Pharmacogenomics, Personalized Medicine and the Role of FDA

Bio-IT World Conference
Hynes Convention Center
Boston, Massachusetts
May 18, 2004

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Food and Drug Administration
Rockville, Maryland

Outline of Presentation

- Problem of heterogeneity in disease and variability in drug response
- FDA initiatives to facilitate innovation including pharmacogenomics (PGx)
- Current status with examples of successes and failures
- Outlook on future challenges and barriers

The Big Picture

Most popular Google satellite maps…..Bill Gates' house, Michael Jacksons' Neverland Ranch and Bostons' Hynes Convention Center…….

Boylston Street

http://www.aaccessmaps.com

How Advances in Technology Will Impact Health Care Systems?

November 28, 1983

"Men are only so good as their technical developments allow them to be"

George Orwell, 1903-1950
Essayist, Novelist and Satirist

I. Patient Digitized Health Records Using a Web-Based Program

- Patients fill in their medical history, including drugs and allergies, online
- Patients decide when and where to share it with doctors and hospitals
- Patients choose to transfer their records to new doctors
- Patients receive emails about drug recalls and related health information

Medem's iHealthRecord, Wall Street Journal, May 9, 2005

II. Patient Medical Record Information on Implantable Microchips

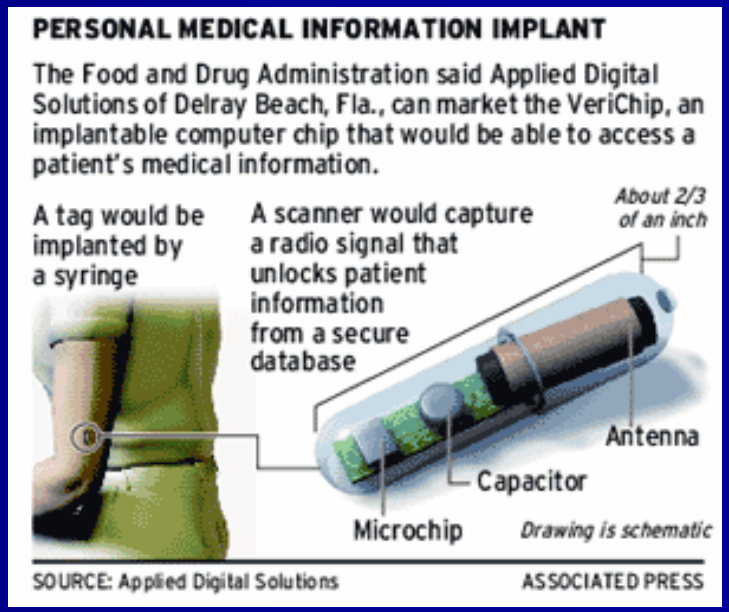
Medical chip implant given FDA approval

By Barnaby J. Feder and Tom Zeller Jr.
NEW YORK TIMES NEWS SERVICE

October 14, 2004

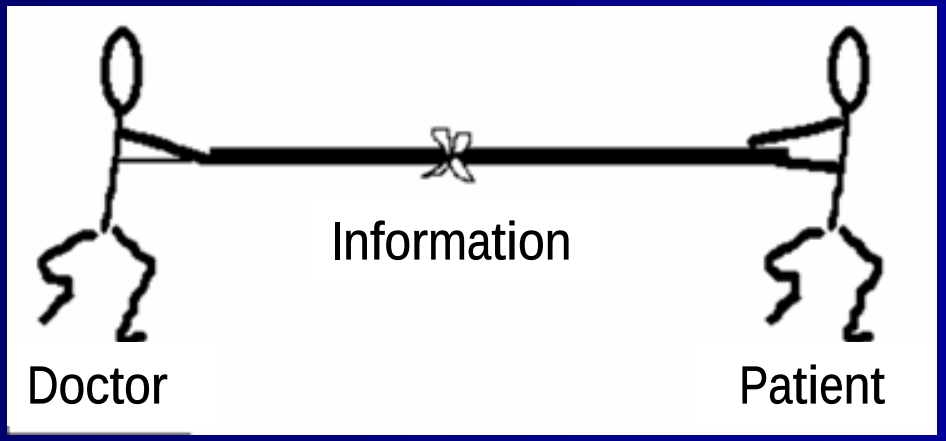
The Food and Drug Administration has cleared the way for a Florida company to market implantable microchips that would provide easy access to individual medical records.

The approval, which the company announced yesterday, is expected to take the lid off a simmering debate over a technology that has evoked Orwellian overtones for privacy advocates and fueled fears of widespread tracking of people with implanted radio frequency tags, even though that capability does not yet exist.



