Precision Medicine in the Pharmaceutical Industry: Why Interindividual Variability is Important

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Interindividual Variability Workshop
Washington, DC
30 September 2015
Outline

• Why interindividual variability is important to the pharmaceutical industry
• An overview of drug development & assessing potential for interindividual variability of the target
• Examples of precision medicine approaches used in the discovery, pre-clinical, clinical, and post-marketing stages of drug development
• Summary and Conclusions
Why Interindividual Variability is Important to the Pharmaceutical Industry

“Precision Medicine as a Tool to Improving R&D Productivity”
Why Do We Need Precision Medicine?

“Health care today is in crisis as it is expensive, reactive, inefficient, and focused largely on one size fits all treatments for events of late stage disease. An answer is personalized, predictive, preventive and participatory medicine.”

Ralph Snyderman, M.D.
Chancellor Emeritus, Duke University
Founder and Chairman, Proventys
Why Now is the Right Time?

Strong unmet need among patients\(^1\)

High % of patients for which particular drug is ineffective on avg.

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>% Ineffective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Depressants (SSRIs)</td>
<td>38%</td>
</tr>
<tr>
<td>Asthma Drugs</td>
<td>40%</td>
</tr>
<tr>
<td>Diabetes Drugs</td>
<td>43%</td>
</tr>
<tr>
<td>Arthritis Drugs</td>
<td>50%</td>
</tr>
<tr>
<td>Alzheimer’s Drugs</td>
<td>70%</td>
</tr>
<tr>
<td>Cancer Drugs</td>
<td>75%</td>
</tr>
</tbody>
</table>

Emerging Science/Technology to drive PM\(^2\)

Rapidly decreasing cost of sequencing human genome

- $10,000,000
- $1,000,000
- $100,000
- $10,000
- $1,000
- $100
- $10
- $1
- $0.1
- $0.01

Cost per Mb vs. Cost per Genome (2005-2014)

- 2005: $10,000,000
- 2008: $1,000,000
- 2011: $100,000
- 2014: $10

2 Average cost of sequencing a genome for NHGRI funded sequencing technology.

- PM has the opportunity to characterize complex diseases and identify targets to address the unmet medical need
- Patient non-responders experience no benefit but are still at risk for drug side effects
# FDA Table of Pharmacogenomic Biomarkers in Drug Labels

[(FDA Website Link)]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic Area*</th>
<th>Biomarker†</th>
<th>Referenced Subgroup</th>
<th>Labeling Sections</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abacavir</strong></td>
<td>Infectious Diseases</td>
<td>HLA-B</td>
<td>HLA-B*5701 allele carriers</td>
<td>Boxed Warning, Contraindications, Warnings and Precautions</td>
</tr>
<tr>
<td><strong>Ado-Trastuzumab Emtansine</strong></td>
<td>Oncology</td>
<td>ERBB2</td>
<td>HER2 protein overexpression or gene amplification positive</td>
<td>Indications and Usage,WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, CLINICAL PHARMACOLOGY, CLINICAL STUDIES</td>
</tr>
<tr>
<td><strong>Afatinib</strong></td>
<td>Oncology</td>
<td>EGFR</td>
<td>EGFR exon 19 deletion or exon 21 substitution (L858R) positive</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
</tr>
<tr>
<td><strong>Amitriptyline</strong></td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>CYP2D6 poor metabolizers</td>
<td>Precautions</td>
</tr>
<tr>
<td><strong>Anastrozole</strong></td>
<td>Oncology</td>
<td>ESR1, PGR</td>
<td>Hormone receptor-positive</td>
<td>Indications and Usage, Adverse Reactions, Drug Interactions, Clinical Studies</td>
</tr>
<tr>
<td><strong>Arformoterol (1)</strong></td>
<td>Pulmonary</td>
<td>UGT1A1</td>
<td>UGT1A1 poor metabolizers</td>
<td>Clinical Pharmacology</td>
</tr>
<tr>
<td><strong>Arformoterol (2)</strong></td>
<td>Pulmonary</td>
<td>CYP2D6</td>
<td>CYP2D6 intermediate or poor metabolizers</td>
<td>Clinical Pharmacology</td>
</tr>
<tr>
<td><strong>Aripiprazole</strong></td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>CYP2D6 poor metabolizers</td>
<td>Dosage and Administration, Clinical Pharmacology</td>
</tr>
<tr>
<td><strong>Arsenic Trioxide</strong></td>
<td>Oncology</td>
<td>PML-RARA</td>
<td>PML-RARα translocation positive</td>
<td>Clinical Pharmacology, Indications and Usage</td>
</tr>
<tr>
<td><strong>Atomoxetine</strong></td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>CYP2D6 poor metabolizers</td>
<td>Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology</td>
</tr>
</tbody>
</table>

