The objective of this class is to give you an overview of Pharmacogenomics, to teach you the basic concepts and how to apply Pharmacogenomics in clinical trials.
Genetic variation is responsible for all inherited aspects of our lives

Human genome:
We are 99.9% identical at the DNA level – it’s the remaining 0.1% that makes a difference.
RECENT BREAKTHROUGH: PERSONAL GENOME SEQUENCE and GENOME WIDE SCREEN ASSOCIATIONS

1953 DNA Double Helix
2003 H. Sapiens $3 Billion-13 years

Personal Genome-Costs are decreasing!
2007 Venter/Watson $1M
2009 NHGRI $100K
2012 Archon X Prize $10K
2013 NHGRI $1000

Biotech offering DNA services
Affymetrix/Illumina: 1M DNA SNP chip

23andme/Navigenics: Personal Genome Service
Genetics.match.com

Genome Wide Screen associations identified for complex disorders: Type I/II Diabetes (29 associations), Cardio Vascular Disease (8 associations), Breast Cancer (9 associations), Colorectal Cancer (7 associations), Lung Cancer (4 associations), Prostate Cancer (15 associations), Alzheimer’s Disease/Parkinson’s Disease (2 associations), Bipolar Disorder (1 association), Multiple Sclerosis (5 associations), Lupus (7 associations), Rheumatoid arthritis (2 associations), Crohn’s Disease (15 associations), Celiac Disease (6 associations), Inflammatory Bowel Disease (2 associations)
Drug Development: Challenges

- Cost to bring new drug to market: US $800 million
- FDA approvals of NME continue to decline despite increase of expenditures
- Difficulty to identify relevant targets in discovery
- Decline in blockbusters
- Drug Development process is lengthy (~11 years) and inefficient
- Increase in rate of attrition in late stage phase of development
  - 80-90% INDs fail before they reach the market due to lack of efficacy, toxicity, adverse events, PK,
  - Lack of strategic fit…
- Post Marketing withdrawal is not uncommon (drug-drug interactions, drug induced liver toxicity, long QT, other)
Can We Do Better and How Can Pharmacogenomics Help?
Pharmacogenomics and Pharmacogenetics

Pharmacogenetics or Pharmacogenomics is genetics/genomics as applied to pharmaceutical compounds

Definitions

- Pharmacogenetics: is the study of inherited factors (DNA variations) and their influence on inter-individual variation in drug response-a few genes
- Pharmacogenomics: as a research tool to identify genes which correlate with response using gene expression profiling or large scale genomics studies (DNA or RNA chips)-thousands of genes

We will focus on clinical pharmacogenetics studies rather than expression studies
Drug Metabolism Example:

- After drug intake, the drug is processed (much like food) in the human body.

- A group of enzymes called “drug-metabolizing enzymes” (DMEs) is responsible for the breakdown of drugs in the body.

- Many of these enzymes are present in different forms/amounts in different individuals.

- This causes different people to process the same drug differently
If Your Dose is Wrong, What Does It Mean For You?

- Different forms of DMEs have an effect on Drug-Safety:
  - Some individuals require up to e.g. 10-fold less medication than “standard” dose
  - They are at risk to be overdosed and exposed to potential adverse events.

- Efficacy:
  - Some individuals require up to e.g. 5-fold more medication than “standard“

- Where it matters: cancer treatment vs. common cold
# Phenotypic Effects of Cytochrome P450 Pharmacogenomics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Slow Metabolizer Phenotype</th>
<th>Fast Metabolizer phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodrug needs metabolism to work (e.g. codein is metabolized by CYP2D6 to morphine)</td>
<td>Poor efficacy Accumulation of prodrug</td>
<td>Good efficacy, good effect</td>
</tr>
<tr>
<td>Active drug is inactivated by metabolism (example is omeprazole)</td>
<td>Good efficacy Accumulation of active drug might lead to unwanted side effect Might need lower dose</td>
<td>Poor efficacy Need greater dose or slow release formulation</td>
</tr>
</tbody>
</table>
Targeted” Therapy:

- Personalized Medicine as a Means to Identify Responders and Non-Responders to Specific Therapies

- Interaction of drugs with targets they are “designed” for
In a normal breast tissue cell, the Her-2 gene is expressing cell surface receptor required for normal cell growth.

In certain types of breast cancers, the Her-2 gene is over-expressing this cell surface receptor, contributing to cancerous cell growth.

