The Critical Path Initiative Meets Genomics

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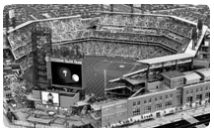
Philadelphia Phillies Are In 1st Place

If Citizens Bank Park were filled to capacity with fans who were going on warfarin for atrial fibrillation, 3200 of them would have a major bleeding event within 1 year.
250 would die!



Can this be prevented? Which fan is at risk?

With Choices, Comes Decisions

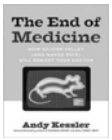
Physicians have basically two decisions to make when treating patients:

1. **Selecting the right drug**
2. **Choosing the right dose**

The Problem: Interpreting Inter-Individual Variability in Outcomes

"If it were not for the great *variability* among individuals, medicine might have well been a science and not an art"

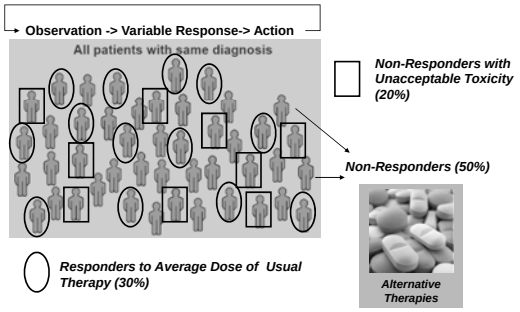
Sir William Osler (1849 – 1919)
The Father of Modern Medicine



"One important characteristic of biology is its diversity, its *variation*. It's why personalized medicine is so important"

Dr. Andy Kessler
NY Times Best Selling Author

The Challenge of Individualizing Drug Therapy: Trial and Error Medicine



Rational Prescibing

Rudolph Buchheim (1820-1879) Founder of Translational Science

"Fortunately a surgeon who uses the wrong side of the scalpel cuts his or her own fingers and not the patients……..

…….if the same applied to drugs they would have been investigated very carefully a long time ago"

Beitrage zur Arzneimittellehre, 1849

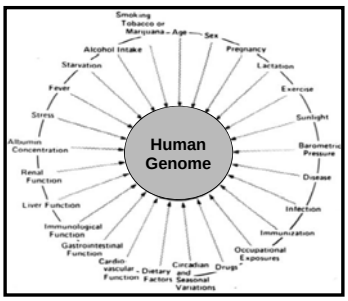
Clinical Problem: Can We Do Better?

- Co-existing diseases
- Concomitant therapies
- Lifestyle issues
- Financial constraints

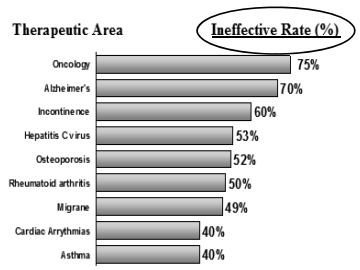
With choices, comes decisions

With decisions, comes commitment

Interpreting Variability Includes a Wide Spectrum of Sources

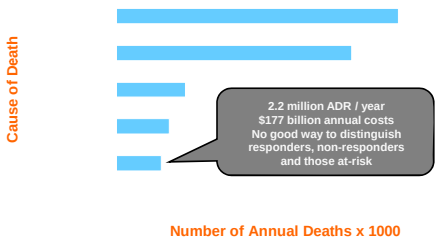


Fact: We Don't Know Enough About How Drugs Work



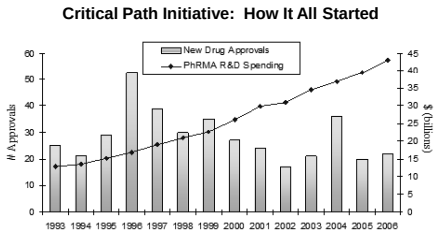
Source: Spear, Trends in Medicine 2001: 7(5), and Aspinall, ACMG Presentation March 13, 2008

