Personalized Medicine – Today !

Clinical Ligand Assay Society
32nd International Meeting
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CDER/FDA


THE
DA VINCI
CODE
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Personalized Medicine

Can We Crack the Code ?

Case Study

- Patient is diagnosed with atrial fibrillation
- Warfarin is being described
- healthy, 41 yrs old male, 210 pounds
- SOC starting dose for warfarin at hospital is 10 mg, but doctor orders a blood test to determine CYP2C9 and VKORC1 genotypes
- Patient is a CYP2C9*3 homozygote and starting dose is reduced to 3 mg
- Maintenance dose turns out to be 3.5 mg
- Patient would have been 3x overdosed and exposed to the potential of experiencing a serious adverse event (bleeding)
- Genotype, sex, age, BSA, co-medication have been considered to adjust warfarin dose

What Does this Case Tell Us ?

- Personalized Medicine works (today!):
  - The consideration of several factors is important for finding the correct dose
  - The patient's genetic profile is one of these factors
  - These factors may not all have the same weight, but together they can significantly reduce the uncertainty about the treatment decision
  - We need to be able to measure the factors (biomarkers): technology to determine the patient's genetic profile has been available and knowledge existed that genotyping can help to make a better clinical decision

What I want to talk about:

- Personalized Medicine is about the knowledge – and the use of it – to make smarter decisions to treat patients on an individual basis
- There is life after Herceptin and Gleevec – but perhaps it's a bit more complicated than we thought...
- What we do at the FDA to promote scientific progress in the field of Personalized Medicine and to ensure its translation into clinical practice

What Is Personalized Medicine ?

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The PATH TO **personalized medicine** :: Bio-IT World
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Personalized medicine - The Boston Globe - Boston.com - Op-ed - News
So, what's in it for me? That question probably crossed many minds five years ago following the news that scientists had successfully assembled the first **...**
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Metabolomics: Working Toward **Personalized Medicine**
Metabolomics, the evaluation of body fluids such as urine for metabolic changes, provides clues to how a person may react to a drug.
www.fda.gov/fdac/features/2005/605_metabolomics.html - 23k - Cached - Similar pages

[PDF] **Personalized Medicine**
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Personalized Medicine: The Emerging Pharmacogenomics Revolution. The following is a summary of the primary findings. This report is based on third-party and **...**
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IV. Definition of Personalized Medicine

Personalized medicine means different things to different people. Some have suggested that personalized medicine is the application of genomic data to better target the delivery of medical interventions. Others have suggested that it is a crucial tool in the discovery and clinical testing of new products. And others have suggested that it involves the application of sophisticated, clinically useful diagnostic tools that may help determine a patient's predisposition to a particular disease or condition. In fact, personalized medicine can encompass all of those concepts.

In theory, personalized medicine is the management of a patient's disease or disease predisposition, by using molecular analysis[2] to achieve the optimal medical outcomes for that individual — thereby improving the quality of life and health, and potentially reducing overall healthcare costs.

In practice, personalized medicine is a comprehensive approach utilizing:

- Molecular analysis of both patients and healthy individuals to guide decisions throughout all stages of the discovery and development of pharmaceuticals and diagnostics; and
- Applying this knowledge in clinical practice for a more efficient delivery of accurate and quality healthcare through improved prevention, diagnosis, treatment, and monitoring methods.

V. Public Policy Issues Impacting Personalized Medicine

Several clusters of significant public policy issues mark the pathway to the growth and acceptance of personalized medicine. While none of these issues is unique to personalized medicine, government regulation of clinical trials, intellectual property rights, licensing practices, healthcare reimbursement, and privacy are among the areas that may need to be re-examined.

Currently, public policy decisions in the healthcare arena are made in a fragmented and uncoordinated way, without considera-

Pages Attachments Comments
2 of 3
Done Unknown Zone

What Does It Mean for Me ?

- For me, Personalized Medicine means that when I go to the doctor, s/he can tell me that due to my disease-, family-, and treatment-history, age, gender, body weight, diet, smoking habit, co-medication, etc., and molecular (e.g., genetic) profile, the therapy proposed is the one I will benefit from. Then, my doctor will tell me if I'm at a risk of a particular adverse event and what we can do about it.

- It's about knowing all the factors that are responsible for an individual's reaction to therapy, which allows to make an individualized recommendation/ decision about treatment.

