Genomic Medicine: Regulatory Science Perspective

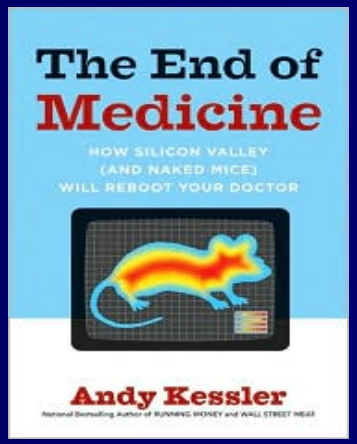
House of Lords Inquiry on Genomic Medicine Visit
Lawton Chiles International House
June 6, 2008

Lawrence J. Lesko, Ph.D., FCP
Director, Office of Clinical Pharmacology
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, Maryland, USA

Century-Old Challenge: Identifying Causes of Variability in Medicine

"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 (2005)

What I Will Address in My Presentation

- Why genomic applications are important to to new drug development
- How genomic knowledge can be used to improve previously approved drugs
- What are the challenges and solutions to further enabling genomics

Conceptual Foundation for Policies in Genomic Medicine and Pharmacogenomics

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

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

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

http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf

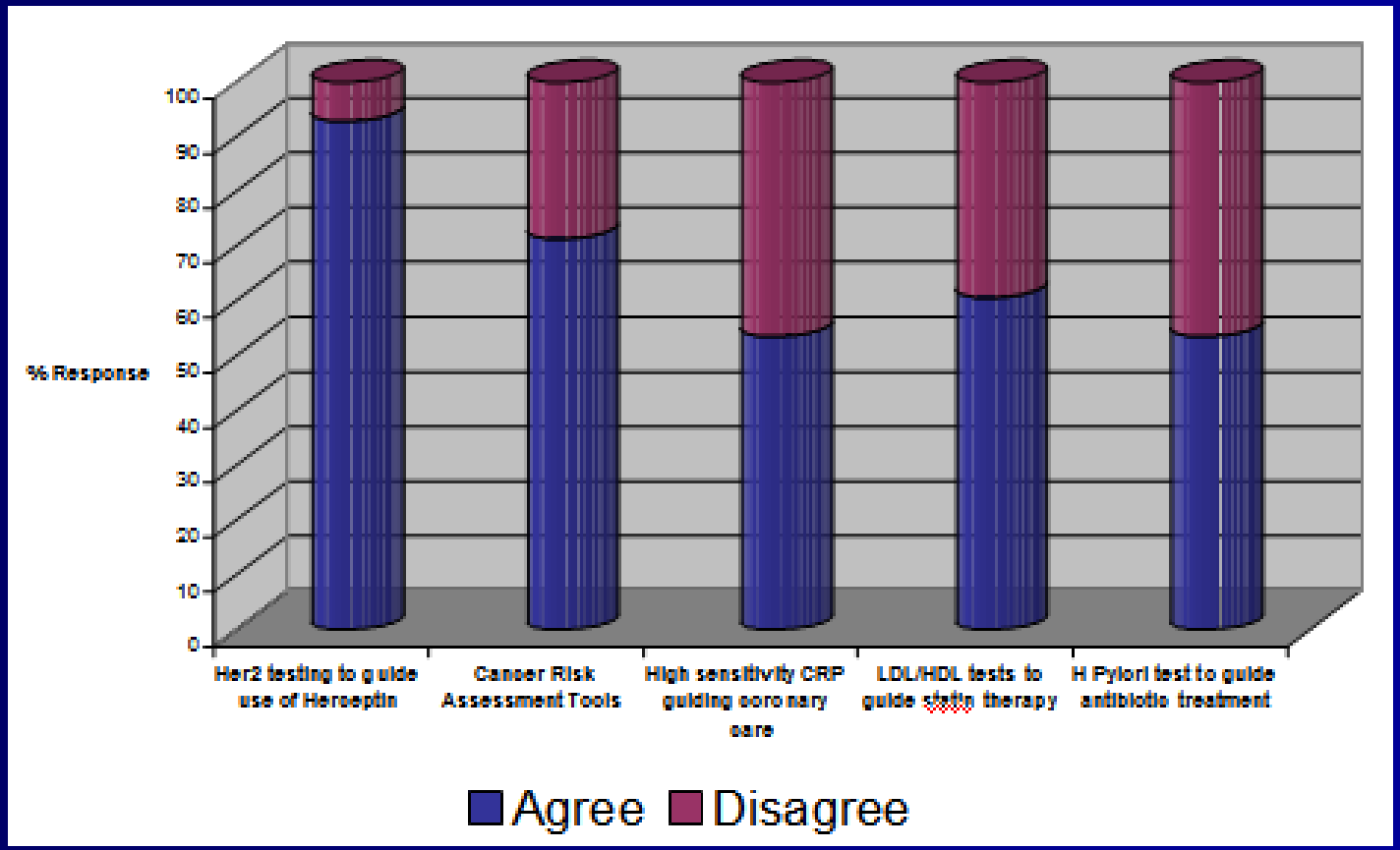
Genomic Medicine Is A Component of Personalized Health Care

Science of using genomic biomarkers as diagnostic tests to target therapies

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

Personalized Health Care Doesn't Have to Be Based Only on Genomic Biomarkers

Are These Cases of Personalized Medicine?