This is the case in ~30% of breast cancers.

Herceptin (trastuzumab) is an antibody that blocks the cell surface receptor and thereby prevents further growth. As a result, disease progression is slowed down.
What Does It Mean?

- Often, drugs are only effective in specific “sub-populations” (responders).
- Early identification of responders can have dramatic effect of treatment success.
- Treatment of non-responders puts these individuals at unnecessary risk of adverse events, while providing no benefit.
- Personalized Medicine allows the identification of responders and non-responders for targeted therapies.
- This is happening today!
“If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, the labeling shall describe the evidence and identify specific tests needed for selection and monitoring of patients who need the drug.”
## How Does It Read?: Examples of Pharmacogenomic Information in the Drug Label

<table>
<thead>
<tr>
<th>Brand Name Labeling section</th>
<th>Labeling section</th>
<th>Labeling Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERCEPTIN® (trastuzumab)</td>
<td>INDICATIONS AND USAGE</td>
<td>HERCEPTIN should be used in patients whose tumors have been evaluated with an assay validated to predict HER2 protein overexpression (see PRECAUTIONS: HER2 Testing and CLINICAL STUDIES: HER2 Detection.).</td>
</tr>
<tr>
<td>August 2002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STRATTERA (atomoxetine)</td>
<td>Drug-Drug Interactions Laboratory Tests</td>
<td>In EMs, inhibitors of CYP2D6 increase atomoxetine steady-state plasma concentrations to exposures similar to those observed in PMs. Dosage adjustment of STRATTERA in EMs may be necessary when.coadministered with CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine (see Drug Interactions under PRECAUTIONS). In vitro studies suggest that coadministration of cytochrome P450 inhibitors to PMs will not increase the plasma concentrations of atomoxetine. CYP2D6 metabolism –Poor metabolizers (PMs) of CYP2D6 have a 10-fold higher AUC and a 5-fold higher peak concentration to a given dose of STRATTERA compared with extensive metabolizers (EMs). Approximately 7% of a Caucasian population are PMs. Laboratory tests are available to identify CYP2D6 PMs. The blood levels in PMs are similar to those attained by taking strong inhibitors of CYP2D6. The higher blood levels in PMs lead to a higher</td>
</tr>
<tr>
<td>March 2003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Indication</td>
<td>Gene and label</td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>6-MP</td>
<td>ALL</td>
<td>TPMT-Recommendation</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Colorectal cancer</td>
<td>UGT1A1-Recommendation</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Anti-coagulant</td>
<td>CYP2C9 and VKORC1-Recommended</td>
</tr>
<tr>
<td>Strattera</td>
<td>ADHD</td>
<td>CYP2D6-Information</td>
</tr>
<tr>
<td>Erbitux (Cetuximab)</td>
<td>Colorectal cancer</td>
<td>EGFR-Required initially KRAS?</td>
</tr>
<tr>
<td>Gleevec</td>
<td>Gastrointestinal stromal tumors</td>
<td>c-kit-Information</td>
</tr>
<tr>
<td>Tarceva</td>
<td>NSCLC</td>
<td>EGFR-Information</td>
</tr>
<tr>
<td>Selzentry</td>
<td>HIV</td>
<td>Tropism test Required</td>
</tr>
<tr>
<td>Carbamezapine</td>
<td>Epilepsy, Bipolar</td>
<td>HLA testing Recommended</td>
</tr>
<tr>
<td>Herceptin</td>
<td>Metastatic Breast Cancer</td>
<td>Over expression of HER 2 receptor-Required</td>
</tr>
<tr>
<td>Clodipegrel</td>
<td>Blood Clot</td>
<td>CYP2C9 (ongoing)</td>
</tr>
<tr>
<td>Vectibix (Panitumamab)</td>
<td>Colorectal cancer</td>
<td>KRAS (Ongoing)</td>
</tr>
<tr>
<td>Abacavir</td>
<td>HIV</td>
<td>HLA testing Recommended</td>
</tr>
</tbody>
</table>
Pharmacogenomics

New FDA Approved Tools for “Personalized Medicine”

- **Roche’s amplichip**: (CYP2C19 & CYP2D6)
  - Metabolization of 25% of drugs- Dosing decisions

- **Genzymes invader UGT1A1 Molecular assay**
  - Designed for Irinotecan-Dosing decisions