Personalized Medicine Is About Knowledge:

"Reports that say that something hasn't happened are always interesting to me, because as we know, there are known knowns; there are things we know we know. We also know there are known unknowns; that is to say we know there are some things we do not know. But there are also unknown unknowns -- the ones we don't know we don't know."

Donald Rumsfeld

“Things We Know” Lead to a Decision

- Decision Making:
  - Decidere (Latin) = to decide, but literally “to cut off”
    - Romans worshipped Fortuna, goddess of randomness
    - Persians (around 430 BC, according to Herodotus) made important decisions when drunk (they reconsidered the next day, however)
  - There are WRONG decisions and BAD decisions:
    - A WRONG decision is a lousy decision – the fault lies in the method (not enough knowledge). They are inevitable.
    - A BAD decision is an unforced error (not using the knowledge). They are preventable.

What It means for Personalized Medicine: Asking the Right Questions

- Questions to ask:
  - Is it the right drug for this patient and why? Are there alternatives?
  - Is it the right dose?
  - What factors do we know of that influence a patient's response to this drug and have we considered them all?
- The decision must be based on all available relevant information – but too often we don't have all the information necessary to make an individualized decision
- (However, *what* do decide is a different issue and can be a personal decision too: therefore, personalized medicine means also that different people might decide differently, even if the information for reaching a decision is the same.)

Our Job is to improve and provide the knowledge needed for making better treatment decisions.

How can we do this ?

How We Can Make Better Decisions Today and Tomorrow?

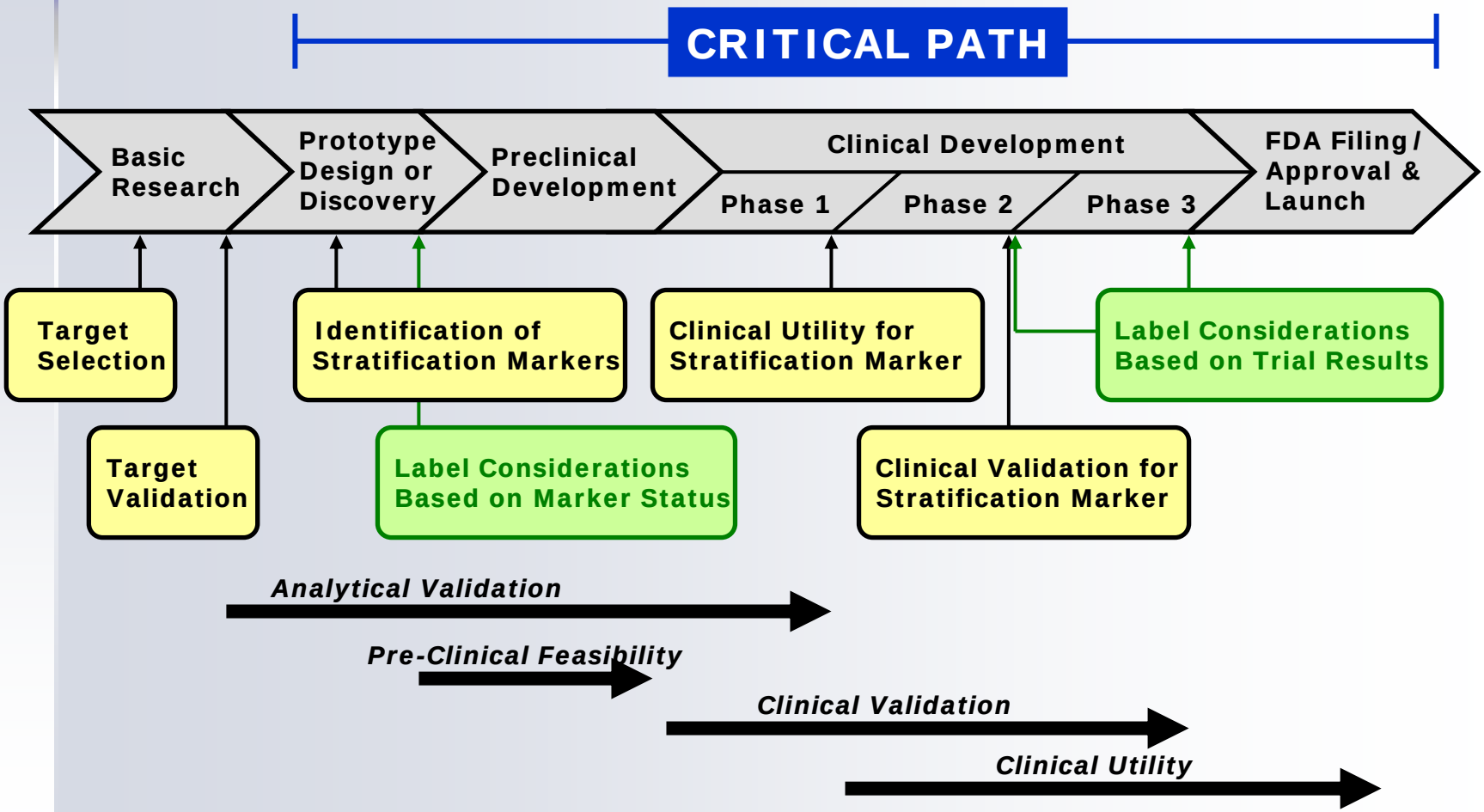
- Use the knowledge we have, e.g.:
  - Update existing drug labels with relevant pharmacogenomic information
  - Provide better information (education, guidelines, but also more informative labels)
- Generate new knowledge, e.g.:
  - New and better characterized biomarkers
  - More innovative trial designs
  - Via new models, e.g. collaborations, consortia