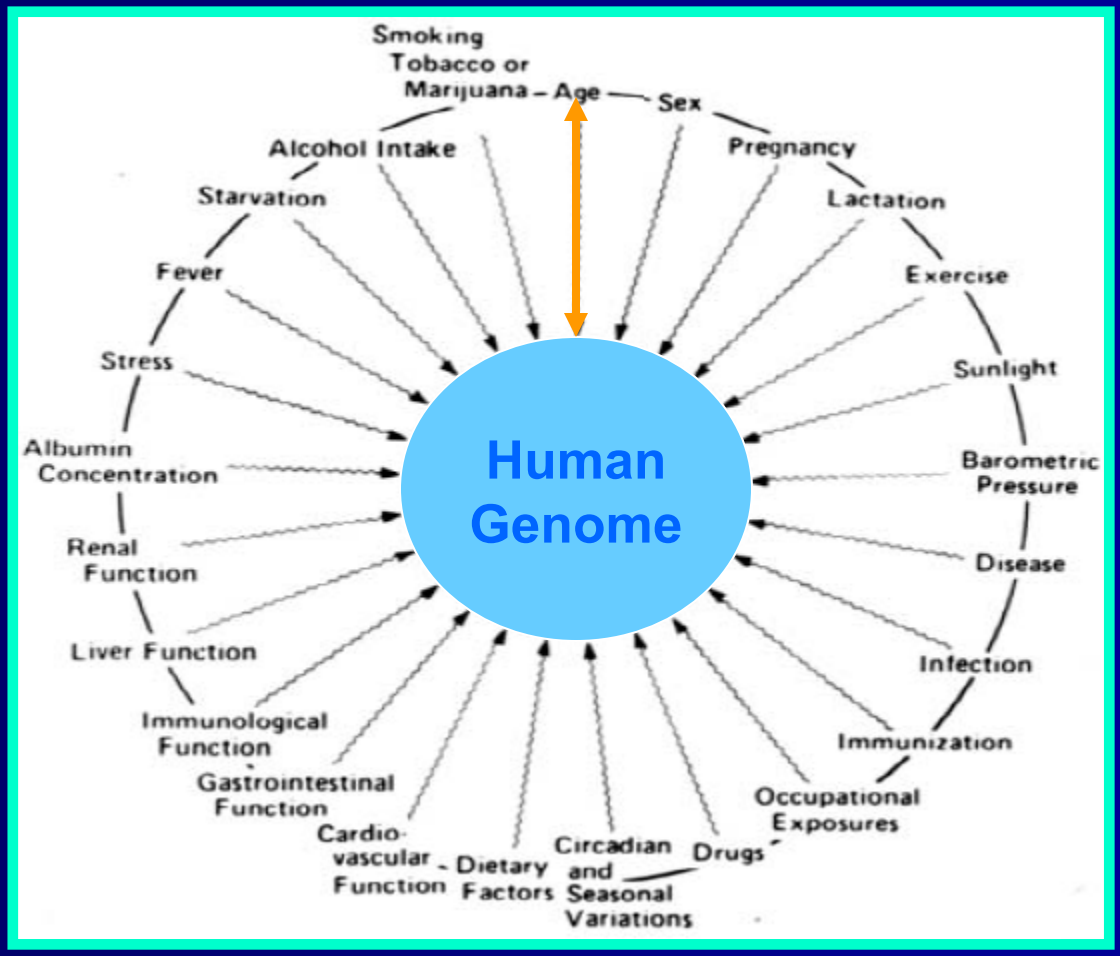


Pharmacogenomics: Component of Genomic Medicine

- Science of using inherited variations in genes that influence drug selection, drug exposure (PK) and/or 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

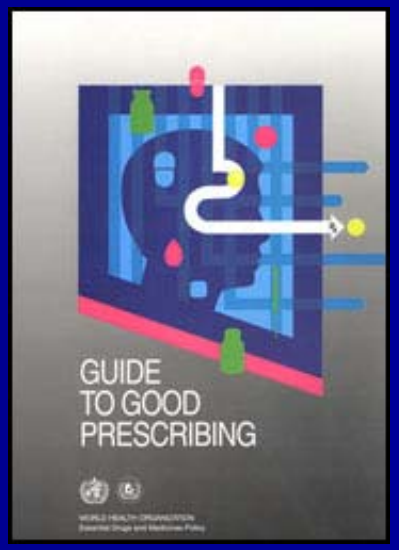
Genomics: Understanding Heterogeneity in Disease Biology and Drug Response



Once the Symptoms and Diagnosis Is Complete

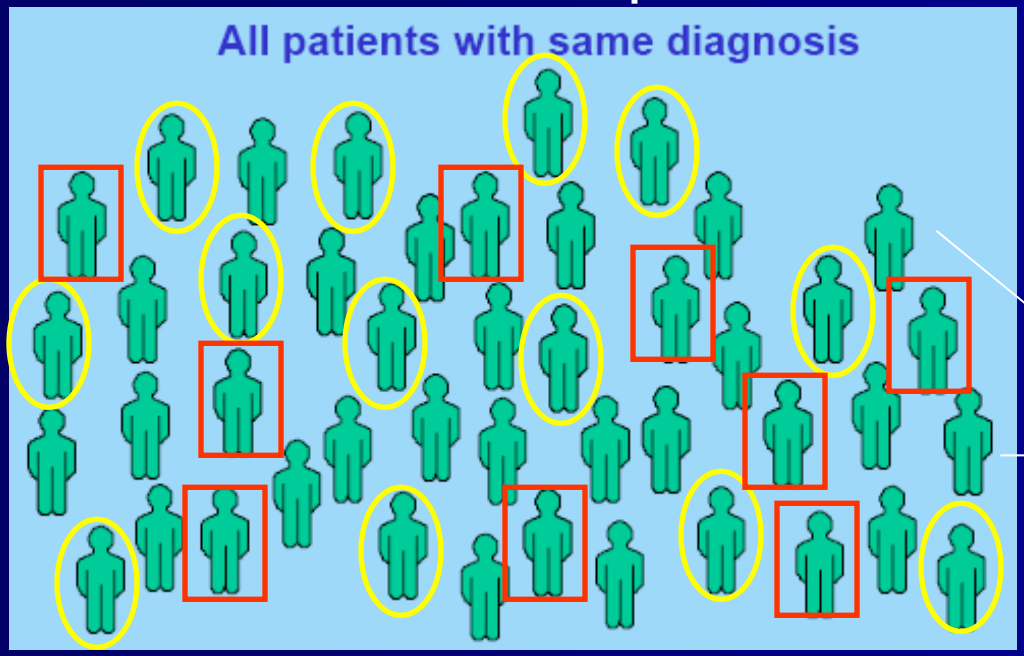
Physicians have basically two decisions to make when treating patients:

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



Consequences of Empirical, Not Mechanistic, Approach to Medicine

Observation -> Variable Response-> Action

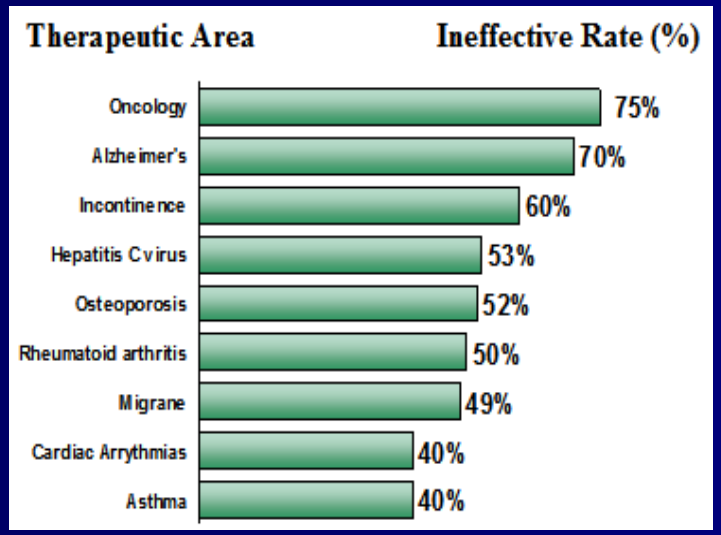


Non-Responders with Unacceptable Toxicity (10%) – Avoid drug

Modest Non-Responders with moderate AE (60%) – adjust dose or consider alternative drug