Fact: We Don't Know Enough About The Risks of Drug Toxicity



Source: National Vital Statistics Reports 2005: 53 (17) – US data from 2001

Number of New Drugs Is Not Keeping Pace With Spending: High Attrition Rate



Average Response in Clinical Trials vs. Individual or Individual Group Outcomes

"…..if a clinical trial doesn't work, they just throw the drug away, when in fact the averages of the trial data may hide stuff that did work…..*there's something that makes patients different*"

"A good drug wrongfully convicted means the loss of benefits goes on forever"

Source: Andy Grove, Former CEO of Intel, Newsweek, November 4, 2007

Will The Human Genome and Genomics Change Your Life?

Government Thinks It Can and Should Lead the Way: Initiatives Including Genomics

Personalized Health Care Initiative of HHS Secretary Michael Leavitt (2007)

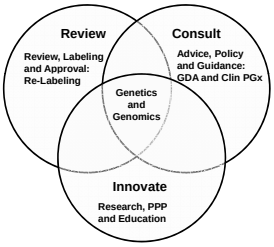
http://www.hhs.gov/myhealthcare/

Critical Path Initiative of FDA Acting Director of CDER Janet Woodcock (2005)

http://www.hhs.gov/myhealthcare/

Role of FDA in Supporting Genomics

Protect and Promote Public Health



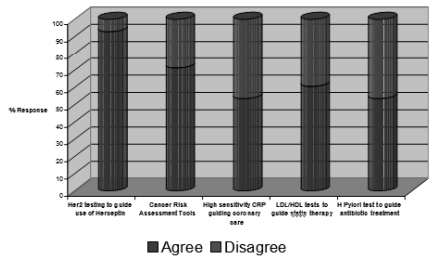
Definitions and Concepts: Personalized Medicine

Personalized medicine (PM) is the science of individualizing medical intervention based on certain diagnostic tests

1. Total patient populations are "stratified" into subgroups based on similar test results
2. Subgroups of patients follow different treatment strategies with "probabilities" for outcomes
3. Major goal is make clinical outcomes in individuals and individual subgroups more predictable and optimal

Personalized Medicine Doesn't Have to Be Genomics

Are These Cases of Personalized Medicine?



Other Definitions and Concepts

Pharmacogenomics (PGx): science of using inherited variations in genes that influence drug exposure (PK) and drug action (PD)

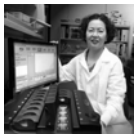
Genomic biomarkers: measurable DNA or RNA characteristics in human, tumor or virus samples that are indicators of:

-- normal biologic processes
-- pathogenic processes
-- response to drugs

Source: Adapted from ICH E15 Guideline on Definitions and Coding, January 2008

Genomic Biomarker Are the Basis for Diagnostic Tests

Diagnostic tests are the linchpin of *personalized medicine*



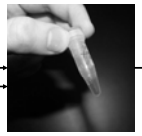
Collection of the DNA Biospecimen Is Key to Understanding Variability

BIOLOGY OF DISEASE

Changes in biology caused by gene mutations and environment

GENETICS OF PATIENT

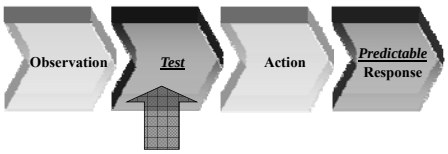
Changes in systemic drug exposure and response of drug target



INDIVIDUALIZED TREATMENT PLAN

New Paradigm of Medicine: Personalized Medicine

Linking Diagnostic Tests to Drug Choice and Dose Selection



Breaking The Cycle of Trial and Error Medicine

DNA-Based Biomarkers Are Ready: PhRMA Industry Survey

- DNA collection
  - 80-90% of companies in phase I studies; PK, DDI etc as a study requirement
  - 40-50% of companies in phase II – phase III studies; POC, D/R and pivotal RCT as an optional activity
- 70% of companies use ADME genotype as inclusion or exclusion analysis
- DNA analysis
  - Only 15% of companies have performed genotyping
    - Preclinical data indicates PGx will influence PK
    - An adverse event suggests PGX is at fault
    - Failure of efficacy that is unexpected
    - Intention to make a label claim

Source: Dr. Lisa Shipley, CPAC, March 18, 2008. Data collected from 2003-2005.

