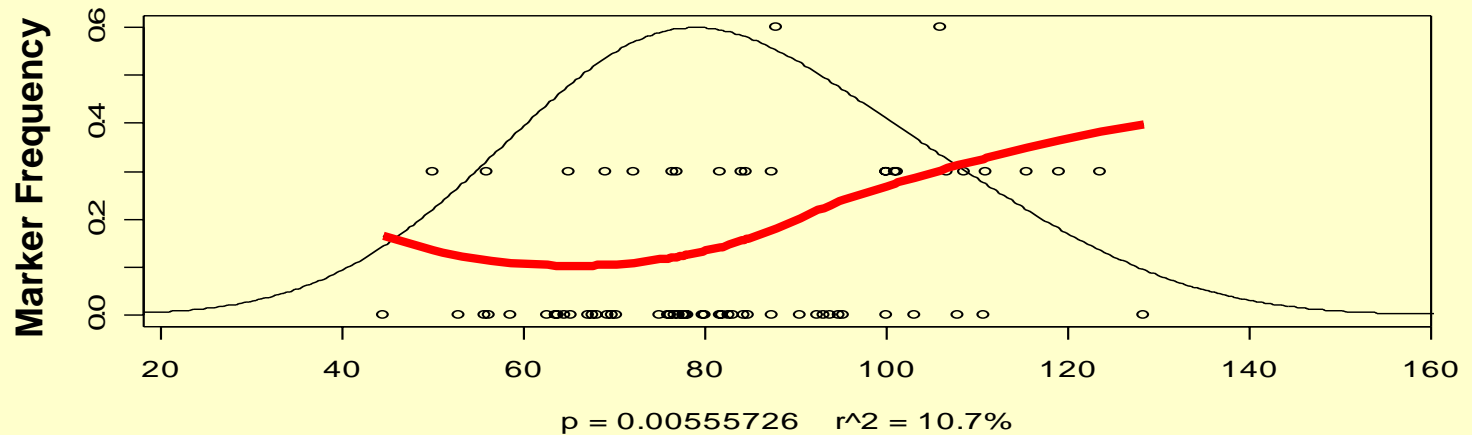
Ruaño, Holford, Windemuth, *Biomedical Engineering Handbook* 2006
Holford, Windemuth, Ruaño, *Personalized Medicine* 2005