*Therapeutic Area*: The area of medicine where the drug is used.
†**Biomarker**: The specific biomarker identified within the drug.

[Source: Pfizer]
Analysis of the FDA Table of Pharmacogenomic Biomarkers in Drug Labels (2011 Analysis)

- Of the pharmacogenomic (PGx) biomarkers, 62% are used to exclude patients or adjust therapeutic dose based on safety concerns and 89% of these biomarkers are genetic.
- Hence, evaluation of the target’s genetic variants can potentially assist in understanding safety and efficacy much earlier in drug development.
Drug Development and Variability Challenges and Solutions During the “Discovery Phase”

“Genetic Approaches to Evaluate the Target for Efficacy and Safety”
Sources of Benefit When Genetics Are Applied in the Drug Development Process

- High attrition at proof of concept
  - Right targets?
  - Right patient population?

- High variability in drug response
  - Safety
  - Efficacy

Understanding of diseases of unmet need/Target ID → Targeted patient populations → Understanding clinical response → Targeted medicines

Target ID, Screening → Lead Development → Candidate Selection → Early Clinical Trials → Phase III → NDA

ADME, Ceff PD, Nonclinical Safety → Efficacy, Safety, D/R, C/R
Using Genetics to Select Targets Reduces Attrition
(*Nelson et al, Nature Genetics, 2015*)

- The proportion of drug mechanisms with direct genetic support increases from 2% at the preclinical stage to 8.2% among mechanisms for approved drugs.
- By selecting genetically supported targets, the success rate in clinical development could double.
- Therefore, allowing genetic data to guide selection of targets should lower failure due to lack of clinical efficacy.

**Table 1** The relative value of genetic support for the probability that a target-indication pair progresses along the drug development pipeline, based on historical drug trial information

<table>
<thead>
<tr>
<th>Progression</th>
<th>GWASdb and OMIM</th>
<th>GWASdb</th>
<th>OMIM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I to II</td>
<td>1.2 (1.1–1.3)</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Phase II to III</td>
<td>1.5 (1.3–1.7)</td>
<td>1.4</td>
<td>1.6</td>
</tr>
<tr>
<td>Phase III to approval</td>
<td>1.1 (1.0–1.2)</td>
<td>1.0</td>
<td>1.1</td>
</tr>
<tr>
<td>Phase I to III</td>
<td>1.8 (1.5–2.1)</td>
<td>1.8</td>
<td>1.9</td>
</tr>
<tr>
<td>Phase I to approval</td>
<td>2.0 (1.6–2.4)</td>
<td>1.8</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Values give the ratio of the probability of a target-indication pair progressing given genetic support to the probability of progressing without genetic support; 95% confidence intervals are given in parentheses.
### Examples of Precedence - From Gene to Target for Support of Efficacy (2011)