How Will PGx and Diagnostic Tests Enable Personalized Medicine?

Traditional Medicine	Example	Personalized Medicine	Example
Diagnosis – disease as collection of symptoms	High blood pressure has many causes	Diagnosis – disease by underlying biology of physiology	Breast cancer where tumors overexpress HER2
Treatment guidelines treat symptoms as single disease	Non-Hodgkin's lymphoma defines many cancers of immune system	Customized guidelines based on disease stratification	Subclasses of B-Cells and T-Cells -- Use of rituximab if CD-20 antigen positive
One size fits all dosing	5 mg/day of warfarin for all patients	Patient stratification and genotype-guided dosing	Genotypes defined by 2C9 and VKORC1 need 0.5 to 6 mg/day
Lack of physician and patient awareness	Little formal education and access to genetic testing	New, educated generation of health care providers and patients	Continuing education by AMA, consumer genomics such as 23andMe, SNPedia

Drugs Where Genome-Based Diagnostic Tests Have Been Recommneded

EFFICACY

Drug	Test
Herceptin	HER2
Gleevec	BCR-ABL
Rituxan	CD20
Donepezil	ApoE4
Erbitux	EGFR
Selzentry	Tropism

SAFETY

Drug	Test
6-MP	TPMT
Camptosar	UGT1A1
Warfarin	2C9, VKORC1
Ziagen	HLA-B5701
CBZ	HLA-B1502
Tamoxifen	2D6

Success Example # 1

Efficacy – Responsive Patient Subset

Example of HIV-AIDS: Provides an Alluring Target for PGx and PM – Why?

- HIV-AIDS has many disease subtypes
- Rapid disease progression and high mortality
- Drugs that target cellular disease pathways
- Many viral biomarkers and gene mutations
- Relatively low efficacy rate over time
- Potentially frequent and serious adverse events
- Patient stratification using resistance testing
- Physician familiarity with diagnostic tests

Examples: PhenoSense GT assay for complete picture of viral resistance and susceptibility to guide drug selection; HIV viral load (viral RNA) in blood to monitor response

Selzentry^{R} (Maraviroc): Drug-Test Combination Approved in August 2007

- Selzentry^{R} antagonizes CCR5 co-receptor and not effective in dual or mixed CXCR4 HIV-1
- *Trofile*^{R} test stratifies HIV strains based on which receptor virus uses to enter CD4-positive T cells
- RCT could not have been conducted in patients without first identifying CCR5-tropic patients
- *Selzentry*^{R} reduces viral load and increases CD4-positive T cell counts by blocking CCR5-tropic virus
- Approval based on 24 week data from phase IIB-III clinical trial in treatment-experienced HIV patients

Selzentry^{R} (Maraviroc) Label and Success Factors

- *Selzentry*^{R} label requires use of tropism assay before prescribing to identify likely responders
- Tropism assay also identifies non-responders and lack of response was confirmed
- Generally well-tolerated although label has warning of hepatotoxicity

Guiding Principles

- **Knowledge of disease pathology and drug target**
- **Ability to identify disease subsets to increase efficacy signal**
- **Validation of test clinical utility during pivotal drug efficacy trials**