Genomic Biomarkers

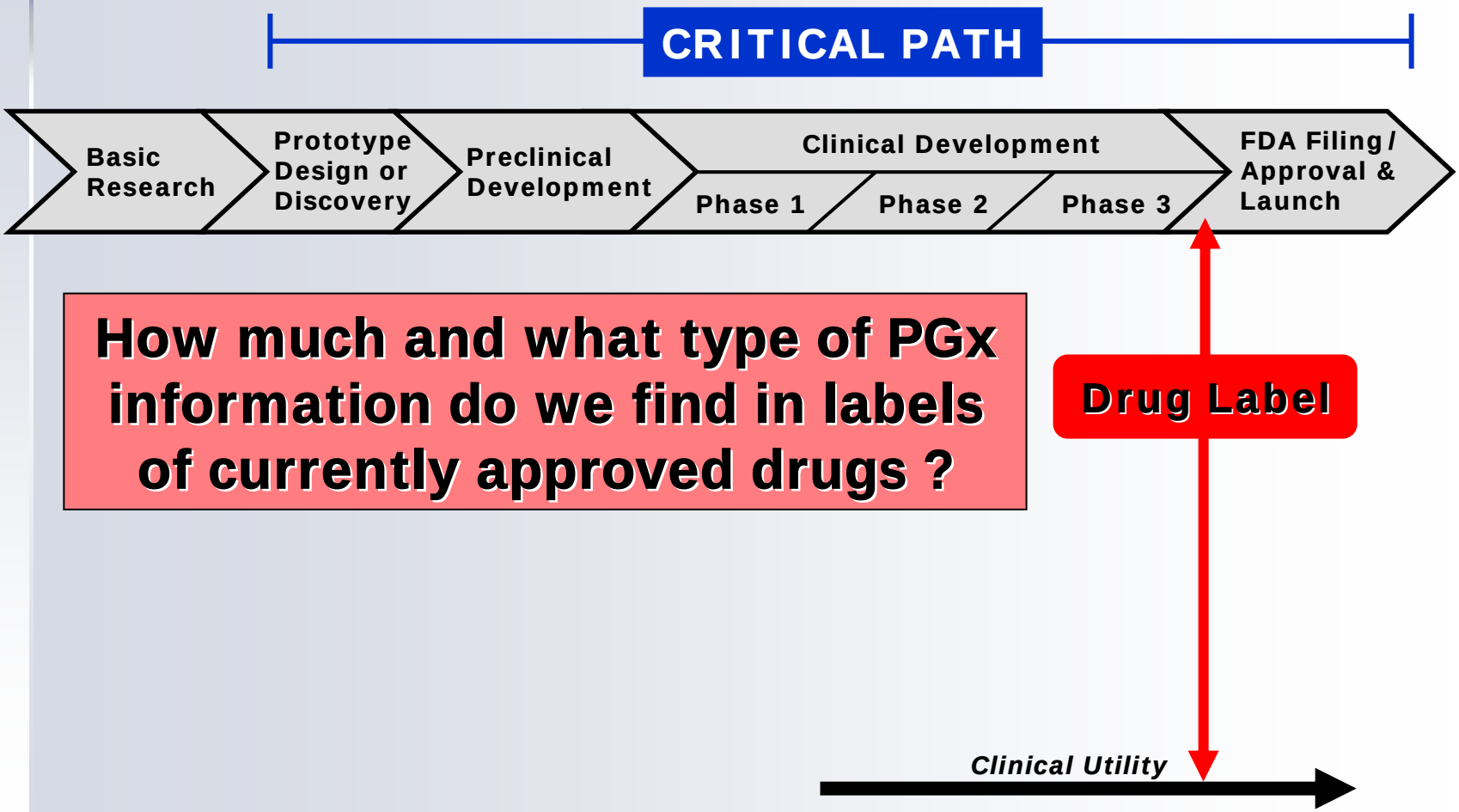
- "If the 1938 FD&C act started the age of safety for drugs, and 1962 the age of efficacy, we are now in the AGE OF INDIVIDUALIZATION."
  (*Robert Temple, Keystone, 2004*)
  - Pharmacogenomic biomarkers have the potential to be used as key decision tools in drug development, and review, and therefore play a key role in Individualization (Personalized Medicine)