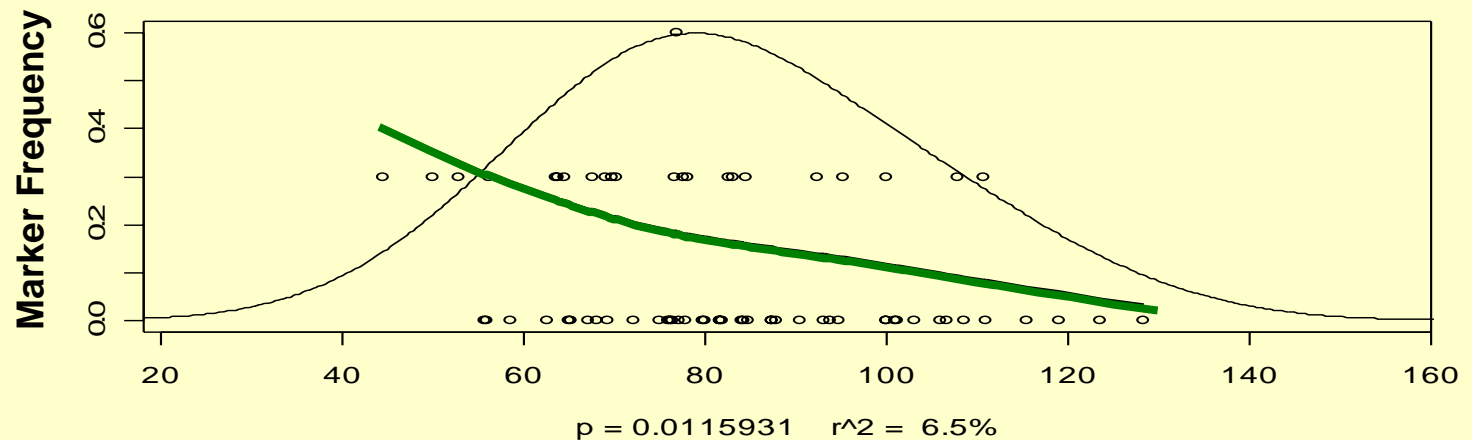
PhysioGenomics of DiMS: Olanzapine

Discovery from Side Effect Spectrum: Weight

ApoE
Apolipoprotein E

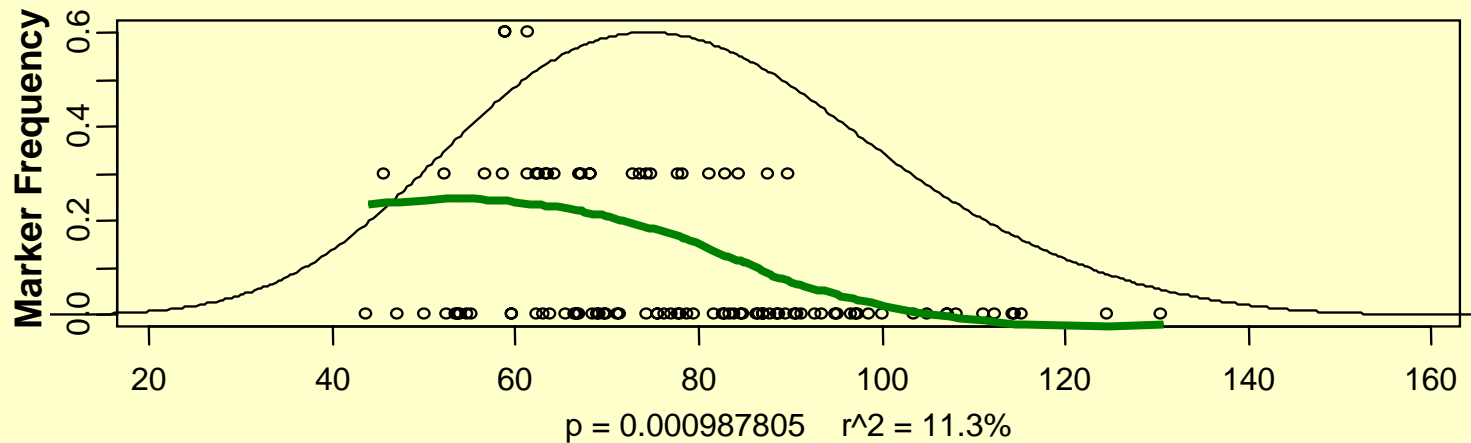


ApoA4
Apolipoprotein A4

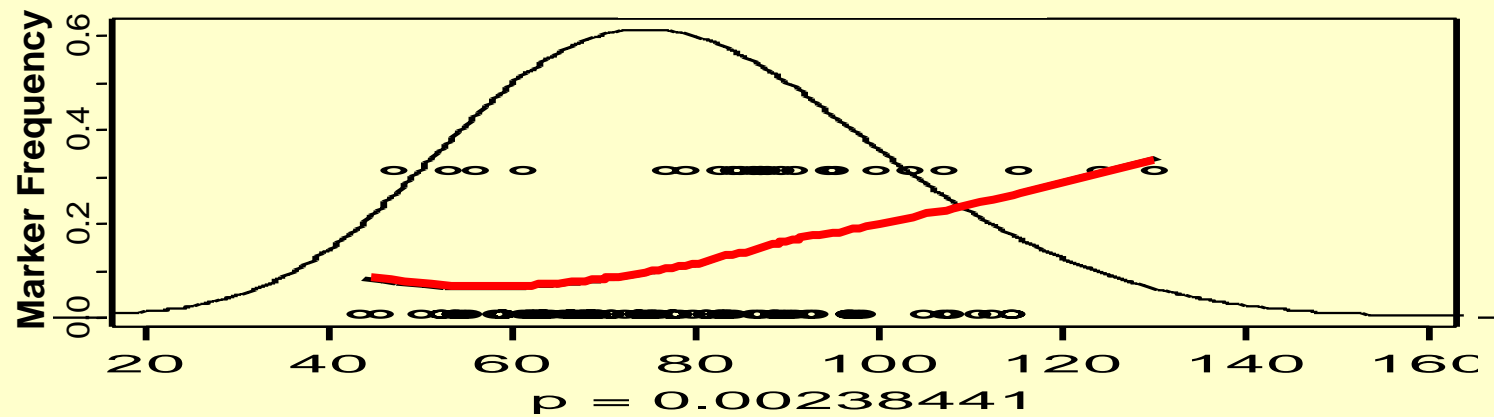


PhysioGenomics of DiMS: *Risperidone* Discovery from Side Effect Spectrum: Weight