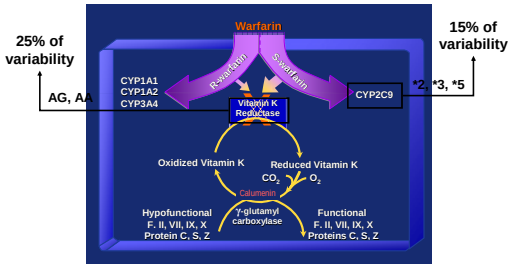
Success Example # 2

Dosing – Optimizing Benefit/Risk Ratio

Warfarin As An Anticoagulant: Taking the Guesswork Out of Dosing

- Risks of warfarin over-anticoagulation not in doubt: one of top 3 drugs for ER visits and AE reports
- Bleeding is serious, sometimes fatal, and results in poor long-term compliance
- INR used as biomarkers to monitor rate and extent of anticoagulation; target range of 2-3
- Greatest risk occurs in initial dosing phase of 4-6 weeks until INR and dosing stabilizes
- Problem is NTI and large inter-invidiual variability in maintenance doses due to PK and PD differences

Warfarin Genetic Variants That Influence Dosing – Especially Induction Doses



Source: Gage and Eby, Pharmacogenomics J, 2004

Genetic (55%) and Clinical Factors (25%) Determine Induction Dose of Warfarin

Entry	Variable	Effect on Dose	R^2	*P* value
1	VKOR-1639/3673	–28%	25%	<0.0001
2	BSA, per 0.25 m^2	11%	34%	<0.0001
3	CYP2C9*3	–33%	40%	<0.0001
4	Age, per decade	–7%	45%	<0.0001
5	CYP2C9*2	–19%	50%	<0.0001
6	Target INR	11%	51%	<0.0001
7	Amiodarone	–22%	52%	<0.0001
8	Smokes	10%	52%	0.0022
9	AA race	–9%	53%	0.0023
10	Prior DVT or PE	7%	53%	0.0132
	INR After 3rd Dose		80%	

Source: Brian Gage Presentation at American College of Medical Genomics, March 2008

New Warfarin Label Containing Recommendation for Genetic Testing

Source: Medco Health Solutions, 2007

Adoption of Warfarin Gene Tests: It's Not Only About the Science

- Scientific issues
  - Debate over evidence; surrogate (INR) vs clinical endpoints (bleeding) and absence of RCT
  - No specific genetically-based dosing recommendation in revised warfarin label
  - Lack of agreement on 2C9, VKORC1 and other genes that addresses needs of all ethnic or racial groups
- Other issues
  - Perception that INR-stabilized patients don't need test
  - Assumption that current INR monitoring system works
  - Concern that PGx tests will not eliminate need for INR
  - Cost of gene tests ($500) not paid by insurance
  - Surveys show < 10% of physicians have heard of tests

Factors Influence the Timeline for Personalized Medicine

Opportunity
Fear ⇒ And ⇒ Acceptance
Value

- Reduce market share
- Added costs with no return
- Inhibit practice of medicine
- Denied insurance or jobs
- Regulatory framework
- Poor reimbursement of tests
- Healthcare provider education
- Clear and favorable regulation
- Standards for clinical utility
- Appropriate reimbursement
- Compelling business model
- Value and impact on outcomes

What Will Accelerate the Personalized Medicine Timeline?

1. **Focus on real problems in drug development and clinical practice; find effective solutions**
2. **Translation of GWAS and SNP analysis to clinical utility; understand disease biology**
3. **Weight and strength of evidence that documents usefulness of PGx; clinical utility**
4. **Cost structure for reimbursement of genetic testing; support sustainable business model**
5. **Changes in medical infrastructure to accelerate adoption; physician education, electronic records**

Philadelphia Phillies Are In 1st Place

If Citizens Bank Park were filled to capacity with fans who were going on warfarin for atrial fibrillation, 320 of them would have a major bleeding event within 1 year.
25 would die!

Can this be prevented? Which fan is at risk?

Take Home Message

PM and PGx are not “hype” but are here now

Simply the next step in applying science to understanding disease biology and drug response

Driving forces are:

- technology not available 10 years ago
- advances in bioinformatics and EPR
- decreased productivity in drug development,
- consumer interest in genomics and health care
- societal expectations for safe and effective drugs