- **Goal:**
  - Identify who benefits (does not benefit) from a treatment
  - Identify who is at risk (not at risk) for an adverse event

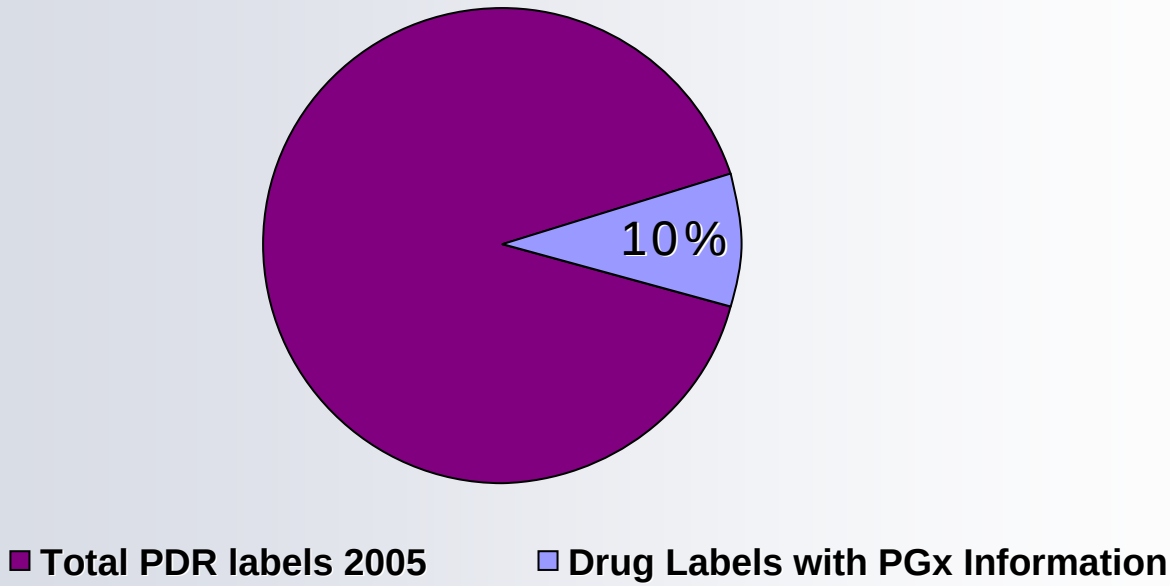
Biomarkers and Drug Development



Goal: Use of Biomarker Information in Drug Label to Make Better Decisions

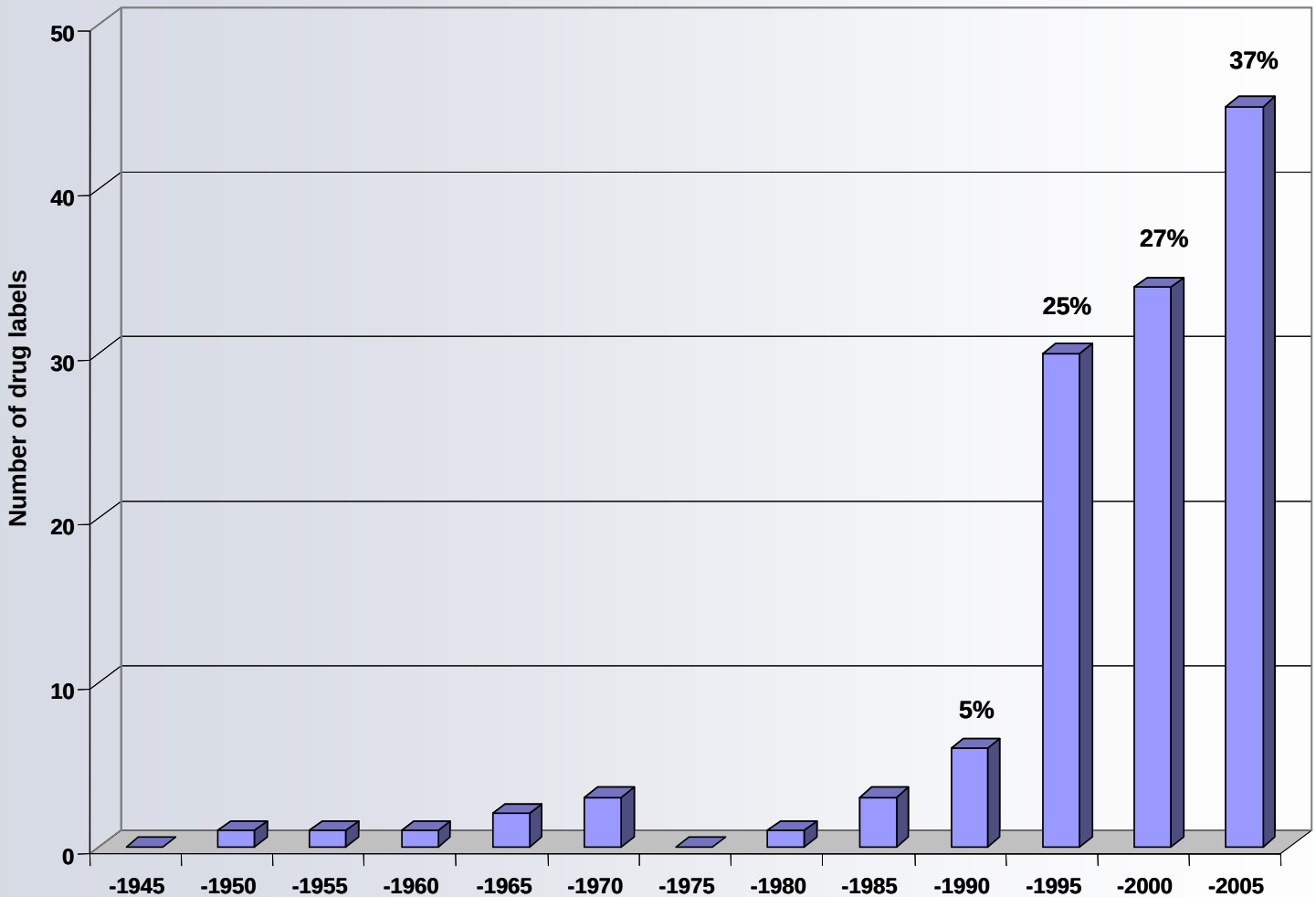


How Many Drug Labels Contain Pharmacogenomic Information ?



~ 1200 labels screened (PDR, Drugs@FDA)
121 found to contain pharmacogenomic information

Labels of Approved Drugs with Pharmacogenomic Information

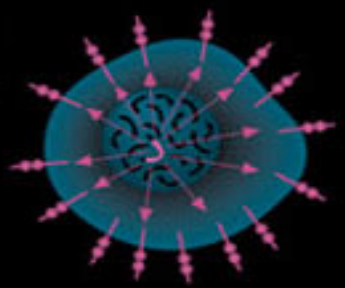


What Type of Pharmacogenomic Information is Provided in Label ?

- Mostly pharmacokinetic (e.g., drug metabolizing enzymes) – relevance for drug dosing, AEs
- Increasingly, pharmacodynamic information is found (e.g., receptors) – relevance for identification or responders, non-responders
- Broadly, the impact of pharmacogenomic information on the treatment decision can be put into 3 categories:
  - "Test required" e.g., Herceptin, Erbitux
  - "Test recommended" e.g., Irinotecan, 6-MP
  - "Information only" e.g., Tarceva, Strattera

Trastuzumab (Herceptin®)

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.