LEPR
Leptin
Receptor



NPY5R
Neuropeptide
Y receptor Y5



Phyziotype Systems

Next Generation DNA-Guided Medicine

PHYZIOTYPE



SYSTEMS



**Genotype
gene D**



**Genotype
gene A**



**Genotype
gene E**



**Genotype
gene B**



**Genotype
gene F**



**Genotype
gene C**

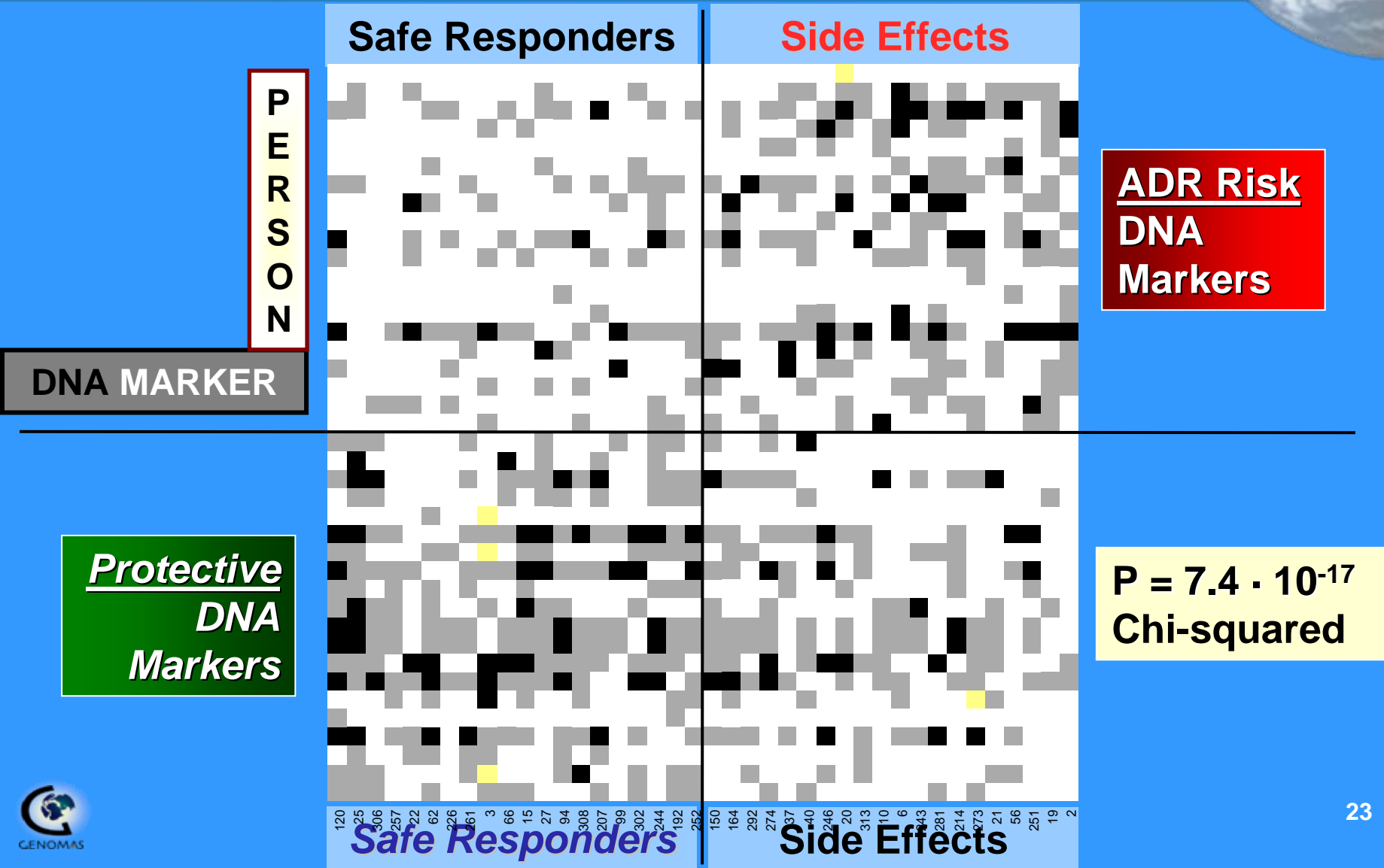