- 16-digit number on chip retrieved by handheld radio scanner
- Access to records on chip authorized by patient

Shift in Balance of Power from Physicians to Patients



Smarter Patients
More Patient-Focused Doctor
Delivering Health Care with Greater Precision
Personalized Medicine

Technology Affects Society in General: From Smart*Cameras* to Smart*Drugs*

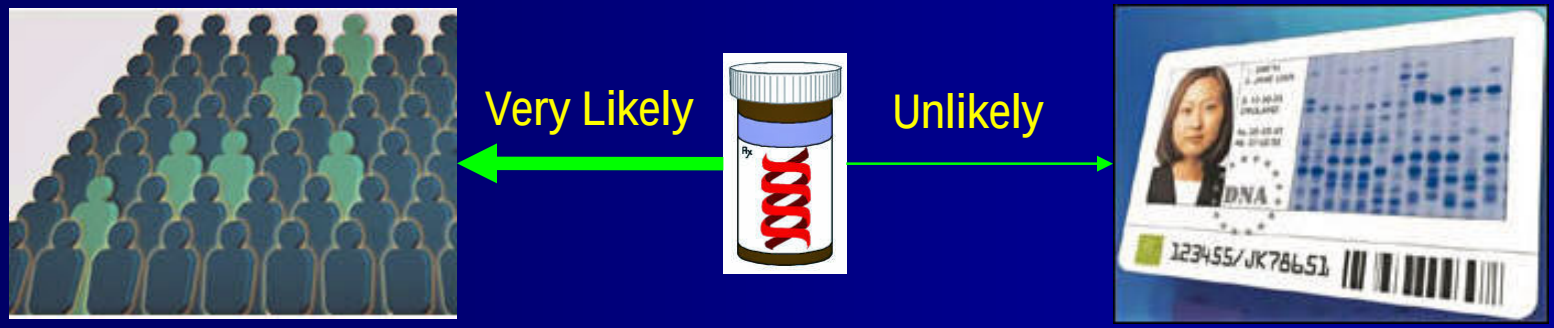
Storrow and Memorial Drives

Your name here

Personalized Medicine ~ So, What Is It Anyway? More Than Just Medicine!

"The *right medicine* for the *right person* at the right *dosage regimen*"

"Individualized guide to proper therapeutic options among *predictable segments of the populations*"



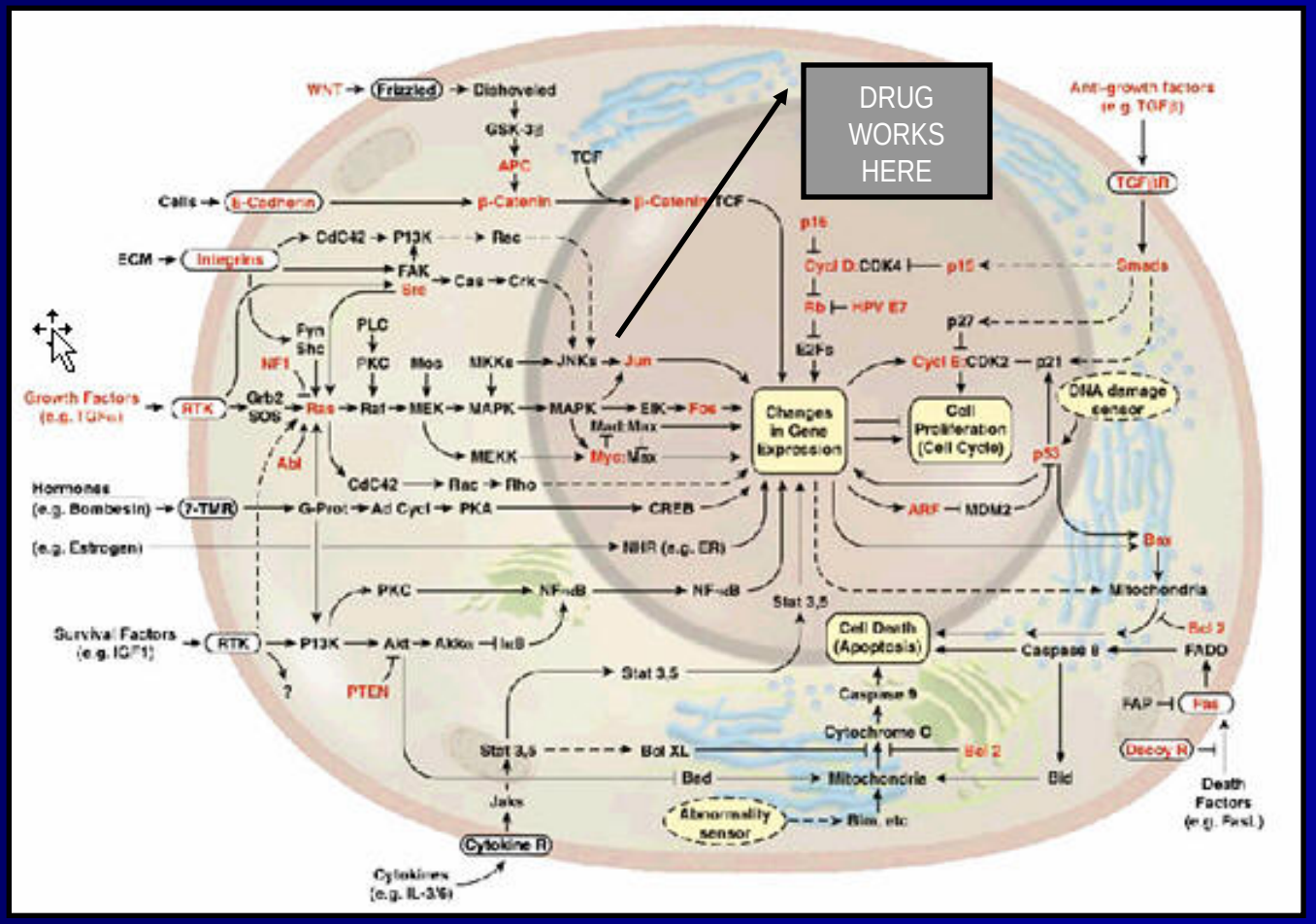
Personalized Medicine is Evolutionary: Understanding the Disease and the Drug

"You cannot be sure of the success of your remedy, while you are still uncertain of the nature of the disease"

"Poisons and medicines are often times the same substance given with different intents"

Peter Latham (1789-1875)

Molecular Understanding of Tumor Pathophysiology ~ Technology Rules



Heterogeneity From Genetic Diversity ~ Major Barrier to Personalized Medicine

Sir William Osler
1892

The Practice of Medicine

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

To the Dictionary!