<table>
<thead>
<tr>
<th>Target</th>
<th>Indication</th>
<th>Genetic data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nav1.7</td>
<td>Pain</td>
<td>Rare mutation results in loss of pain sensation</td>
</tr>
<tr>
<td>SLC30A8</td>
<td>Type 2 diabetes</td>
<td>Common exonic polymorphism increases risk to T2D</td>
</tr>
<tr>
<td>FTO</td>
<td>Obesity</td>
<td>Homozygous carriers of risk allele ~ 3Kg heavier than non carriers</td>
</tr>
<tr>
<td>SLC30A8</td>
<td>Type 2 diabetes</td>
<td>Common exonic polymorphism increases risk to T2D</td>
</tr>
<tr>
<td>JAK-3</td>
<td>Transplant rejection, RA</td>
<td>Rare mutation results in severe immunodeficiency</td>
</tr>
<tr>
<td>TNFRSF11B (osteoprotegerin)</td>
<td>Osteoporosis</td>
<td>Common polymorphisms increase risk of osteoporosis (ODD ratio ~1.4)</td>
</tr>
<tr>
<td>CCR5</td>
<td>HIV</td>
<td>Homozygosity for a common polymorphism results in resistance to HIV</td>
</tr>
<tr>
<td>CETP</td>
<td>LDL levels</td>
<td>Common polymorphisms explain a modest proportion of the variance of LDL levels</td>
</tr>
<tr>
<td>PPARG</td>
<td>Type 2 diabetes</td>
<td>Common polymorphisms increase susceptibility to T2D (ODD ratio = 1.12). Rare mutations lead to MODY</td>
</tr>
<tr>
<td>KCNJ11</td>
<td>Type 2 diabetes</td>
<td>Common polymorphisms increase susceptibility to T2D (ODD ratio ~1.2). Rare mutations lead to MODY</td>
</tr>
<tr>
<td>PTGS2 (COX-2)</td>
<td>Osteoarthritis</td>
<td>Common polymorphisms increase risk of Knee OA, and Influence response to Cox inhibitory drugs</td>
</tr>
</tbody>
</table>

### Targets
- Nav1.7
- SLC30A8
- FTO
- PCSK9
- JAK-3
- TNFRSF11B (osteoprotegerin)
- CCR5
- CETP
- PPARG
- KCNJ11
- PTGS2 (COX-2)

### Compounds in Development
- SLC30A8
- FTO
- PCSK9
- JAK-3
- TNFRSF11B (osteoprotegerin)
- CCR5
- CETP
- PPARG
- KCNJ11
- PTGS2 (COX-2)

### Marketed Drugs
- Nav1.7
- SLC30A8
- FTO
- PCSK9
- JAK-3
- TNFRSF11B (osteoprotegerin)
- CCR5
- CETP
- PPARG
- KCNJ11
- PTGS2 (COX-2)
Human Genetic Databases Used to Assess a Efficacy and Safety of a Target

- Human Genetic Mutation Databases (HGMD)
  - http://www.hgmd.cf.ac.uk/ac/index.php
- Exome Variant Server (EVS)
  - http://evs.gs.washington.edu/EVS/
- NHGRI GWAS catalogue
  - http://www.genome.gov/26525384
- OMIM
- HuGE navigator
  - http://hugenavigator.net/HuGENavigator/home.do
- Disease Genetic Association Database (GAD)
  - http://geneticassociationdb.nih.gov/cgi-bin/simple.cgi?table
- Phenotype-Genotype Integrator
De-selection of a Target Based on Safety Concerns from Genetic Analysis

<table>
<thead>
<tr>
<th>Questions</th>
<th>Guanylate Cyclase 2C (GUCY2C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is there discernible genetic variation in the target gene?</td>
<td>❑ Yes</td>
</tr>
</tbody>
</table>
| 2. Are these variants associated with altered phenotypes in the human population? | ❑ Yes. Ser840Ile – Familial diarrhea\(^1\)  
❑ Asp387Gly – Meconium Ileus\(^2\)                                              |
| 3. Is there known functional impact of the genetic variants?              | ❑ Yes. Ser840Ile – Gain of Function\(^1\).  
❑ Asp387Gly – Loss of function\(^2\).                                             |
| 4. Are there any human populations that under or over-represent the risk-associated allele? | ❑ Frequency information was not found for the S840I variant. The D387G variant is rare (i.e. \(\sim0.01\%\)). |
| 5. Do humans that are hetero- or homozygous for the risk-associated allele have a phenotype that is similar to that observed in knock-out or knock-in mice for this target | ❑ Mice lacking GUCY2C exhibit diarrhea in addition to a number of other phenotypes. |

- Guanylate cyclase 2C gain of function mutation (c.2519G→T; p. Ser840Ile) identified in humans
  - Disease-causing mutation for severe familial diarrhea so therapies activating GUCY2C could lead to severe diarrhea in patients
Variability Challenges and Solutions During the Pre-clinical Phase

“Preclinical Approaches to Assess Genetic Diversity: The Mouse Diversity Panel (MDP)”
The Mouse Model of the Human Population (MMHP) consists of a panel of ~35 inbred mouse strains encompassing a genetic diversity equal to or greater than that found in the human population.