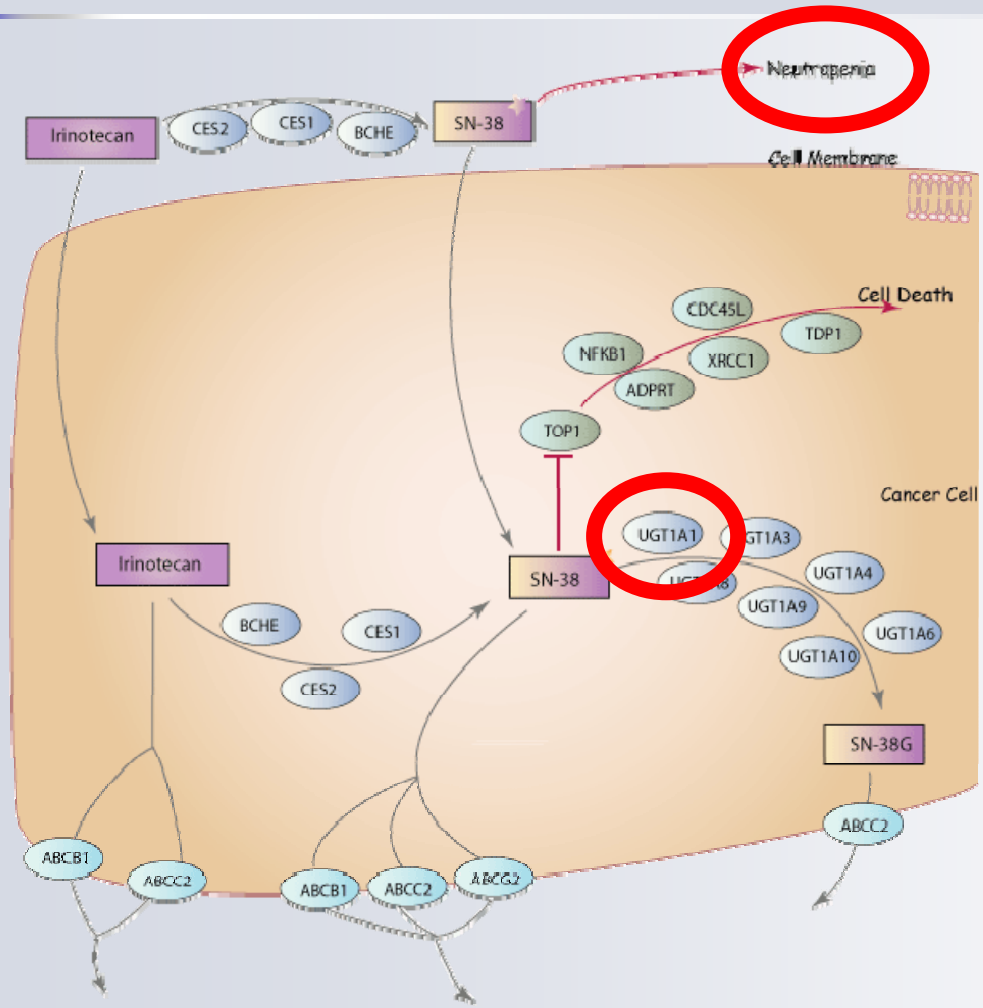
Herceptin: A Quick Detour on a Different View on Personalized Medicine

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**

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

Label Update Example 1: Irinotecan



UGT1A1 is a "polymorphic" enzyme:

The form (allele) *28 is common (30%) in Caucasians and is associated with a significant decrease in UGT1A1 activity.

Carriers of UGT1A1*28 when treated with irinotecan can experience AEs (neutropenia, diarrhea)

Identifying Who Is at Risk: Genotyping for UGT1A1*28

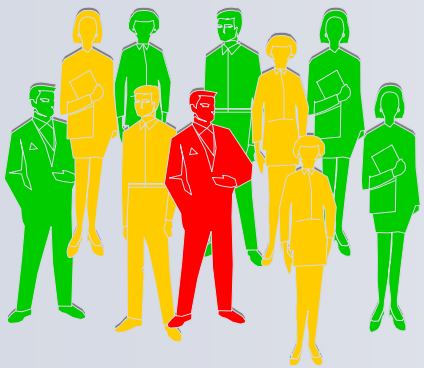
Group	Prevalence	Risk of Toxicity
All Patients	-----	10%
Patients That Are 7/7	10%	50%
Patients That Are 6/7	40%	12.5%
Patients That Are 6/6	50%	0%

After Innocenti et al (2004)

- 20 patients need to be tested to exclude one patient from potential harm
- One also can tell 50% of the patients that they are at no risk

What to Do With the Information: An opportunity for making a better informed treatment decision