Protective
DNA
Markers

ADR Risk
DNA
Markers

SNP Ensemble, Assays, Algorithms, Portal

Phyziotype System: Psychotropics

Predicting Olanzapine Weight, Patient LPH1



Phyziotype System: Psychotropics

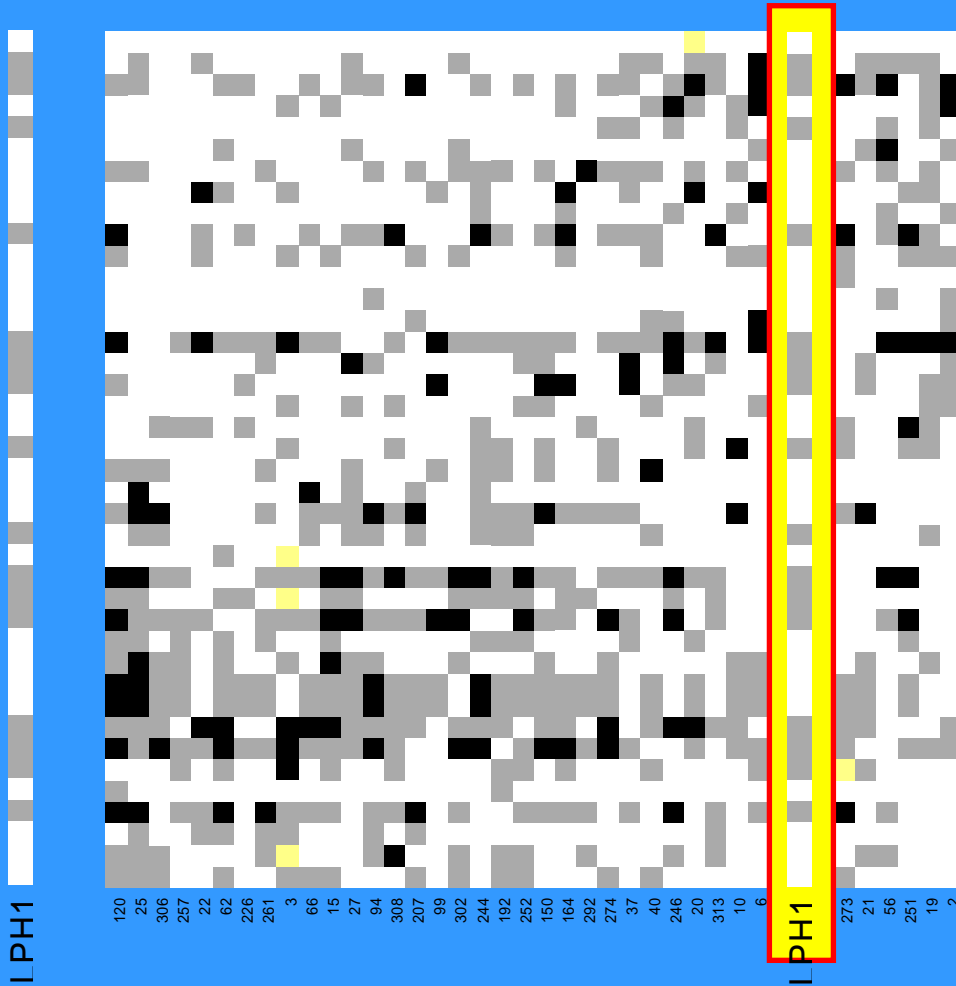
Predicting Olanzapine Weight, Patient LPH1