The Hamner Institutes successfully used this model to map polymorphisms that infer susceptibility to acetaminophen-induced liver injury:

- Demonstrated that genetic variation in the CD44 gene was associated with susceptibility in humans.
Isoniazid-induced steatosis is caused by multiple events involving lipid retention in livers of genetically-sensitive strains:

- Transcriptomics (mitochondrial dysfunction), metabolomics (reduced GSH – oxidative stress, reduced lipid export), GWAS (perilipin-2 polymorphisms)

- Highlights value of using a MMHP to investigate drug-induced responses across a diverse population using a systems biology approach
Variability Challenges and Solutions During the Clinical Phase

“Example - CCR5”
A deletion in the CCR5 gene called CCR5Δ32…

…results in a non-functional CCR5 protein that is not expressed on cells.

People with 2 copies of the CCR5Δ32 gene are resistant to HIV infection

Progression to AIDS  
Delayed progression  
No CCR5 tropic HIV infection!
Variability Challenges and Solutions During the Post-marketing Phase

“Understanding Adverse Events”
MOA for Statin-induced Myopathy: SLCO1B1 LOF Variant (Ramsey et al, Clinical Pharmacol & Ther, 2014)

The Clinical Pharmacogenetics Implementation Consortium Guideline for SLCO1B1 and Simvastatin-Induced Myopathy: 2014 Update

Table 2 Dosing recommendations for simvastatin based on SLCO1B1 phenotype

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Implications for simvastatin</th>
<th>Dosing recommendations for simvastatin&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Classification of recommendations&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal function</td>
<td>Normal myopathy risk</td>
<td>Prescribe desired starting dose&lt;sup&gt;b&lt;/sup&gt; and adjust doses of simvastatin based on disease-specific guidelines</td>
<td>Strong</td>
</tr>
<tr>
<td>Intermediate function</td>
<td>Intermediate myopathy risk</td>
<td>Prescribe a lower dose or consider an alternative statin (e.g., pravastatin or rosuvastatin); consider routine CK surveillance</td>
<td>Strong</td>
</tr>
<tr>
<td>Low function</td>
<td>High myopathy risk</td>
<td>Prescribe a lower dose or consider an alternative statin (e.g., pravastatin or rosuvastatin); consider routine CK surveillance</td>
<td>Strong</td>
</tr>
</tbody>
</table>

CK, creatine kinase.

• The SNP, rs4149056T>C, in SLCO1B1 increases systemic exposure to simvastatin and increases the risk for muscle toxicity
Summary & Conclusions
Summary

- Precision Medicine approaches provide a component of addressing interindividual variability

- Human molecular genetics is an important part of the drug development toolbox
  - Understanding biology, target selection, efficacy, and safety
  - Focus on genes/pathways with compelling genetic evidence

- Using genetic databases to understand variability in targets and ADME, as well as nonclinical models such as the MDP, are potential approaches for the EPA to consider in studying interindividual variability
Hurdles Remain but Significant Momentum Driving Advancement in Precision Medicine

Evolving Regulatory Attitude

“Advanced diagnostics such as these are the cornerstone of personalized medicine, and their development can only foreshadow the many advances on the horizon. This is truly an exciting time in the history of cancer therapies and their companion diagnostics.”

– Margaret Hamburg, FDA Commissioner, 2013 ASCO

“Doing a single trial to answer each question raised by each marker/candidate therapeutic and combinations thereof is not feasible. [We] need to 'turn paradigm on its head' - set up ongoing trials with broad intake and many strata based on biomarkers.”