- **Art** ~ A skill acquired by experience, study or observation

- **Science** ~ Knowledge covering general truths as obtained and tested through the scientific method

Efficacy of Medicine in 2005 Is Very Much as Art

- Efficacy of Selected Drug Classes ~ ACE inhibitors (10-30%), beta blockers (15-35%), SSRIs (10-25%), TCA (20-50%) and statins (10-60%)

Spear et al, Trends in Molec Medicine 2001;7:201-204

Safety of Medicines in 2005 Is Also Very Much as Art

- Efficacy of Selected Drug Classes ~ ACE inhibitors (10-30%), beta blockers (15-35%), SSRIs (10-25%), TCA (20-50%) and statins (10-60%)
- Safety ~ A meta-analysis of the incidence of serious (6.7%) and fatal (0.3%) ADR in hospitalized patients claimed 100,000 Americans die each year from drugs
  - 2.2 million Americans experience serious ADR that are an economic burden to the health care system
  - *Study released TODAY showed things haven't changed***

*Lazarou et al, JAMA 1998;279:1200-1205, Spear et al, Trends in Molec Medicine 2001;7:201-204,** In JAMA as Reported in USA Today, May 18, 2005*

Serious Implications for the Quality of Public Health and Personalized Medicine

Should I, a 60 yo male, take a statin for high LDL levels? Will it help me?

Number needed to treat:

65 previously well middle-aged men with high LDL, will take over 200,000 statin pills, over the course of 5 years to prevent **one** stroke or transient ischemic attack

Pederson TR, Lancet 1994;334:1383-1389 (Scandinavian Simvastatin Survival Study)

…..And, Serious Implications for the Productivity and Success of Drug Development Process

"Committee members expressed concern about the heterogeneity of the trial population and the difficulty determining which patients would benefit from the drug…..that is, when patients are going to respond, when patients are not going to respond….."

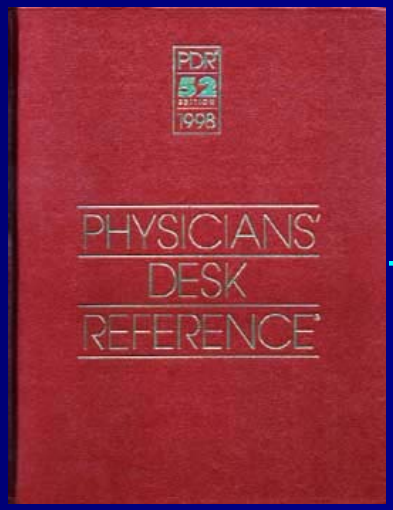
FDA's Oncologic Drug Advisory Committee on Zarnestra from acute AML, upon rejecting the drug for accelerated approval, May 5, 2005

Difficult to identify an appropriate population for labeling

Root Cause Analysis ~ One-Size-Fits Dose Selection and Dosage Regimens

Trial and Error

Symptoms
Diagnosis
Treatment



Nonspecific,
Nonselective
Medicines

Phenotype

We can, and should, do better

Why Is FDA Interested in Personalized Medicine?

- Its' mission is to protect and advance public health.....

  ".....by helping to speed innovations that make medicines and foods more effective, safer and more affordable."

The Pink Sheet, February 3, 2003

Improving Innovation in Medical Technology: Beyond 2002

Set direction from the top, engage people below

Dealing with the Failure of Prediction: Drug/Test Co-Development

"Certain new therapies will be developed along with genetic or phenotypic tests that can identify an appropriate treatment population and detect patients who need different doses or are prone to certain toxic effects. Development of these test and therapy combinations must be facilitated because they have the potential to maximize drug benefits while minimizing toxicity."

Mark McClellan, M.D., FDA Commissioner, Washington Drug Letter, April 13, 2003

FDA's Call to Arms for Modernization of Drug Development Process

"Critical Path" Paper Calls for Academic Researchers, Product Developers, and Patient Groups To Work With FDA To Help Identify Opportunities to Modernize Tools for Speeding Approvable, Innovative Products To Improve Public Health

www.fda.gov/oc/initiatives/criticalpath/whitepaper.html

Critical Path Focus: Genomics, Biomarkers, and Targeted Therapies

"Change is inevitable, except from vending machines"