Good Responders (30%) – Use drug at usual or standard doses; mild AEs likely

Fundamental Paradox: Develop Drugs for Populations But Treat Individual Patients

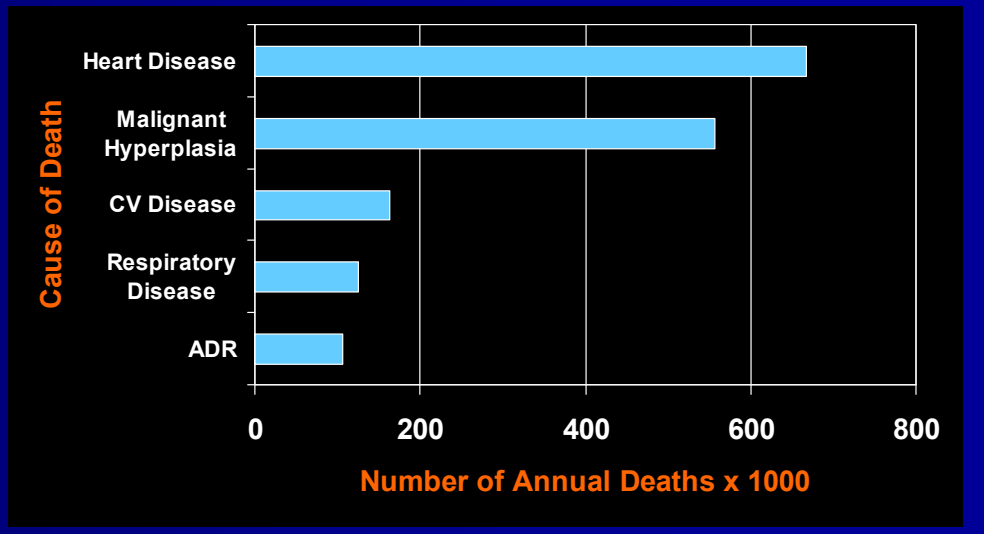


Risk:

Will This Drug Hurt Me?

Benefit:

Will This Drug Work for Me?



Sources: Spear, Trends in Medicine 2001: 7(5), and Aspinall, ACMG Presentation March 13, 2008
National Vital Statistics Reports 2005: 53 (17) – US data from 2001

THE WALL STREET JOURNAL.

As of 9:30 a.m. EST Friday, February 29, 2008

Heightened Media Challenges

FDA to Increase Warnings and Advisories on Side Effects

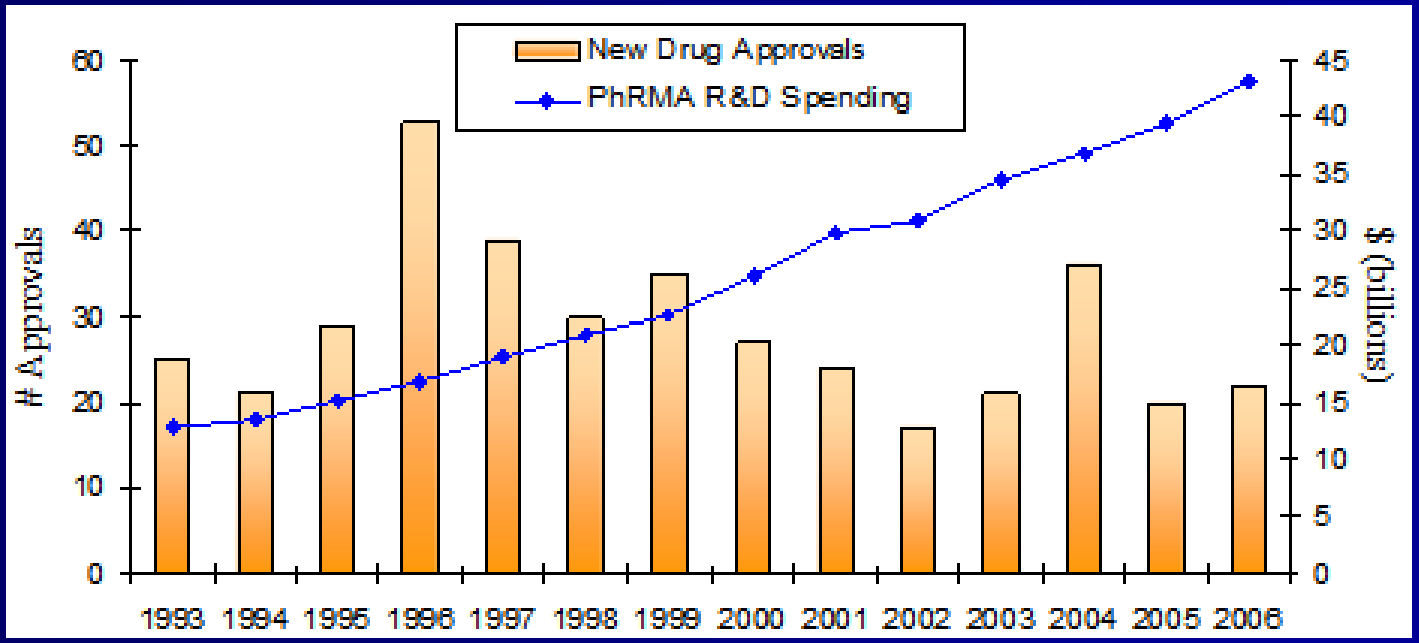
Wall Street Journal, Feb 29, 2008

"Consumers will know we are the case. The Agency's goal is to find out which consumers benefit the most from a particular drug and which ones should avoid it, rather than pulling drugs off the market. This notion is becoming more of a reality with increased use of genetic testing."

Dr. Janet Woodcock, Director
Center for Drug Evaluation and Research
Food and Drug Administration

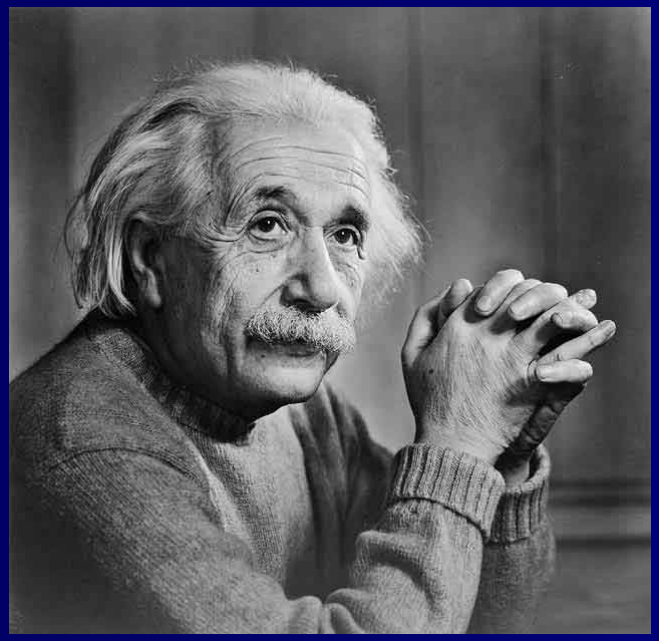
Consequences to Studying Drugs in Total Populations

Improve Productivity of New Drug Development



- Success rates of phase 3 trials is 56%
- Attrition in 1/2 of cases is due to lack of efficacy-
- 1/3 of failure rate is lack of differentiation
- Formula for success = signal/noise x square root of sample size

How Can We Do Better? How Can We Increase Benefit or Decrease Risk?