- **Visible genetics TRUEGENE HIV-1 genotyping kit**
  - Detects variation in HIV sequences to identify correct drug for form of virus

- **Cell Search Technology** (Veridex)
  - Metastatic Breast cancer- Prediction of progression free survival and overall survival
Potential of Pharmacogenetics

All patients with same diagnosis

39% respond (17/44)

GCCCGCCTC
Non-responders and toxic responders
Treat with alternative drug or dose

GCCCAACCTC
Responders and patients not predisposed to toxicity
Treat with conventional drug or dose

57% respond (17/30)
Pharmacogenomics in R&D process

LEARN

Drug Discovery

LEARN

Early Development

CONFIRM

Full Development

APPLY TO DRUG LABEL

Life Cycle Management

IDENTIFY

Genetic Biomarkers

VALIDATE

Genetic Biomarkers

TARGETED MEDICINE DIAGNOSTICS
Complex diseases and complex outcomes such as drug response are likely to involve several genes and environmental variables.
Prerequisite: DNA samples and phenotypic information
Clinical trials: Provide cases-controls for association studies
Methods: SNP Association studies
- Candidate Gene
- Genome Wide Screening

Identify Genetic Biomarkers
- Disease Genetics (disease prognostics/Diagnostics)
  - Rare Mendelian diseases
  - Causal genes
- Common complex Disorders; Susceptibility genes
- Candidate genes for drug metabolism, action (targets), disease
- SNP profiles for drug metabolism and mode of action

Genetic Testing
Pharmacogenetics (drug response profiles)
- Pharmacogenetics (drug response profiles)
SNP Association Studies

Patients *without* a side effect

Patients *with* a side effect

Predictive of **NO** side effect

Predictive of **A** side effect

Section of SNP profile

Prognostic test
What is a SNP?

**SNP** = Single Nucleotide Polymorphism

- Coding regions (exons)
- Non-coding regions (e.g. introns)
- Regulatory regions (e.g. promoter)
- Splicing regions (intron/exon boundaries)

**Why SNPs?**

- Can lead to altered activity or altered level of expression
- Can be useful biomarkers
- High frequency (approximately 1 SNP every 1,000 bp)
- Currently >17,000,000 SNPs publicly available
- Stability through populations (from generation to generation)
- SNP genotyping is amenable to automation
What Can Pharmacogenetics Potentially Do?

- Improve discovery of drugs targeted to human disease
- Improve proof of principle for efficacy trials
- Improve drug safety, reduce drug-drug Interaction studies, and understand adverse events in development and post-approval
- Improve identification of patients who will benefit from genetically-defined therapy, and avoid futile therapeutic attempts
Pharmacogenomics

Better understanding of the disease process helps to define:

**Drugs targeted to disease subtypes**

**New targets**

- One target for monogenic diseases
- Many targets for complex disorders

**Better targets**

- Select target with less variation reducing potential for differences in response
- Select compound in HiTS working against all genetic variants or most common variant of target
Genetic Polymorphism in Drug Target Can Affect Therapeutic Efficacy and Safety

responders

Non-responders

SNP information can be used for better target selection
Impact of Genetic Variability in Target on Drug Response

- Variations in drug target genes and correlation with efficacy

  “Pharmacogenetic prediction of Clozapine response using a combination of six polymorphisms in neurotransmitter-receptor-related genes”


- Impact of Genetic Polymorphisms in serotonin, 5-HT-2A receptor on anti-depressant side effect

Pharmacogenomics

Utilize data to identify-retrospectively
- Adjust dosage requirements
- Explain outliers
- Prioritize drug-drug interaction studies
- Responders/non responders/MOA
- Adverse responders

Subject stratification for entry into clinical trials- prospectively
- Enrich trial for responders based on genotype-salvage failed drugs
- Enroll CYP2D6 PM or EM to determine optimal dose or to study impact on efficacy/safety
- Reduction of time & cost
Challenges for Early Development

- How to obtain reliable proof of principle for efficacy and safety given small sample size of clinical trials and stringent timelines?