– Janet Woodcock, FDA CDER Director, 2013

Accelerated Industry Activity

Erlotinib/Vectibix (EGFR)
Zelboraf (BRAF V600E)
Gilotrif (EGFR Del 19 & L858R)
Xalkori (EML4-ALK)
Mekinist/Tafinlar (BRAF V600E)

Rapid Technological Advancement

"A naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated."

– US Supreme Court Decision in Association for Molecular Pathology vs. Myriad Genetics, 2013

Evolving Legal Framework

"Advanced diagnostics such as these are the cornerstone of personalized medicine, and their development can only foreshadow the many advances on the horizon. This is truly an exciting time in the history of cancer therapies and their companion diagnostics."
Acknowledgements

• Karissa Adkins
• Katrina Loomis
• Sara Paciga
• Morten Sogaard
• J. Claiborne Stephens
• Hong Wu
Appendix

- Genetics 101 Primer
- Additional drug examples (Xalkori, CETPi)
Genetics 101 Primer

“Understanding Basic Terminology”
Human Genetics

- 3,100,000,000 base pairs
- 23,500 protein coding genes (1% of genome)
- Many types of genetic variation, Single nucleotide polymorphisms (SNPs) most common
  - 15 million common SNPs (freq >5 %)
  - Larger number of rare SNPs

A>C
denovo mutation @ germline

Genetics aims to identify and quantify relationship between genotypes and phenotypes

recombination preserves segments and is the reason for SNP correlation (LD)
drives variation and evolution

We share common ancestors which makes disease mapping possible
**Functional Impact of a Variant**

- **Promoter variant**
  - **No change**
    - **gene expression**
  - **gene expression**

- **Coding variant**
  - **Synonymous:** limited/no effect
    - Encode same aa
      - AGA → AGG
        - Arg → Arg
  - **Non-Synonymous:** potential effect
    - Encode diff aa – Potential effect on protein
      - AGA → ACA
        - Arg → Thr
    - Encode premature stop codon – Truncated protein
      - AGA → TGA
        - Arg → stop
    - Insertion/deletion – Truncated protein
      - cause frame shift (new aa added then stop codon)

- **Intronic variant**
  - **No change**
  - Create splice site
  - Destroy splice site
Genetic Association (And Literature Advice)

Prior to 2006

**Candidate genes** – based on known biology

- Bad at selecting the right genes!
- Small studies gave many false positive associations

**LOOK FOR**

- 1000 cases and 1000 controls with replication
- \( p \) -value in relation to how many SNPs were being studied

<table>
<thead>
<tr>
<th>Cases (n=10,000)</th>
<th>Controls (n=10,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA 60%</td>
<td>45%</td>
</tr>
<tr>
<td>AG 30%</td>
<td>35%</td>
</tr>
<tr>
<td>GG 10%</td>
<td>20%</td>
</tr>
<tr>
<td>( p ) = 0.00000050</td>
<td></td>
</tr>
</tbody>
</table>

After 2006

**Genome-wide association** - unbiased, millions of variants are tested across entire human genome

**LOOK FOR**

- Manhattan plot \( p \)-value < 10\(^{-8}\)
- Independent replication
- Consideration to population bias
- Quantile-quantile plot indicating signal
Additional Examples of Drugs Having a Genetic Basis
Changing paradigms in identifying disease subsets
Understanding disease on a molecular basis

Adenocarcinoma 1999
Histology-driven selection

Adenocarcinoma 2010
Targeting oncogenic drivers

- K-ras
- EGFR
- B-raf
- Her2
- PIK3CA
- ALK
- MET
- Unknown

Xalkori © (crizotinib) - Using Genetics to Target & Treat Cancer Subtypes
Identification of the transforming \textit{EML4–ALK} fusion gene in non-small-cell lung cancer

Manabu Soda\textsuperscript{1,2}, Young Lim Choi\textsuperscript{3}, Munehiro Enomoto\textsuperscript{1,2}, Shuji Takada\textsuperscript{1}, Yoshihiro Yamashita\textsuperscript{1}, Shunpei Ishikawa\textsuperscript{5}, Shin-ichiro Fujiwara\textsuperscript{1}, Hideki Watanabe\textsuperscript{1}, Kentaro Kurashina\textsuperscript{1}, Hisashi Hatanaka\textsuperscript{1}, Masashi Bando\textsuperscript{2}, Shoji Ohno\textsuperscript{2}, Yuichi Ishikawa\textsuperscript{6}, Hiroyuki Aburatani\textsuperscript{5,7}, Toshiro Niki\textsuperscript{3}, Yasunori Sohara\textsuperscript{4}, Yukihiko Sugiyama\textsuperscript{2} & Hiroyuki Mano\textsuperscript{1,7}