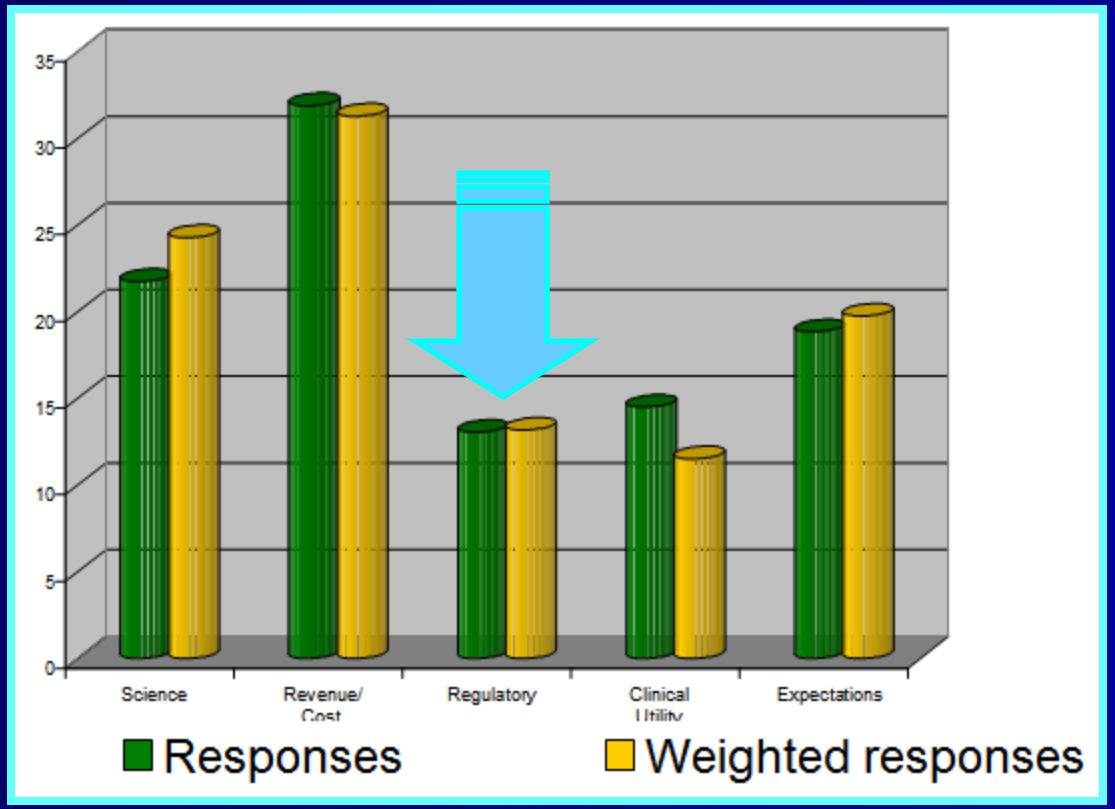


Albert Einstein
(1879 – 1955)

"We can't solve problems by using the same kind of thinking we used when we created them"

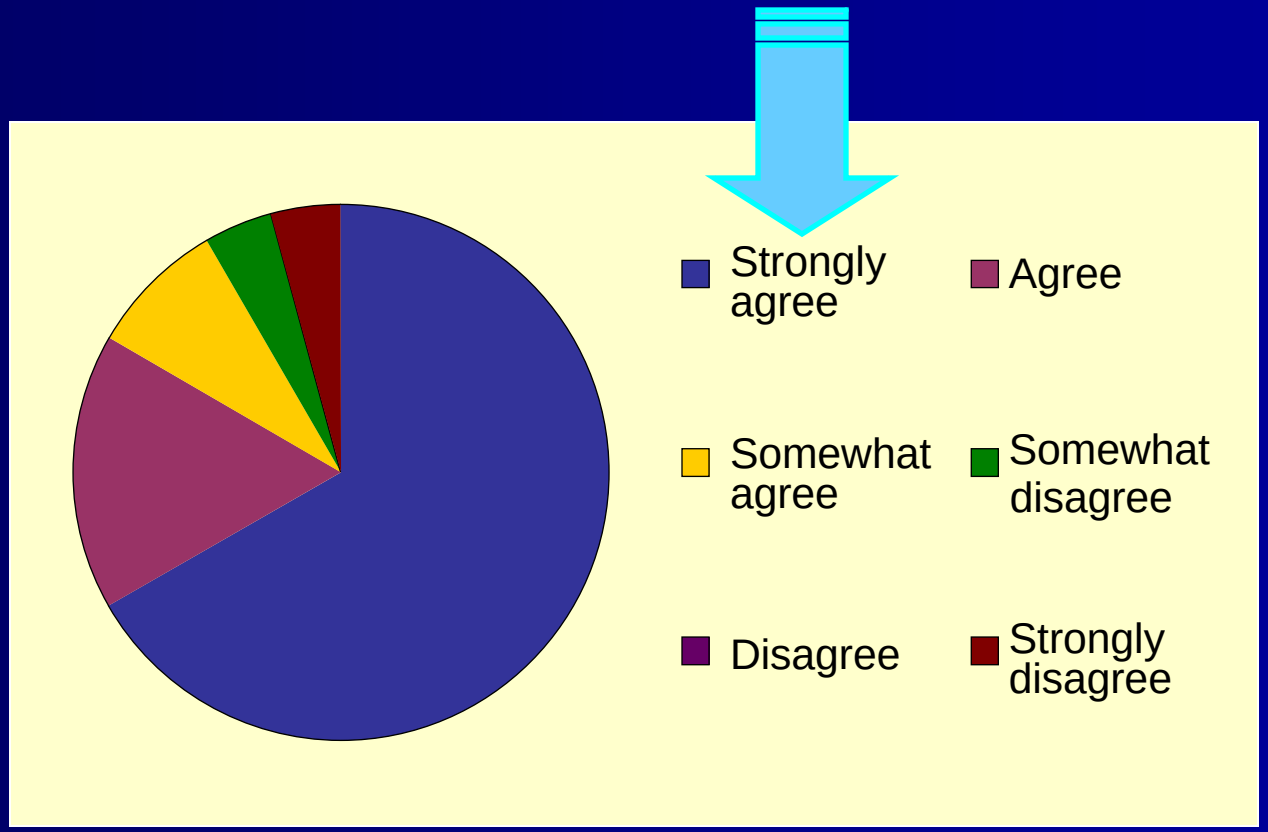
"Insanity is doing the same thing over and over again and expecting different results"

Five Biggest Obstacles to Genomic Medicine and Pharmacogenomics



Adapted from survey conducted by Dr. Mollie Roth, Diaceutics, April 2008

Do You Agree That The Regulatory Framework Affects the Adoption of Genomic Medicine and Pharmacogenomics?