Woody Allen, Satirist

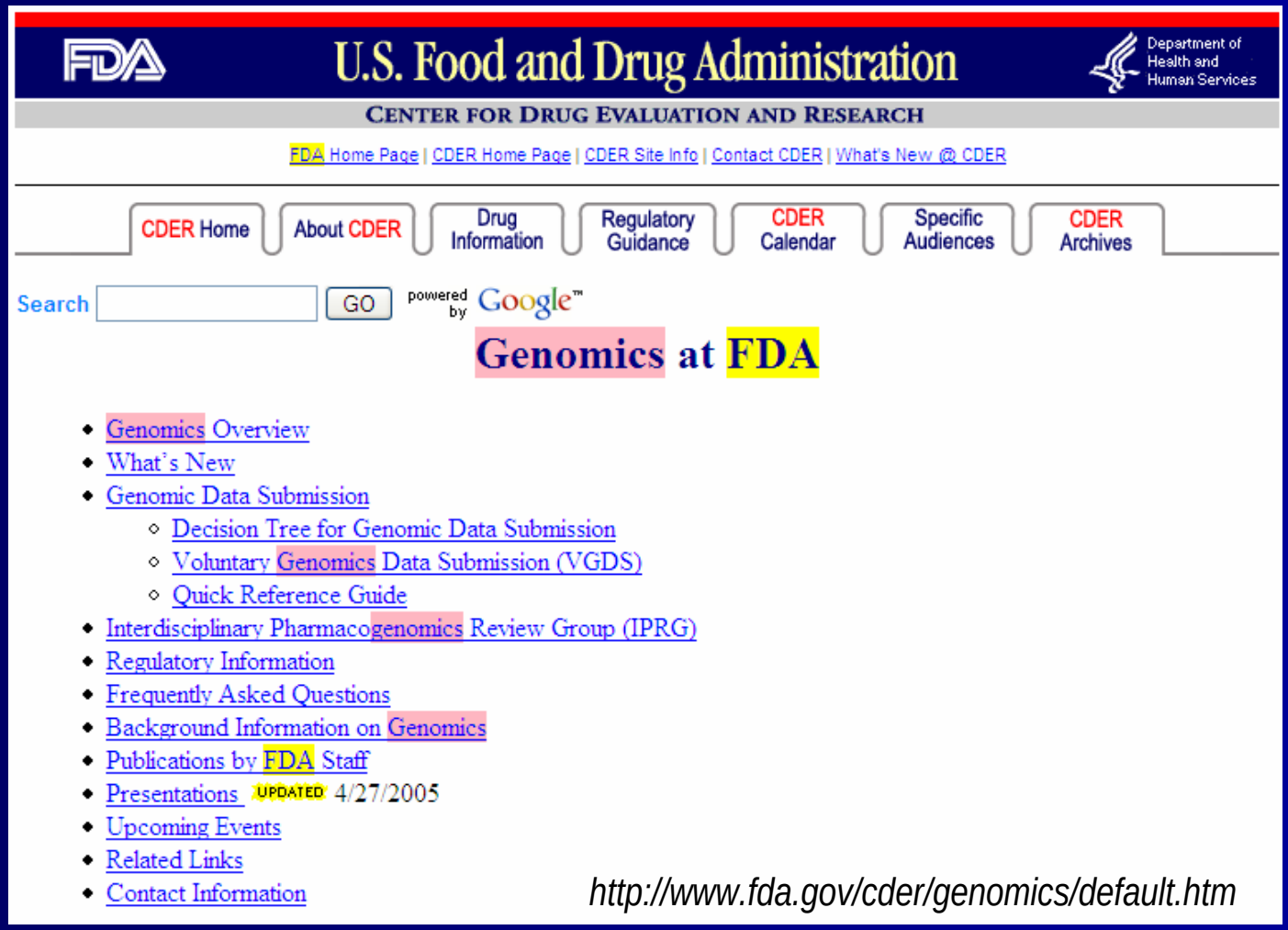
Rhetoric, and Now Actions

What steps has FDA taken to speed up innovations in PGx?

What steps has Industry taken to speed up innovations in PGx?

What steps has FDA and Industry taken together to speed up innovations in PGx?

It's on the Internet and It's Free: There is No Rule Book for PGx



U.S. Food and Drug Administration

Department of Health and Human Services

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Genomics at FDA

- Genomics Overview
- What's New
- Genomic Data Submission
  - Decision Tree for Genomic Data Submission
  - Voluntary Genomics Data Submission (VGDS)
  - Quick Reference Guide
- Interdisciplinary Pharmacogenomics Review Group (IPRG)
- Regulatory Information
- Frequently Asked Questions
- Background Information on Genomics
- Publications by FDA Staff
- Presentations UPDATED 4/27/2005
- Upcoming Events
- Related Links
- Contact Information

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

Guidances for Industry: Standardization of Approaches to Reduce Uncertainty

- *Genomic Data Submission*
  - Proposed new classification of biomarkers
  - Decision trees for voluntary and required submissions
- *Drug Metabolizing Enzyme Genotyping Systems*
  - Supports classification of these systems into Class II and identifies issues related to a 510(k) premarket notification
- *Instrumentation for Clinical Multiplex Test Systems*
  - Supports classification of instrumentation for clinical multiplex test systems into Class II (special controls)
- *Drug and Test Co-Development*
  - Analytical and clinical validation of a genomic assay
  - Evidence of clinical utility and labeling of drug and device