All Patients with Same Diagnosis (10% risk)



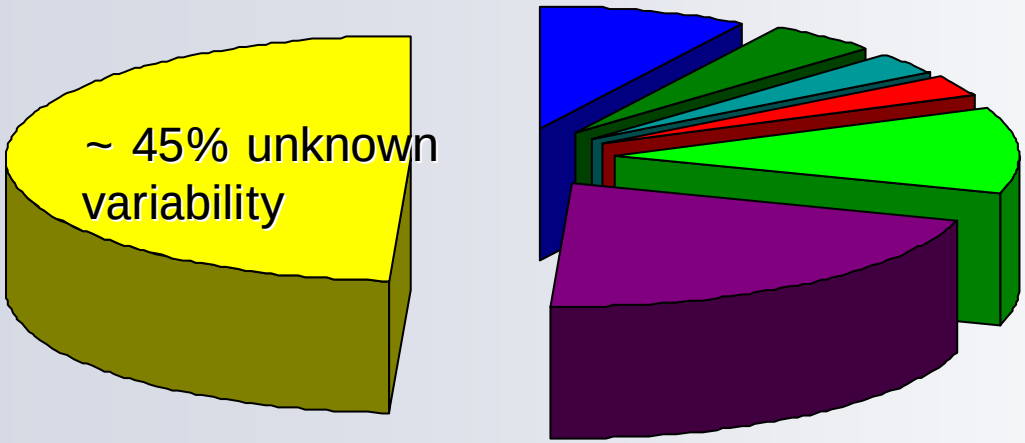
PGx profile for ***high risk*** treat with alternative drug or dose

PGx profile for ***moderate risk*** treat with alternative drug or dose

PGx Profile for ***low risk*** treat with conventional dose

Label recommends a lower starting dose if risk factor is present, but does not tell exactly what this dose is

Label Update Example 2: Warfarin



M. Caldwell, CPSC, November 14 2005

- Age
- BSA
- Valve Replaced
- Male Gender
- CYP 2C9
- VKORC1
- Other

Next: Prospective study to validate dosing algorithm → more specific dosing information in drug label

Personalized Medicine: Progress and successes, no doubt, but questions remain…

Cetuximab Shows Activity in Colorectal Cancer Patients With Tumors That Do Not Express the Epidermal Growth Factor Receptor by Immunohistochemistry

Ki Young Chung, Jinru Shia, Nancy E. Kemeny, Manish Shah, Gary K. Schwartz, Archie Tse, Audrey Hamilton, Dorothy Pan, Deborah Schrag, Lawrence Schwartz, David S. Klimstra, Daniel Fridman, David P. Kelsen, and Leonard B. Saltz

From the Gastrointestinal Oncology Service and Departments of Medicine, Pathology, and Diagnostic Imaging, Memorial Sloan-Kettering Cancer Center, New York, NY.

Submitted August 4, 2004; accepted September 15, 2004.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Ki Young Chung, MD, Gastrointestinal Oncology Service, Memorial Sloan-Kettering Cancer Center, H-816, New York, NY 10021; e-mail: chungk@mskcc.org.

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0732-183X/05/2309-1803/$20.00

DOI: 10.1200/JCO.2005.08.037

A B S T R A C T

Purpose
To establish evidence of activity, or lack thereof, of cetuximab-based therapy in patients with refractory colorectal cancer with tumors that do not demonstrate epidermal growth factor receptor (EGFR) expression by immunohistochemistry (IHC).

Patients and Methods
Pharmacy computer records were reviewed to identify all patients who received cetuximab at Memorial Sloan-Kettering Cancer Center in a nonstudy setting during the first 3 months of cetuximab's commercial availability. Medical records of these patients were then reviewed to identify colorectal cancer patients who had experienced failure with a prior irinotecan-based regimen and who had a pathology report indicating an EGFR-negative tumor by IHC. Pathology slides from these patients were reviewed by a reference pathologist to confirm EGFR negativity, and computed tomography scans during cetuximab-based therapy were reviewed by a reference radiologist. Response rates were reported using WHO criteria.