- Data from pre-clinical research may be helpful to identify relevant candidate genes

- \textit{In vitro} data does not always translate \textit{in vivo} – nor to human
Challenges for Late Development

- If a diagnostic is to be used in submission, it must be ready to use by phase III
- Research phase must be complete by phase II
- Use PGx to identify genes associated with PD in preclinical/early development
- Validation essential for robust results (‘hypothesis testing’)
- Unlikely to get reliable data on clinical efficacy until phase III
- Genotype likely to become part of label
Applications of PGx to Improve PK

<table>
<thead>
<tr>
<th>Research</th>
<th>Early Development</th>
<th>Late Development</th>
<th>Regulatory assessment</th>
<th>Commercialization</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>In vitro</em> PK research identifies genes involved in ADME</td>
<td>PGx research on variation in ADME genes</td>
<td>Genotyping during PK trials allows association with PK <em>in vivo</em></td>
<td>Genetic associations tested in different patient and ethnic populations</td>
<td>Regulatory data supports claims on PK, dosing, ethnic variability and safety concerns</td>
</tr>
</tbody>
</table>
Application of PGx to improve efficacy

- **Research**
  - Screening of target gene to identify major allele

- **Early Development**
  - Check that lead selected for clinical development is active against all major forms

- **Late Development**
  - Correlate gene variation (genetic/genomic) with pharmacodynamic results

- **Regulatory Assessment**

- **Commercialization**
Applications of PGx to Improve Safety

- **Research**
  - Pre-screening for interactions with known risk genes

- **Early Development**
  - PGx sampling includes patients with ADRs

- **Late Development**
  - PGx research identifies genes important in ADRs

- **Regulatory Assessment**
  - Diagnostic to predict patients at risk

**Feedback loop to improve pre-clinical screening**
Special Considerations for PGx and Safety

- ADRs may occur at any phase but may not be seen until phase III-IV
- SAEs typically very low numbers
- High priority to increase understanding of mechanism and identify patients at highest risk
- Genes identified fed back to improve pre-clinical screens
- Sample size (<100 to <10): may not be an obstacle if genetic effect is large enough
- May not be known whether phenotype is just concomitant with/caused by drug treatment
Pharmacogenomics

- DNA diagnostic
- Targeted therapies
- Help in approval of new indications
- More accurate labeling
- Safer and more efficient drugs to market
- Identification of those
  - Likely to recur - maintenance therapy
  - Pre-disposed to disease - prophylactic therapy
- Pharmacovigilance-Collection of samples of subjects with AE
- Extend understanding of disease

<table>
<thead>
<tr>
<th>Discovery</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Phase IV Post-marketing</th>
</tr>
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</table>
Application of PGx in Post-Marketed Products

- **Research**: PGx sampling from patients outside clinical trials, e.g. with ADRs
- **Early Development**: PGx markers to predict clinical outcomes
- **Late Development**: PGx research as part of safety surveillance
- **Regulatory Assessment**: PGx markers of disease prevention
- **Commercialization**: Diagnostic development
Clinical Pharmacogenomics Study

Protocol Development
Informed Consent
Sample Collection
Genetic, Genomic Tools
Data Analysis Interpretation
Reporting

High Quality Laboratory Standards and Processes!!!
Issues/ practicalities

- Phase III trials may include >3000 patients, >50 countries, >100s centres – issues with:
  - Transport
  - Sample processing
  - Genotyping and reporting back of data

- All within defined timelines, GLP-standard

- Simultaneously – develop diagnostic ready for launch

- Development of PGx marker for PK, efficacy, safety or toxicity is a continuum

- PGx research needs to start early in discovery and continues through all phases of clinical development
Pharmacogenomics (PGx)

PGx CONCEPT: Relate genotype to phenotype
**Genotype:** ADME, Transporter, Target, Disease genes
**Phenotype:** Clinical endpoint (PK, PD, safety, efficacy)

- Genotype to Phenotype **association**
  - Provides support for a role for a gene in the clinically-relevant metabolism or mode of action of the drug

- Genotype to Phenotype **lack of association**
  - May help to discount an appreciable role for a gene in the clinically-relevant metabolism or mode of action of the drug

**Genes are selected according to:**

- Potential role in drug metabolism or mode of action or disease
- Goals of the clinical trial
- Known functional polymorphisms
- Acceptable frequency in the population
Genotyping in Clinical Trials

Which Genes?

Which SNPs?