SOPs for FDA: Standardization of Processes to Enable the Science

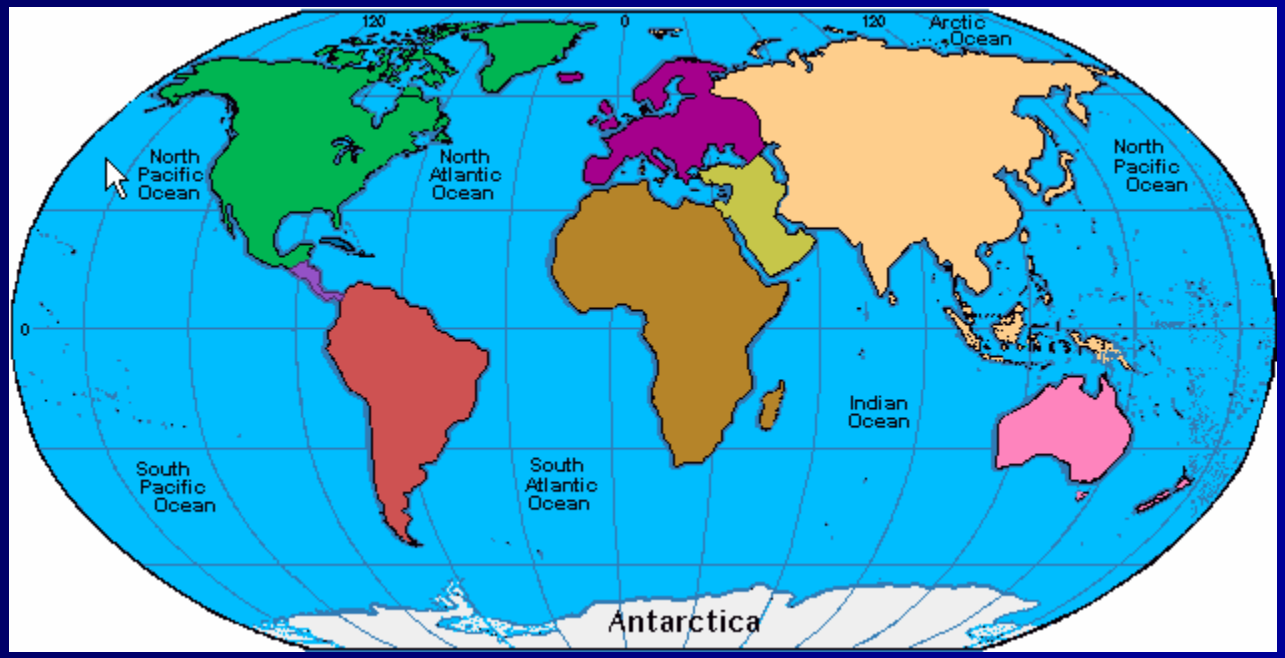
- *SOPs*
  - Processing and reviewing VGDS
  - Management of the IPRG
- *IPRG*
  - Consult to review divisions on INDs and NDAs
  - Offer educational programs throughout CDER
  - Develop research consortia to address the process and standards for biomarker validation

Outreach: Partnering and Bringing Stakeholders Together

- FDA-PhRMA-BIO-PWG workshops in May 2002, November 2003, July 2004 and April 2005
  - Publicly discuss and vetted issues of uncertainty surrounding PGx
- Numerous “partnerships” – consortia, cooperative agreements under the “critical path”
  - Bringing trade associations, individual companies, NIH and academic centers of excellence together to do research on standardization in PGx technology, validation of biomarkers, and proof of principle of clinical utility