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:**
Psychotropic DiMS

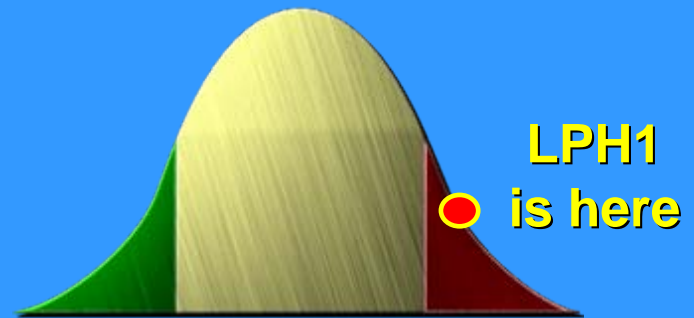
Phyziotype System: Psychotropics

Predicting Olanzapine Weight, Patient LPH1



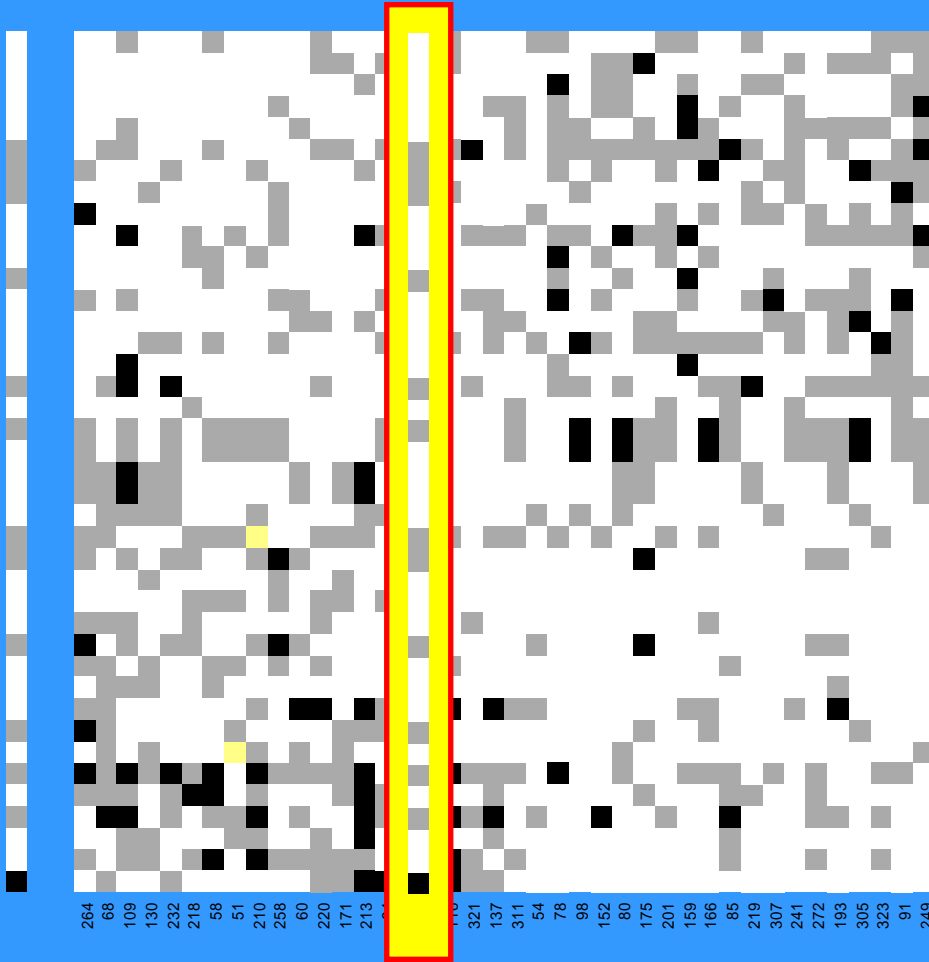
INTERPRETATION

- Phyziotype places patient at 86th ranking of Zyprexa[®] ADR risk
- Patient at very high risk of weight gain
- Evaluate alternative drugs or treat ADR



Phyziotype System: Psychotropics

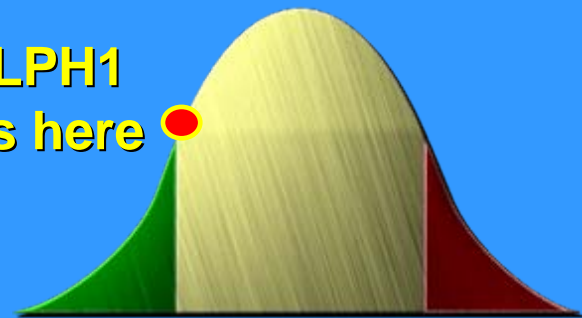
Predicting Risperidone Weight, Patient LPH1



INTERPRETATION

- Phyziotype places patient at 28th rank of *Risperdal*[®] weight ADR