Perform the assays

Analyze-SAP is needed
Interpret & Report the data
SNP Selection

**Challenge**

- What is the minimal number of SNPs that will capture the functional enzymatic status in most individuals?
SNP Selection

Strategy to Overcome Small Sample Size

SNPs are selected according to:

- Functional impact (in vitro, in vivo)
- Allele frequency in relevant population

Develop & Perform the assays
# CYP2D6 Alleles With Functional Consequences

<table>
<thead>
<tr>
<th>INACTIVE</th>
<th>REDUCED</th>
<th>INCREASED</th>
</tr>
</thead>
<tbody>
<tr>
<td>*3 Frameshift</td>
<td>*9 aa deletions</td>
<td>*1XN copies</td>
</tr>
<tr>
<td>*4 Splicing</td>
<td>*10 Non-synonymous</td>
<td>*2XN copies</td>
</tr>
<tr>
<td>*4X2 Duplication of defective</td>
<td>*17 Non-synonymous</td>
<td>*35X2 copies</td>
</tr>
<tr>
<td>*5 Gene deletion</td>
<td>*36 non-synonymous</td>
<td></td>
</tr>
<tr>
<td>*6 Frameshift</td>
<td>*41 promotor</td>
<td></td>
</tr>
<tr>
<td>*7 Non-synonymous</td>
<td>*29 Non-synonymous</td>
<td></td>
</tr>
<tr>
<td>*8 Stop codon</td>
<td></td>
<td></td>
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<tr>
<td>*11 Splicing</td>
<td></td>
<td></td>
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<tr>
<td>*12 Non-synonymous</td>
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<tr>
<td>*13 Frameshift (gene hybrid)</td>
<td></td>
<td></td>
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<tr>
<td>*14 Non-synonymous</td>
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<tr>
<td>*15 Frameshift</td>
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</tr>
<tr>
<td>*16 Frameshift (gene hybrid)</td>
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<td>*18 3X aa insert</td>
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<tr>
<td>*19 Frameshift</td>
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<td>*20 Frameshift</td>
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<tr>
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<td>*38 Frameshift</td>
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<tr>
<td>*42 Frameshift</td>
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### CYP2D6 Alleles With Functional Consequences

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</tr>
<tr>
<td>*5 Gene deletion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*6 Frameshift</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*15 Frameshift</td>
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</tr>
</tbody>
</table>

Will capture most Poor Metabolizers in Caucasian populations

Sachse et al. 1997
### Example: CYP2D6

#### Ethnic Differences in Frequencies of Alleles with Varying Function

<table>
<thead>
<tr>
<th>Allele</th>
<th>Normal Activity</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*1</td>
<td>*2</td>
<td>Tot</td>
<td></td>
</tr>
<tr>
<td>Caucasians</td>
<td>33</td>
<td>33</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Africans</td>
<td>29</td>
<td>29</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Orientals</td>
<td>23</td>
<td>23</td>
<td>43</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Allele</th>
<th>Reduced Activity</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>*9</td>
<td>*10</td>
<td>*17</td>
<td>Tot</td>
</tr>
<tr>
<td>Caucasians</td>
<td>&lt;3</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>4</td>
</tr>
<tr>
<td>Africans</td>
<td>&lt;3</td>
<td>4</td>
<td>21</td>
<td>28</td>
</tr>
<tr>
<td>Orientals</td>
<td>0</td>
<td>50</td>
<td>1</td>
<td>51</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Allele</th>
<th>Super-high Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gene Duplication</td>
</tr>
<tr>
<td></td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Gene Duplication: 5 (14% in Ethiopians)
Decision Tree for Pharmacogenomics

**Entry Points**
- PHASE 1
- PHASE 2
- PHASE 3
- PHASE 4

**Test**
- P450 & ADMET Genes
- P450 & ADMET + Drug Target Genes
- P450 & ADMET + Drug Target/Disease Genes

**Deliverable**
- Dose finding
- Explain outliers
- Prioritization drug-drug interaction studies

- Fast track target validation and POP
- Explain outliers
- Rescue failed compounds

- Confirm mode of action
- Efficacy and safety in subpopulations

- New indications
- Comparator studies
- Rare events
Significant Progress in testing technologies
- DNA most mature technology vs expression, proteomics, metabolomics. Multitude of reagents (DNA chips) and pharmacogenomics services available for genotyping as home brew tests from diagnostic labs
- Next Generation Sequencing not only limited to whole genome sequencing, target sequencing and discovery of novel polymorphisms/mutations. They also can be used for novel structure variation discovery (CNV, epigenetics), digital gene expression analysis, discovery of novel protein coding transcripts and non-coding miRNAs, and metagenomics.