Recognizing the Globalization of Drug Development ~ Harmonization

North America - Europe - Asia

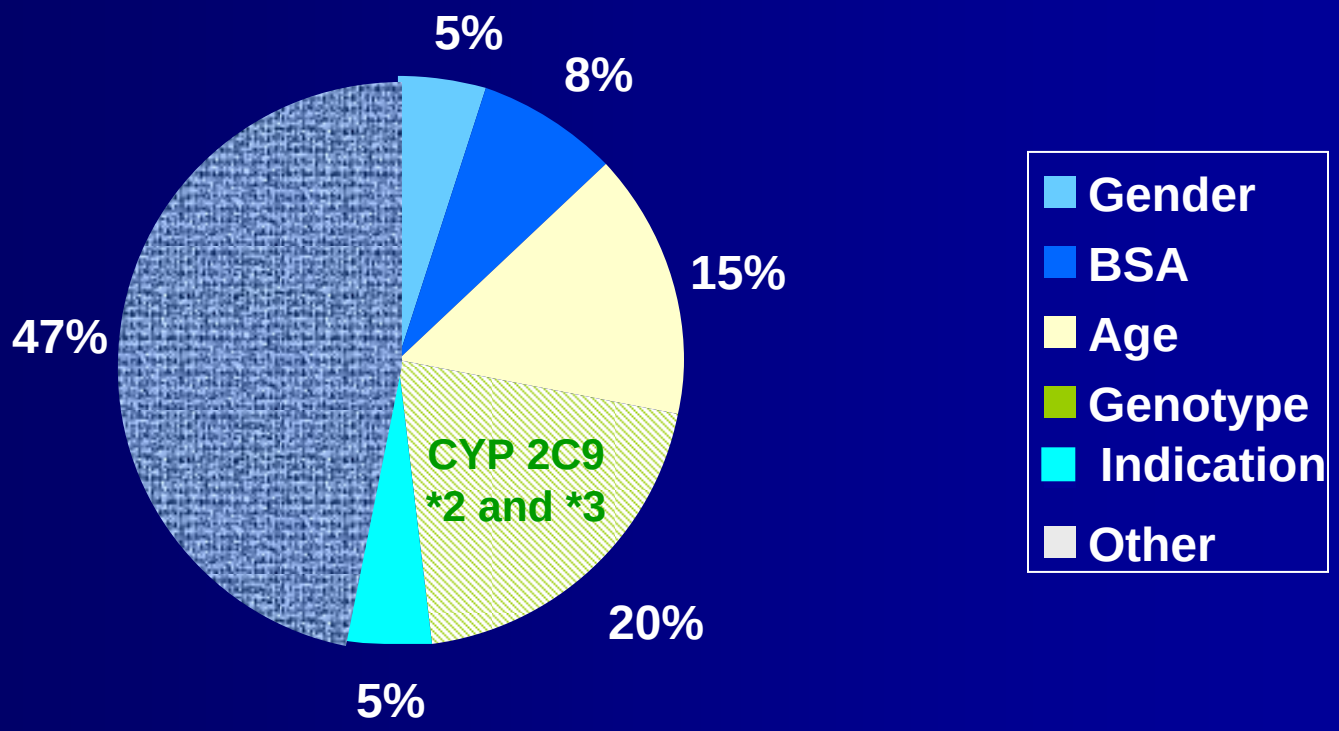


Mantra ~ The type of information needed to support a regulatory filing needs to be clear, and where feasible, harmonized between national drug and device regulatory authorities

FDA Involvement and Leadership in International Activities

- Creating alignment between FDA, EMEA and MHLW on key principles of PGx leading to harmonization
- Provided comments on draft business plan for PGx as an ICH topic
- Discussing PGx at ICH meeting in Nov 2005
- Conducting joint VGDS meetings with EMEA under FDA-EMEA bilateral agreement
- Working with CIOMS and OECD to in policy development for PGx in non-ICH regions

FDA Prospective Research: What is the Clinical Utility of PGX-Guided Dosing of Warfarin?



INR: algorithm if flawed……Dose Range: 5.5 to 36.5 mg/wk
Other Co-factors: Compliance, access to doctors, co-medications, diet

Source: Marshfield Clinic

Results of Actions

What steps is FDA (and Industry) taking to speed innovations in PGx?

Has there been successes?

To Start With…..Example of Confronting the Heterogeneity of Diseases

- Breast cancer in patient A and patient B
  - Same phenotype
  - Identical histology
  - Similar node involvement
  - Same therapeutic regimen
  - Different clinical results
- Molecular expression ~ precision prescribing
  - Response signatures in subsets of patients
  - Basis for predictive tests

Herceptin: The Pioneer Paradigm for Personalized Medicine Based on PGx

- HER2neu ~ target over expressed in 25-30% of breast cancers, approved in 1998
  - Aggressive disease + high risk of relapse/death
- Herceptin ~ monoclonal antibody against HER2neu receptor
  - Therapeutic response more likely, but not guaranteed
  - Response rate ~ 45-50%
- Herceptest ~measures HER2neu over expression
  - Positive test predicts response to Herceptin
  - Negative test redirects therapy elsewhere

Diagnostics for Predicting Prognosis and Guiding Treatment Decisions

Gene expression profile of a panel of 16 cancer-related genes

NEJM, 2004, 351, 2817-2826
http://www.genomehealth.com

- Predict risk of breast cancer recurrence (score: 1 – 100)
- Identify women who will benefit most from chemotherapy
- Avoid chemotherapy AEs in those who will not benefit
- Adjunct test to staging, grading and other tumor markers
- Need to wait to see extent of uptake and long-term utility

Focus on Cancer, The Forgotten Model-HIV ~ Pulling It All Together Since 1996

Predictive, prognostic and response biomarkers: HIV-1 RNA, CD4, Blood levels, and viral genotype
Comp Assist Prescribing

Personalized Medicine

1. Reliance on relevant biomarkers
2. Genomics as an adjunct tool
3. Available diagnostic tests
4. Clinical expertise to interpret data
5. Selecting best drug for individual patient

Gap Between Generalized and Personalized Medicine ~ Closing With Precision Design of Dosage Regimens

"FDA Clears Test for Patient DNA to Screen for Drug Effectiveness"

Wall Street Journal, January 11, 2005

- Chip measures alleles of CYP 2C19 and CYP 2D6
- Adjunct tool to reduce over- and under-dosing
- Estimates of 20% reduction in adverse events
- Potentially useful for hundreds of patients

Diagnostics + Labeling Regulations = PGX-Friendly and Informative Labels – Where It Matters

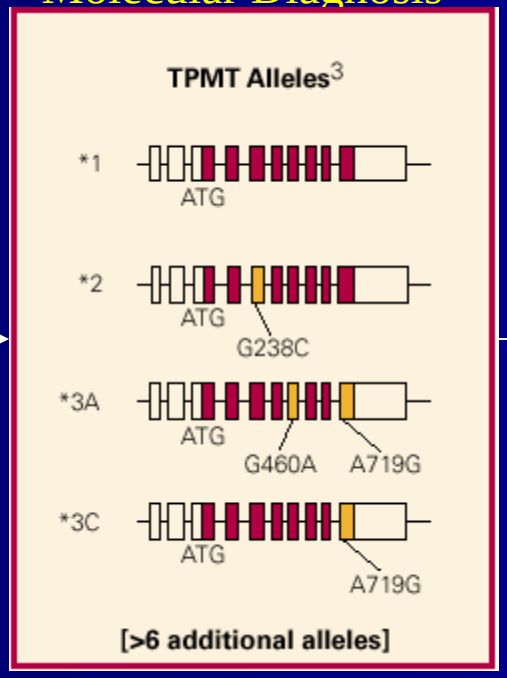
"If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, the labeling shall describe the evidence and identify specific tests needed for selection and monitoring of patients who need the drug."