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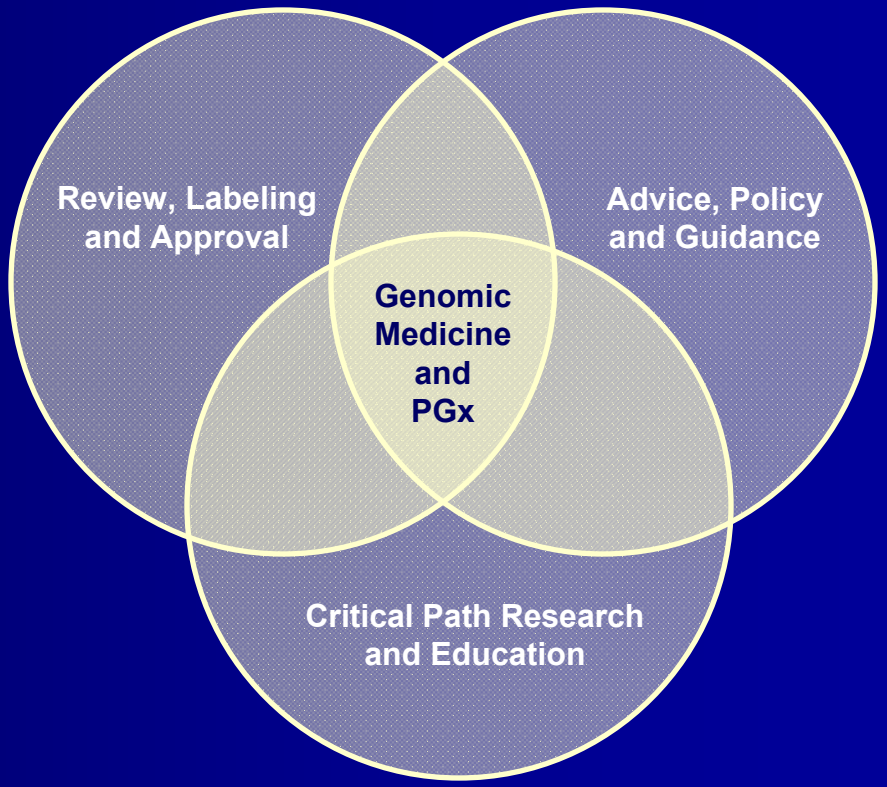
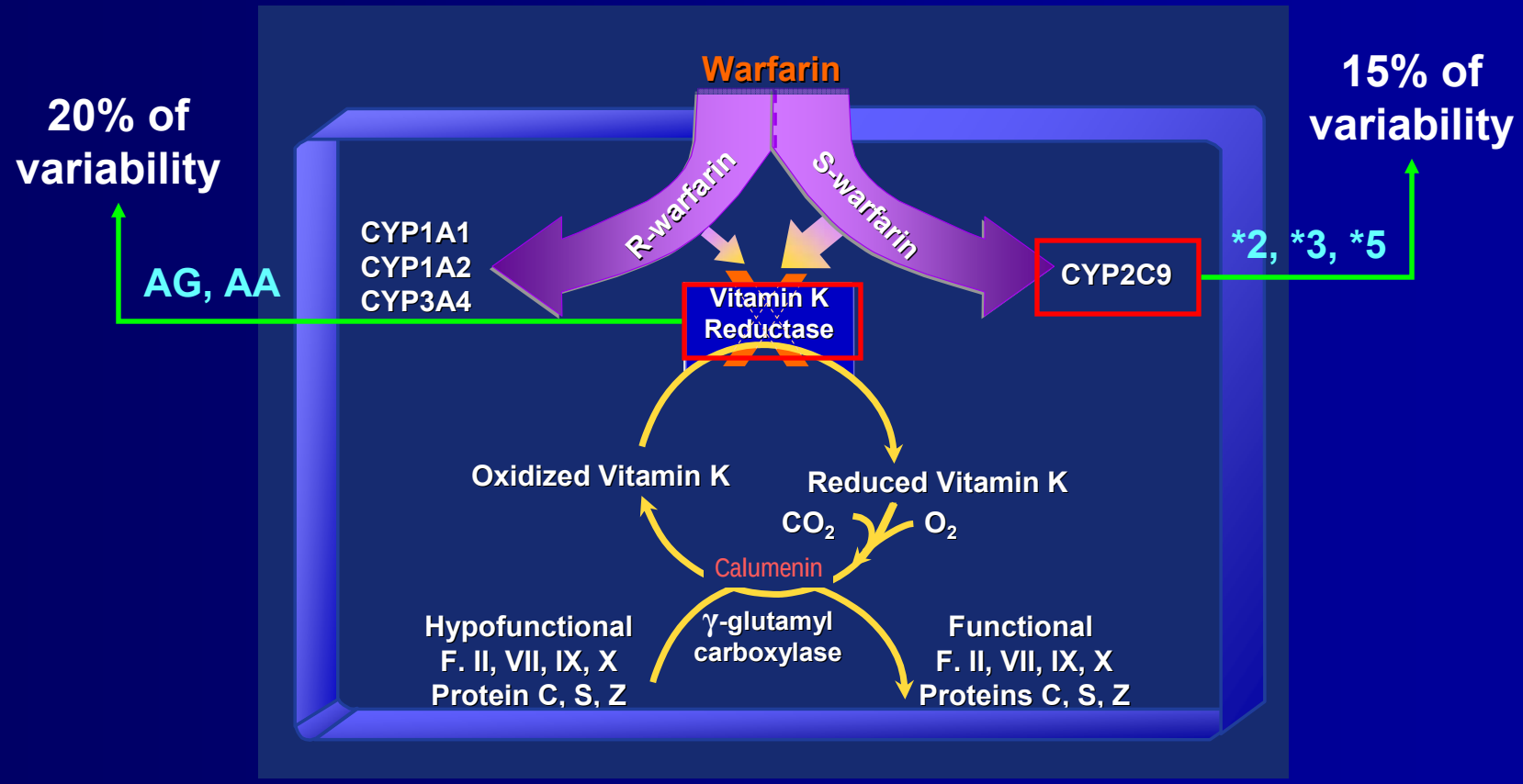
FDA Has Invested Resources in Three Broad Areas