Complexity of science
- Challenges of identifying valid associations and of inherent biological complexity
- Overload of information and computational challenges: storage and analytical capabilities/pathways/multimarker and analyses across several domains needed
- Debate on value of GWAS vs NGS for complex diseases (common vs rare variants)
- Progress seen in Oncology, Metabolic Disorders and in SAEs, but less in CNS

Slow integration of PGx testing in routine clinical practice
- Evidence needs to be established for clinical utility compared to usual care

Education of health care professionals, payors and patients needed

Opportunities to speed progress
- Need additional regulatory guidelines and incentives
- Use of retrospective data for biomarker qualification
- Need for Collaborations (e.g. SAEC)
- Reimbursement of tests and IP
- Regulations on genomics testing: CLIA versus FDA approved
Applying the Results in Clinical Practice
The best consumer is an informed consumer!!!

Ask your doctor if it’s the right drug at the right dose for you!!!
"Here's my sequence..."

The New Yorker
Genetics Quiz
How Many Pairs of Chromosomes do Human Cells Contain?

- 22
- 23
- 46
- 73
- 100
How Many Pairs of Chromosomes do Human Cells Contain?

- 22
- 23
- 46
- 73
- 100
What is the size of the Human Genome?

- 3 million nucleotides
- 10 million nucleotides
- 1 billion nucleotides
- 3 billion nucleotides
- 30 billion nucleotides
What is the size of the Human Genome?

- 3 million nucleotides
- 10 million nucleotides
- 1 billion nucleotides
- 3 billion nucleotides
- 30 billion nucleotides
How Many Genes in the Human Genome?

- 10,000
- 30,000
- 70,000
- 100,000
- 500,000
- 1,000,000
How Many Genes in the Human Genome?

- 10,000
- 30,000
- 70,000
- 100,000
- 500,000
- 1,000,000
How Many SNPs in the Public Domain?

- 1 Million
- 3 Million
- 17 Million
- 20 Million
- 100 Million
How Many SNPs in the Public Domain?

- 1 Million
- 3 Million
- 17 Million
- 20 Million
- 100 Million
Please rank by size of genome?

- Onion
- Mouse
- Human
- Fruitfly
- Yeast
The human genome is not particularly large

- Onion 15000 Mb 8 chromosomes
- Mouse 3000 Mb 20 chromosomes
- Human 3000 Mb 23 chromosomes
- Fruitfly 170 Mb 4 chromosomes
- Yeast 14 Mb 16 chromosomes

Note: haploid genome sizes and chromosome numbers
Thank you
Biotransformation (Metabolism) of Drugs Is Exerted by Enzymes Mainly Expressed in the Liver:

- **Phase I metabolism**
  - Oxidation
  - Reduction
  - Hydrolysis

- **Phase II metabolism**
  - Conjugation reactions: e.g., glucuronic acid, sulfuric acid, acetic acid, amino acids, glutathione

Expression/activity of these enzymes may vary from individual to individual.....

Genetic mutations are responsible for altered expression/activity and are autosomal inherited traits.
Pharmacogenomics

If it is known that the drug is converted by a single polymorphically expressed enzyme (e.g. CYP2D6) than prior to administration of the drug to subjects they are screened for based on their genotype. Hence, trial population is stratified according to genotype.

In vitro and animal experiments indicate which enzymes may be involved in the bio-transformation of a drug in man.

In clinical trials with this drug, genetic mutations of these enzymes are determined (DNA diagnostics) and a phenotype is predicted.

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This predicted phenotype is correlated with either pharmacokinetic or pharmacodynamic determined parameters. Predicted phenotype may also be correlated with occurring adverse events.
Areas Where More Progress Is Needed

- Initiate PGx research early in Drug Discovery and integrate with Drug Development program

- Drug Mode of Action

- Pharmacogenomics and safety
  - High priority to identify patients at highest risk
  - Genes identified fed back to improve pre-clinical screens

- Data on prospective Pharmacogenetics
  - Initiate phase 3 randomized controlled trials stratified by genetic subtype

- Therapeutic & diagnostic linkage
  - Need additional models of success- such as Herceptin
Summary – Pharmacogenetics

- Collecting of DNA samples from clinical trials for retrospective genetic analysis
- Prospective analysis to guide recruitment into clinical trials
- Archiving to address unexpected emerging issues
- Genotyping of thousands of DNA samples

Complexity of Analysis

- The constraints for pharmacogenetics research are of the same type as for all clinical trials - but with an extra level of sensitivity (ethical issues) - need for additional documents