- 21 CFR 201.57

Remember ~ PGx Is Just Not for Old Drugs: Precision Dosage Regimens of 6MP and Azathioprine

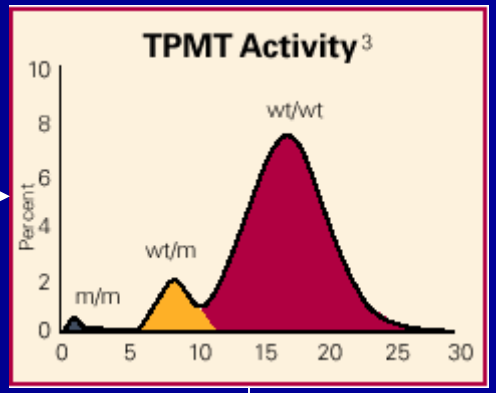
2400 children are diagnosed with Acute Lymphoblastic Leukemia per year

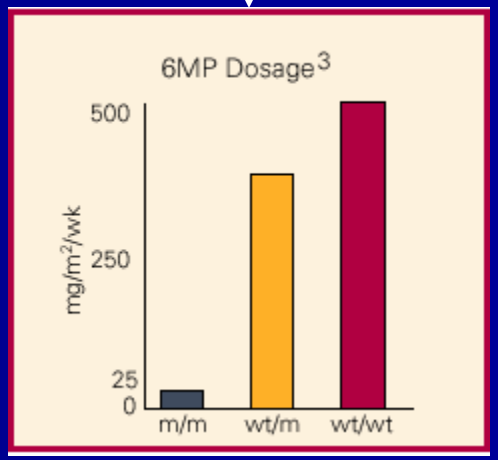
Molecular Diagnosis



- When starting therapy
- First week of therapy
- Overt toxicity

Trimodal Distribution



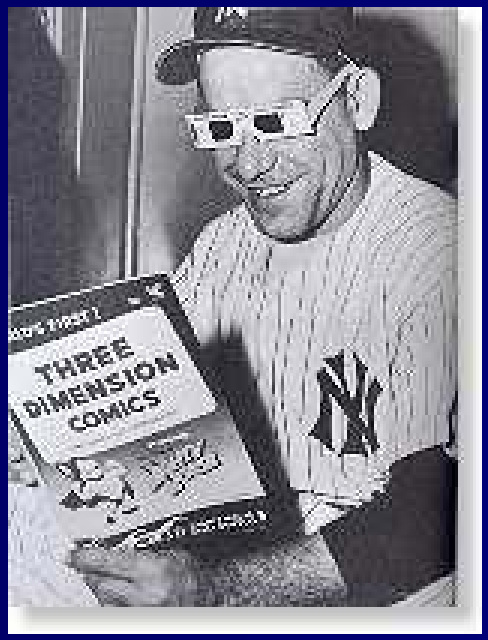


Krynetski and Evans, Amer J Hum Gen 63(1), 11-16, 1998

Reducing the Adverse Events of Irinotecan Using a UGT1A1 Genomic Test

Group	Prevalence	Risk of Toxicity
All Patients	-----	10%
Patients That Are 7/7	10%	50%
Patients That Are 6/7	40%	12.5%
Patients That Are 6/6	50%	0%

Based on data from Innocenti et al in Clin Pharmacol Ther (2004)



"The future ain't what it used to be!"

Yogi Berra

What steps is FDA (and Industry) taking to speed innovations in PGx?

Has there been successes?

Why should anybody care?

PGx Provides Opportunity for Change – Change is Good for Public Health

Internet! Is that thing still around? They have the internet on computers, now!?!

- Homer Simpson

PGx! That thing will play an important role in the development of better medicines for ***populations*** and targeted therapies with improved benefit/risk ratios for ***individuals!!***

- Larry Lesko

Value in the Marketplace: Intellectual Property of the Molecule

"Every company can match every other company in sales force promotion. What matters most today is what you bring to the market in terms of value"

- Ray Gilmartin, Former Merck CEO

PGX will mean subdividing target populations

Herceptin Example: Economic Value Despite Subdividing the Population

Trial Design	With HER2 neu	Without
# of patients	470	2200
Response rate	50%	10%
Years of follow-up	1.6	10

- *Savings in clinical trial costs ~ $35 million*
- *Income from 8 year acceleration of product ~ $2.5 billion*
- *Access to drug from acceleration ~ 120,000 patients*
- *52% reduction in tumor recurrence ~ Extension of value*

** From Press and Seelig, Targeted Medicine 2004, New York, November 2004*

Exclusivity – The Holy Grail of Value

"Profitability in the pharmaceutical industry depends on market exclusivity"

- Drug Discovery Today, 1998

FDA's Regulatory and Exclusivity Incentives Can Help Make the Business Case

- Orphan Drug Act
  - Facilitate development of medicines for treating diseases affecting < 200,000 patients
    - PGx diagnostic may define orphan indication
    - New or old drugs (may have additional indications)
  - 7 yr of market exclusivity for indication
  - Grants and tax credits to subsidize development costs
  - Expedited review