\textbf{EML4-ALK frequency:}

\textit{~4\% (64/1709)}

\textbf{Primarily lung adenocarcinoma}

Xalkori (crizotinib) – Inhibits ALK Positive Tumors
(48-yr old Female Non-smoker with NSCLC ALK Fusion)

Kwak EL, et al. ESMO/ECCO 2009 (Abstract G6 and oral presentation)
Roadmap for Genetic Target Discovery

• Identify the right population and subject cohort(s)
  – Families
  – Unrelated (case/control or QTL)
  – Mixtures

• Deploy appropriate genomic technology
  – GWAS
  – Whole Exome Sequencing
  – Whole Genome Sequencing

• Identify appropriate data analyses
  – Common allele tests
  – Rare allele tests
  – Novel allele tests
Business Case for Conducting Whole Exome Sequencing in Cynomolgus Monkeys

- Widely used in drug development process especially with biotherapeutics
- High genetic similarity with humans
- Genetic information regarding genome sequence, gene expression arrays and a SNP map were not available
- Two major questions for toxicologists
  - How variable is the genetic composition of cynomolgus monkeys used in preclinical toxicology studies?
  - Is it possible to utilize genetic data of cynomolgus monkeys to understand phenotypic variability observed in preclinical studies?
Drug-induced Hypersensitivity Reactions Suggested an Immune-mediated MOA

- **Histopathology**
  - Inflammation of skin and mucous membranes
    - Was widespread including oral/genital mucosa, esophagus, and urinary bladder; liver, kidney, and brain also involved in some animals

- **Microscopic findings**
  - Subepidermal bullae with full thickness epidermal necrosis
  - Lymphocytic inflammation at the interface between the dermis and epidermis (interface dermatitis) with single cell necrosis of basal keratinocytes; Inflammation consisted predominantly of CD3+ T lymphocytes
Could This Response be Associated with MHC Alleles?

- Evidence in the literature to support associations between HLA alleles and drugs that cause hypersensitivity reactions in humans
  - HLA-B*5701, Abacavir and flucloxicillin
  - HLA-B*1502, Carbamazepine,
  - HLA-B*5801, Allopurinol
- MHC genotyping conducted using DNA from monkeys on several toxicity studies
  - DNA isolated from whole blood and FFPE samples
  - A total of 62 samples
  - Genotyping analysis performed at the National Primate Research Center, University of Wisconsin (Dr. David O'Connor’s lab)
- MHC M3 haplotype B alleles were found to be associated with the skin hypersensitivity reactions observed in cynomolgus monkeys.
  - The high sequence homology between MHC M3 B region and HLA alleles suggests that identifying the specific alleles associated with this reaction in the M3 haplotype may allow for potential human translatability
Genetic Evidence For CETPi Failure in Clinical Trials
(Voight et al, Lancet, 2012)

**Drug Intervention**
- Random allocation of intervention at baseline
  - **Intervention**: HDL-C higher, CV event rate ??
  - **Control**: HDL-C lower, CV event rate ??

**Mendel’s Second Law**
- Random allocation of alleles at conception
  - **LIPG Ser396**: HDL-C higher, CV event rate same
  - **LIPG Asn396**: HDL-C lower, CV event rate same

- **Endothelial lipase Asn396 vs. Ser96 carriers**
  - Analogous to drug intervention vs. control
  - HDL-Cholesterol higher in LIPG Ser396 carriers
    - Analogous to PD of drug treatment
  - Myocardial Infarction incidence not changed
    - Analogous to outcome study of drug treatment

  - **20,913 MI cases vs. 95,407 controls**

**Conclusion**: It is questionable whether raising HDL cholesterol alone is a viable approach to reducing myocardial infarction