Protect and Promote Public Health



Knowledge of Disease Biology and Drug Pharmacology Is Key Prerequisite



Source: Gage and Eby, Pharmacogenomics J, 2004

Re-Labeling Previously Approved Products With Genomic Medicine

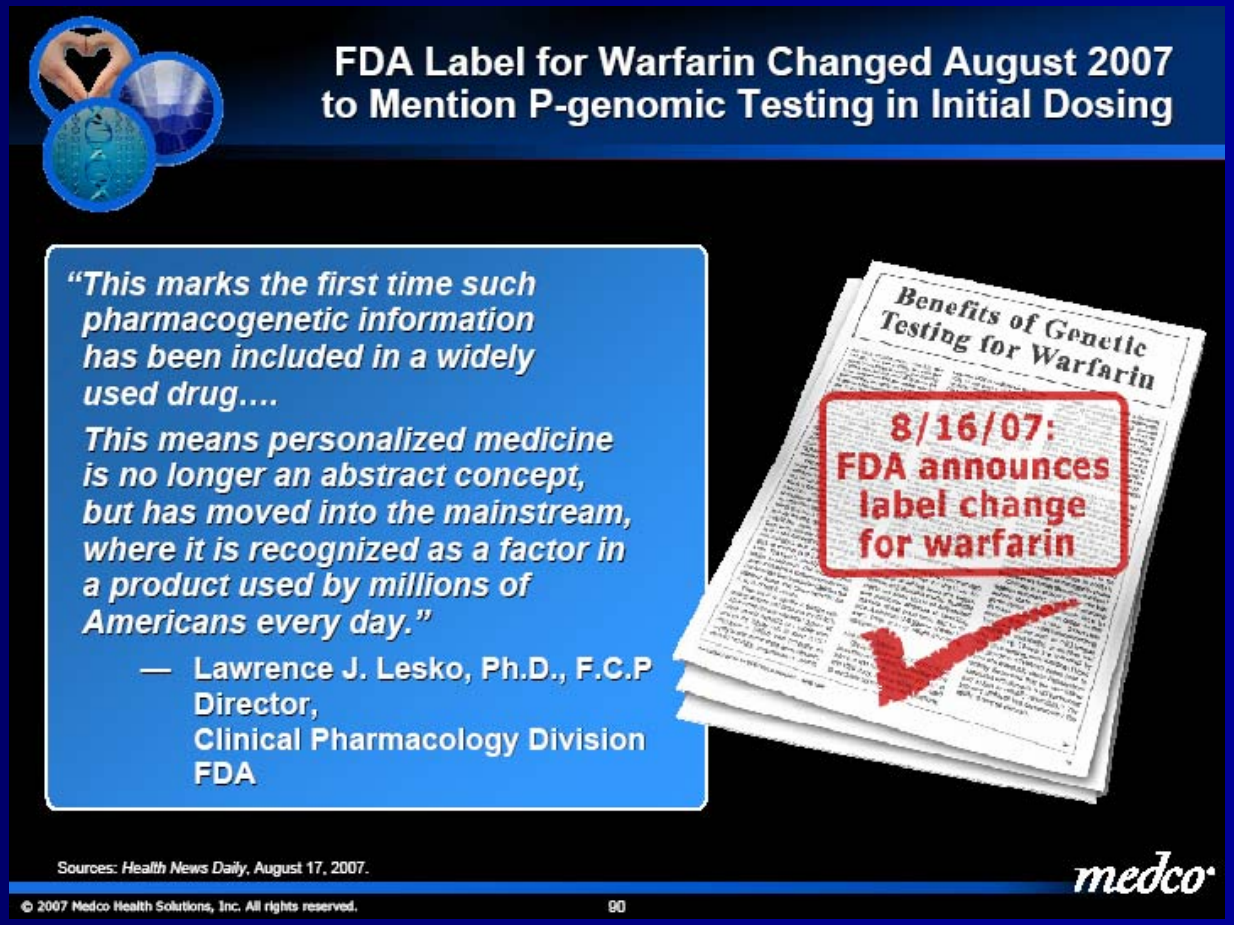
Efficacy: Test Required

Drug	Test
Trastuzumab	HER2 Receptor Positive
Imatinib	C-Kit (CD117) Positive
Rituximab	CD20 Positive B-Cell NHL
Cetuximab	EGFR Expression +
Erlotinib	EGFR Expression +
Maraviroc	CCR5-Tropic HIV-1 Positive

Safety: Test Recommended

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

What Other Genomic Biomarker Can Reduce AEs by 50% and Save $900 Per Person?



Source: Medco Health Solutions, 2007

And Then Lead to Actionable Decisions: Warfarin Dosing Algorithms

http://www.warfarindosing.org

VKORC1	*CYP2C9*			
	*1*1 *1*2	*1*3	*2*2 *2*3	*3*3
BB	5 mg†	4 mg	2.5 mg	1 mg
AB	4 mg†	2.5 mg	2 mg	1 mg
AA	3 mg†	2.5 mg	2 mg	0.5 mg
Approximate time to max. effect for a given dosage regimen	5-7 days	10-14 days	14-21 days	28+ days

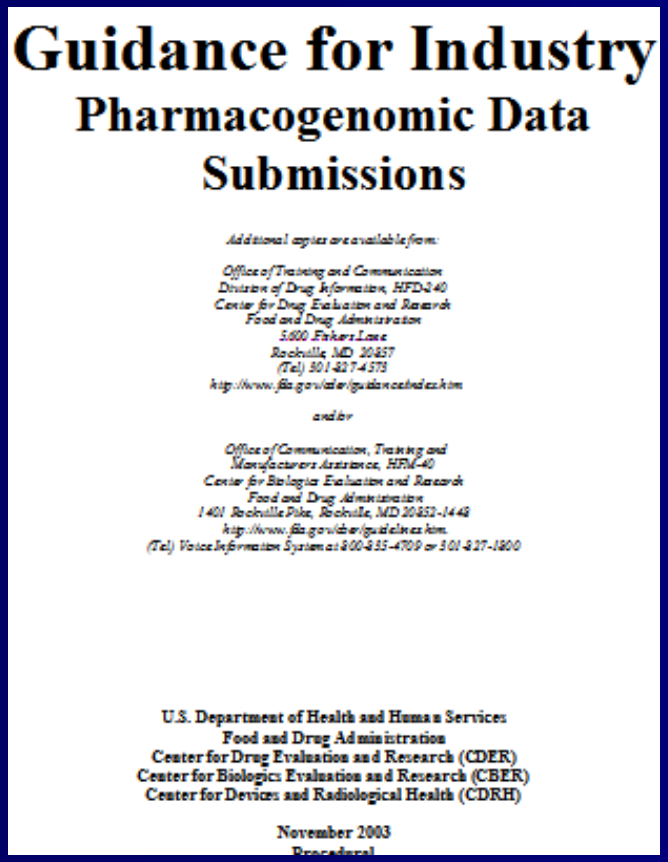
†Dose adjustments for CYP2C9*1*1 or CYP2C9*1*2 genotypes ONLY (yellow column)

Age ≥ 65 years old - subtract 1.0 mg

Height ≤ 155 cm (5'1") - subtract 1.0 mg

Height ≥ 175 cm (5'9") - add 1.0 mg

Challenge: Encouraging the Industry to Explore Genomic Biomarkers



Guidance for Industry

Pharmacogenomic Data Submissions

Additional copies are available from:

Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm

and/or

Office of Communication, Training and Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
http://www.fda.gov/cber/guidelines.htm
(Tel) Voice Information System at 800-835-4709 or 301-827-1800

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

November 2003
Procedural

www.fda.gov/CDER/guidance/5900dft.doc

- Need to build trust that genomics would not be used prematurely
- Need to learn from each other about potential applications
- Need to standardize collection, storage and reporting of data

New VOLUNTARY GENOMIC DATA SUBMISSION pathway as a building block for expansion of genomics into the drug development process

Providing Advice Within the VGDS Program

- Approximately 45-50 voluntary submissions from 12-15 different companies
- Provided shared access to experiments related to
  - Gene mapping and sequencing
  - Genome wide association studies
  - Population genetics
  - New biomarkers
  - Innovative clinical trial designs
  - New “omics”
- Program expanded to collaboration and shared VGDS meetings with EMEA and PDMA

Developing Policies Based on Experience Gained With The VGDS Program

- Biomarker qualification pilot process
  - Provide more rapid “validation” of biomarkers with a defined context for use (“fitness for purpose”)
  - Address uncertainties related to sensitivity and specificity of biomarker “tests”
  - Compare performance (“predictability”) and incremental value to established reference test
- Case study: preclinical nephrotoxicity biomarkers
  - Multiple data sources from industry consortium
  - Review conducted by multidisciplinary review team
  - Sign-off of “validation” package at CDER Director level
  - Joint review with EMEA

www.aapspharmsci.org/view.asp?art=aapsj0901010

Guidance Development Is a Continuous Process to Provide a Regulatory Framework

Guidance for Industry

Clinical Pharmacogenetic Studies:

Study Design, Data Analysis and Recommendations for

Dosing and Labeling

Draft Guidance

This draft document is being distributed for internal purposes only

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
October 29, 2007
Clinical Pharmacology #

TABLE OF CONTENTS

Draft Preliminary Concept Paper

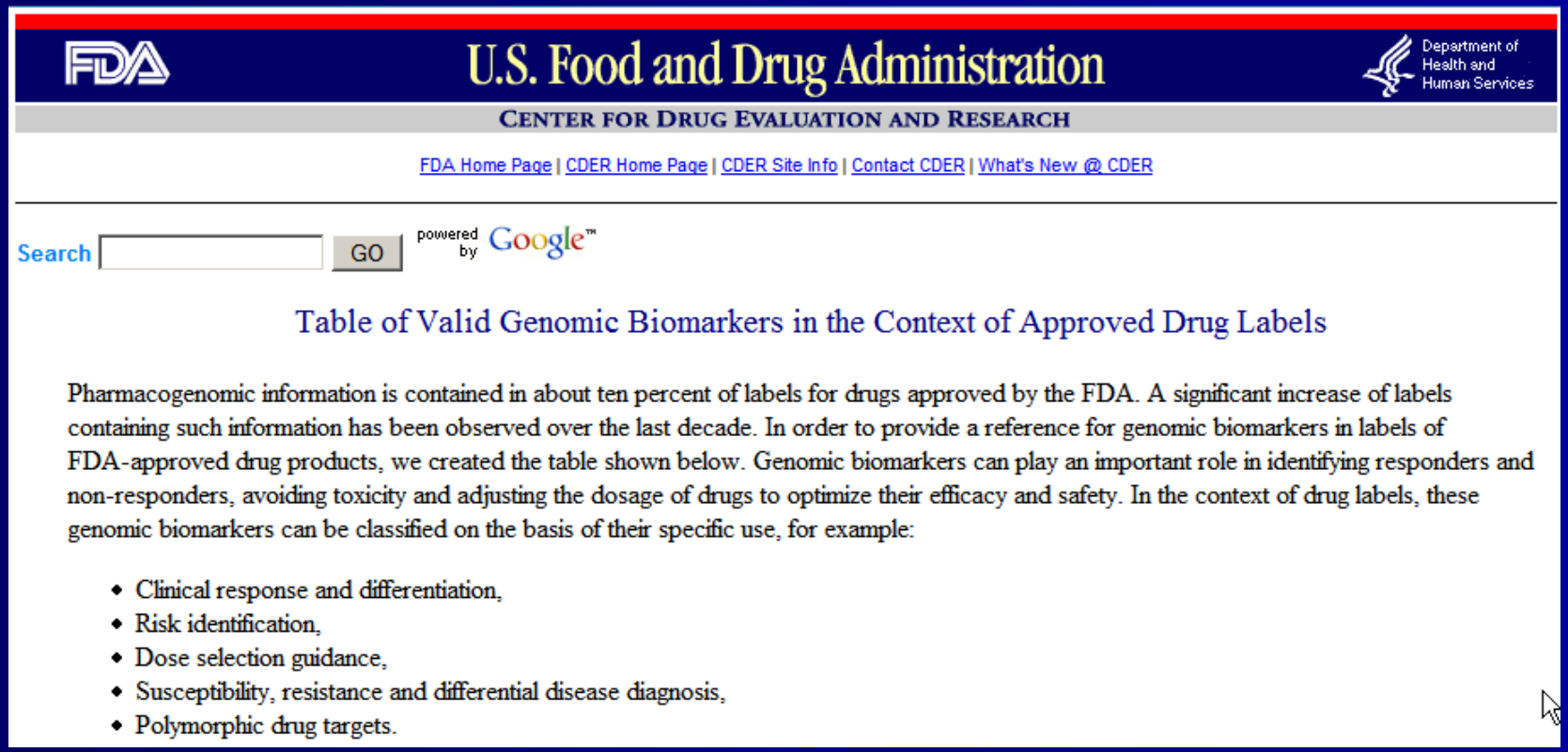
Not for Implementation

Drug-Diagnostic Co-Development Concept Paper

April 2005

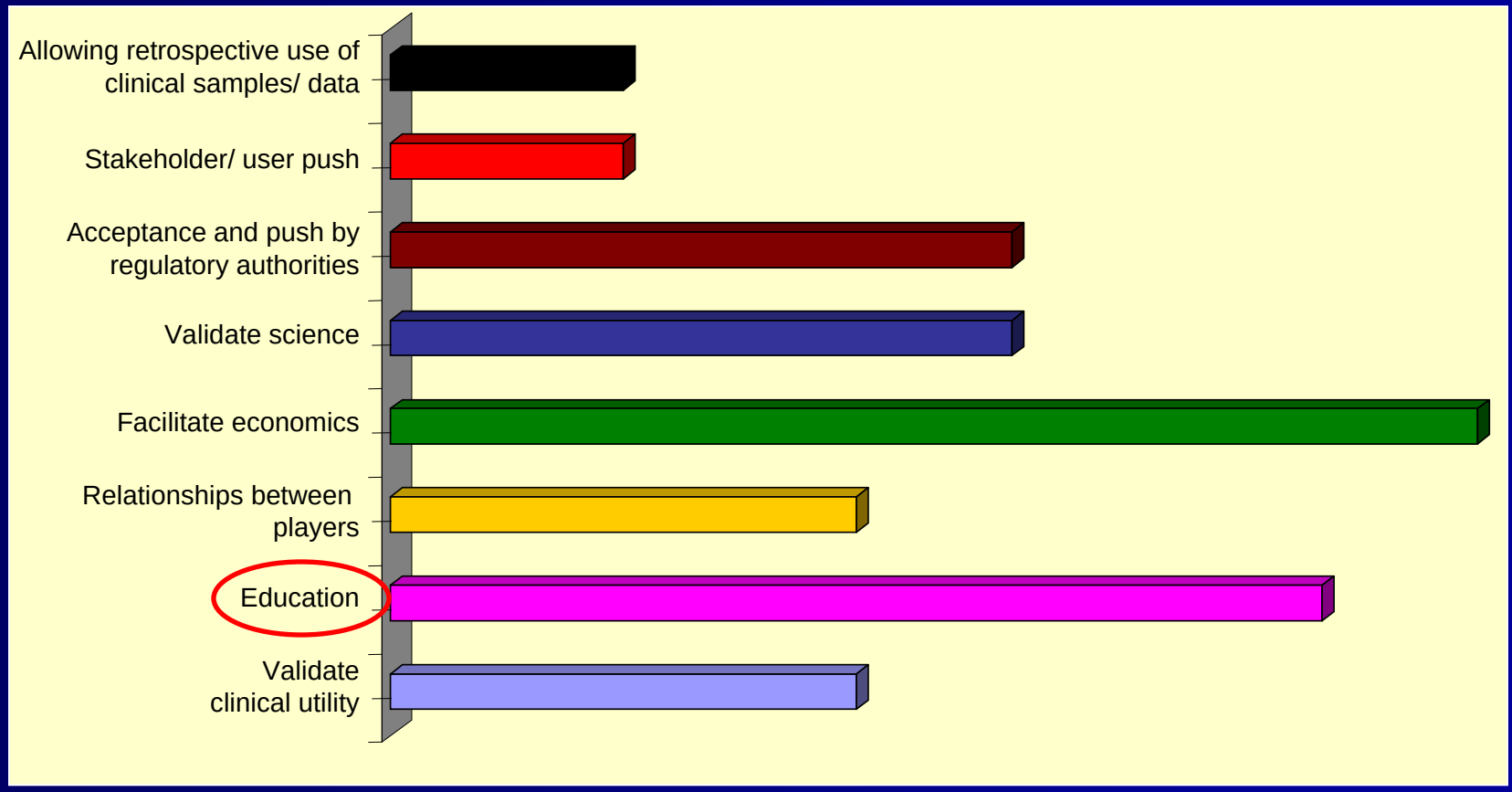
http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf

http://www.fda.gov/cder/genomics/default.htm



http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm

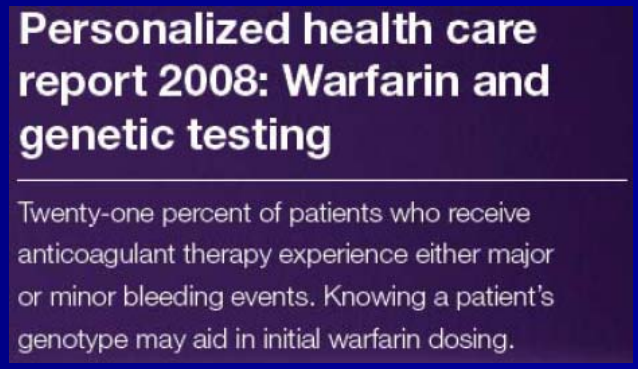
Education Is One Of The Obstacles That Is Holding Back Genomic Medicine



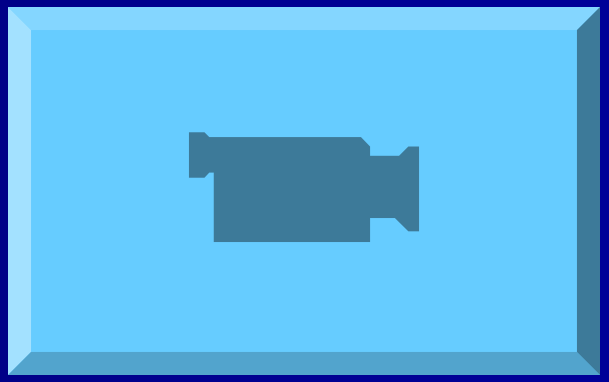
Adapted from survey conducted by Dr. Mollie Roth, Diaceutics, April 2008

Collaborative Web-Based Learning Programs and Literature

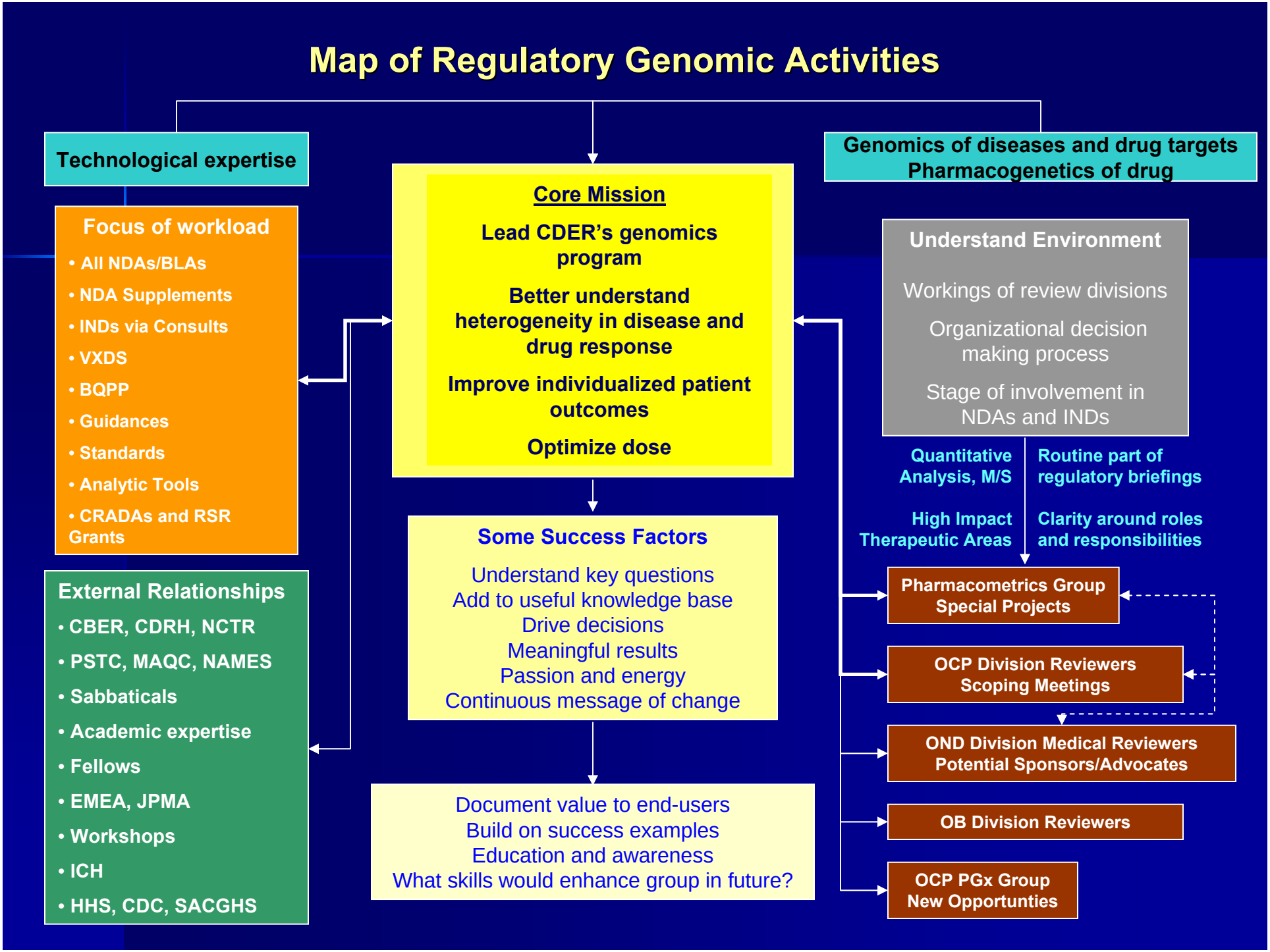
- AMA/FDA Practicing Physician Training in Pharmacogenomics: ***http://ama.learn.com***
- ACCP/FDA Medical and Graduate Student Training in PGx: ***http://www.accp1.org/~user/index.html***
- FDA Patient Safety News Site on Genetic Testing: ***http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/transcript.cfm?show=64#6***



http://www.ama-assn.org/ama1/pub/upload/mm/464/warfarin_brochure.pdf



Map of Regulatory Genomic Activities



Rational Prescribing Based on Genomic Medicine

Rudolph Buchheim (1820-1879) Founder of Translational Medicine

"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

Let Us Apply Genomic Medicine and Pharmacogenomics To Change Their Lives

lawrence.lesko@fda.hhs.gov