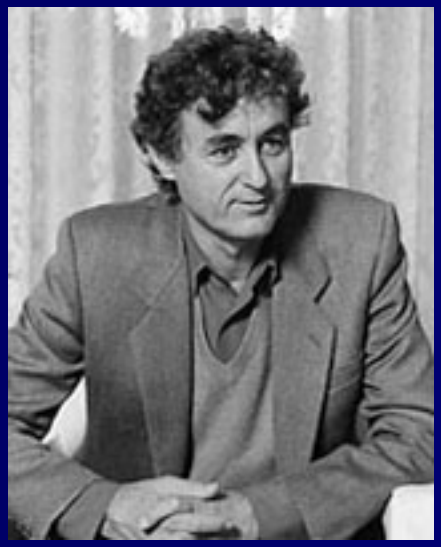
http://www.fda.gov/orphan.htm

Other FDA Regulatory and Exclusivity Incentives Potentially Useful for PGx

- 3 year exclusivity**
  - Facilitate development of new claims for medicines supported by new clinical trails
  - Effect larger than previously demonstrated or a superiority showing = new claim
  - PGx diagnostic may potentially define target population

** *http://www.fda.gov/cder//about/smallbiz/exclusivity.htm*

Set Reasonable Expectations: With Change, There Are Risks



"As long as we do science, some things will always remain unexplained"

Fritjof Capra
Systems Theorist

PGx tests will often be adjuncts, sometimes replacements, to SOC, but always with a measure of uncertainty

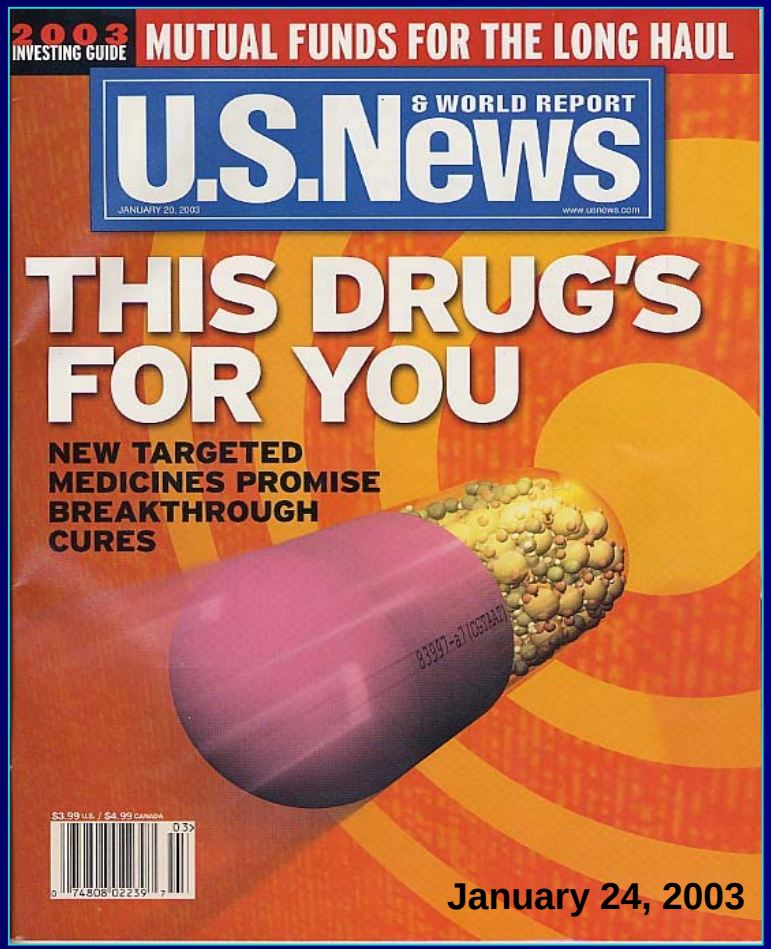
News Flash! Here's One……

WALL STREET JOURNAL. , May 5, 2005. *CANCER DRUG DEEMED FAILURE, HELPS ASIANS*

"Iressa as proved effective at treating lung cancer in Asian patients, even as it flopped in helping Caucasians, Blacks and just about everyone else…..through a curious quirk in medicine. Asians respond well to therapy because they have a certain genetic mutation in their cancer cells that Iressa is good at targeting….."

"…..As a result, Astra-Zeneca which initially planned big sales of Iressa in the US, is now adjusting its marketing plan to focus on Japan, China and other Asian markets."

So, Are We There Yet? No, But We're Moving in the Right Direction



HIV viral genotype ~
NRTI selection
Hepatitis viral genotype ~
PEG-Interferon
HER2 neu ~
Herceptin
BRC-ABL translocation ~
Gleevec
EGFR positivity ~
Erbitux
EGFR positivity ~
Tarceva

Outlook ~ Challenges to Integrate PGx Clinical Practice and Improve Public Health

- *More widespread availability of diagnostic tests*
  - Turn-around-time, patent issues and FDA approval
- *Evidence of clinical utility and cost-effectiveness*
  - Threshold for PPV/NPV compared to cost of disease/AEs
- *Interpretation of results by dedicated professional team*
  - Clinical judgment nor PGx training alone is adequate
- *Reimbursement by CMS, Blues and HMOs (who has clout)*
  - Affordability limits impact on health of segments of population
- *Lack of complete genomic solution in chronic diseases*
  - Disease biomarkers + Dose selection biomarkers + Response biomarkers

Summary of What Will Happen in the Next 3 to 5 Years

- Technology: test platforms will become less complex and more standardized
- Tests: more complete with the availability of additional mutations of CYP enzyme and transporter alleles
- Clinical utility: more prospective clinical trials will provide evidence and cost effectiveness of personalized medicine
- Interpretation: point-of-care test systems with dosage-predicting algorithms (smart systems) will be widely available
- Standard of care guidelines: will incorporate PGx for disease stratification dosage regimen selection and monitoring of outcome

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