- Patient at low risk of weight gain
- Consider prescription if therapeutically indicated

LPH1
is here



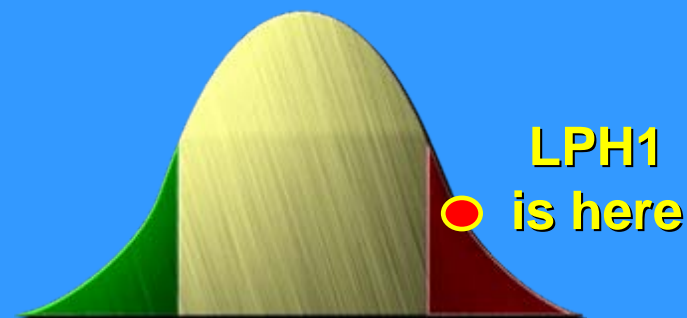
PhyziioType System: Psychotropics

Predicting Weight Side Effect, Patient LPH1

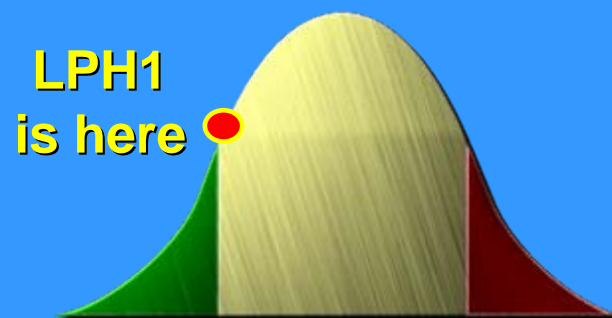
Patient LPH1 on Zyprexa®

- **Clinical Symptoms:**
8 kg weight gain and abnormal lipids
- Referred to LPH and IOL for DNA typing of drug metabolism status
- **PhyziioType Diagnosis:**
Psychotropic DiMS

Risperdal® is predicted to have the least weight gain for this patient and *Zyprexa*® the most.



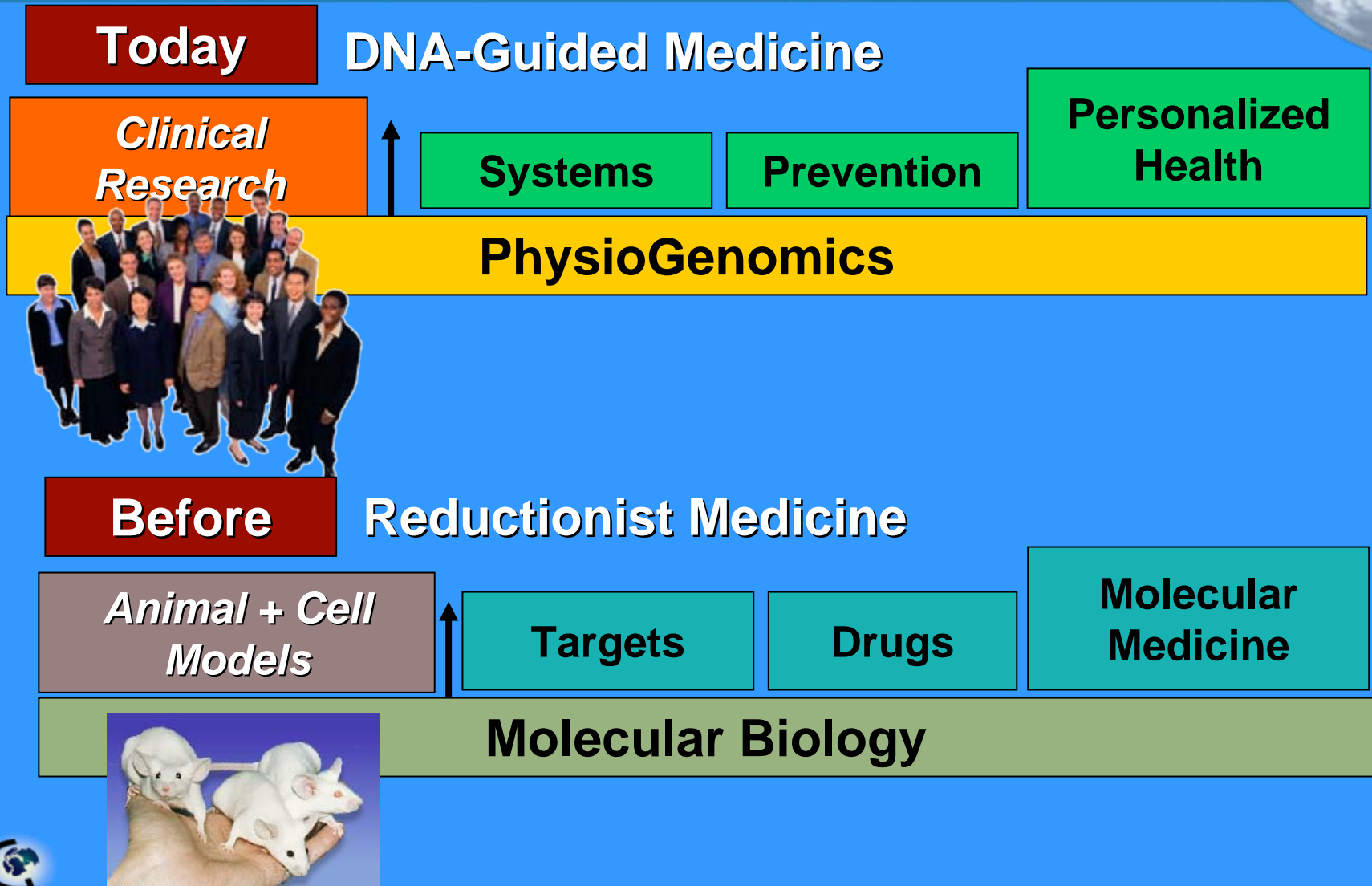
Zyprexa



Risperdal

PhysioGenomics + Personalized Health

Mechanism Discovery from Clinical Research



What Are the Implications for Clinical Neuroscience?

2007

- *Drug metabolism DNA Typing is first: assays available now*
- *FDA spearheading new guidelines for prescription of safest drugs*

2008

- **Diagnostics for drug-induced metabolic syndromes to prevent ADRs**
- **DNA-guided drug selection to minimize risk of ADRs**



New paradigm for medicine

DNA-guided diagnosis, prevention and treatment

***Personalized health will be expected
by patients and their families***



Thank you!

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860-545-3773

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Health Personalized