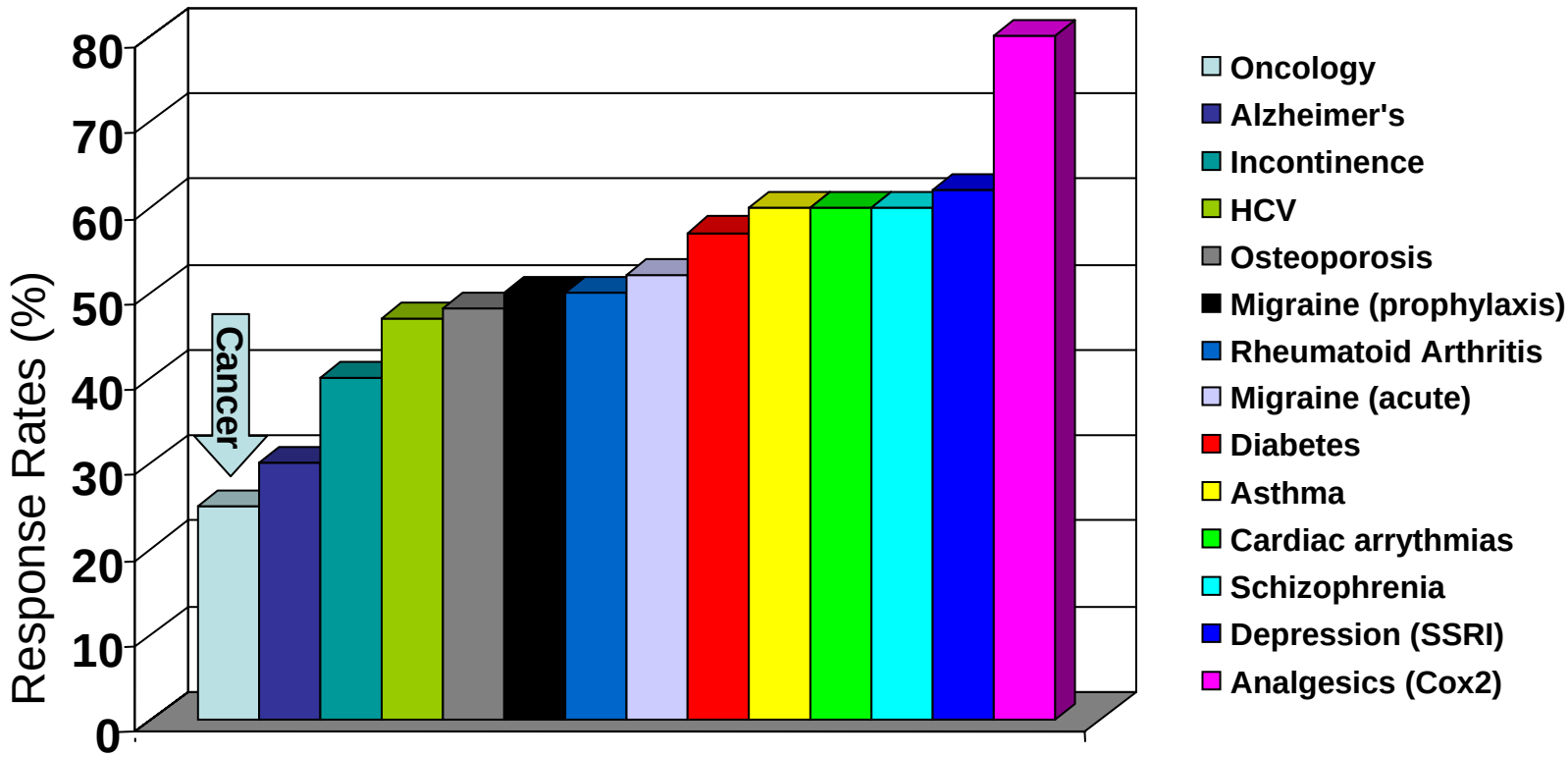
Results
Sixteen chemotherapy-refractory, EGFR-negative colorectal cancer patients who received cetuximab in a nonstudy setting were identified. Fourteen of these patients received cetuximab plus irinotecan, and two received cetuximab monotherapy. In the 16 patients, four major objective responses were seen (response rate, 25%; 95% CI, 4% to 46%).

Conclusion
Colorectal cancer patients with EGFR-negative tumors have the potential to respond to cetuximab-based therapies. EGFR analysis by current IHC techniques does not seem to have predictive value, and selection or exclusion of patients for cetuximab therapy on the basis of currently available EGFR IHC does not seem warranted.

J Clin Oncol 23:1803-1810. © 2005 by American Society of Clinical Oncology

The need for better predictive markers

The average response rate to drug treatment is not acceptable:



Slide: Paul Waring, Genentech (modified)

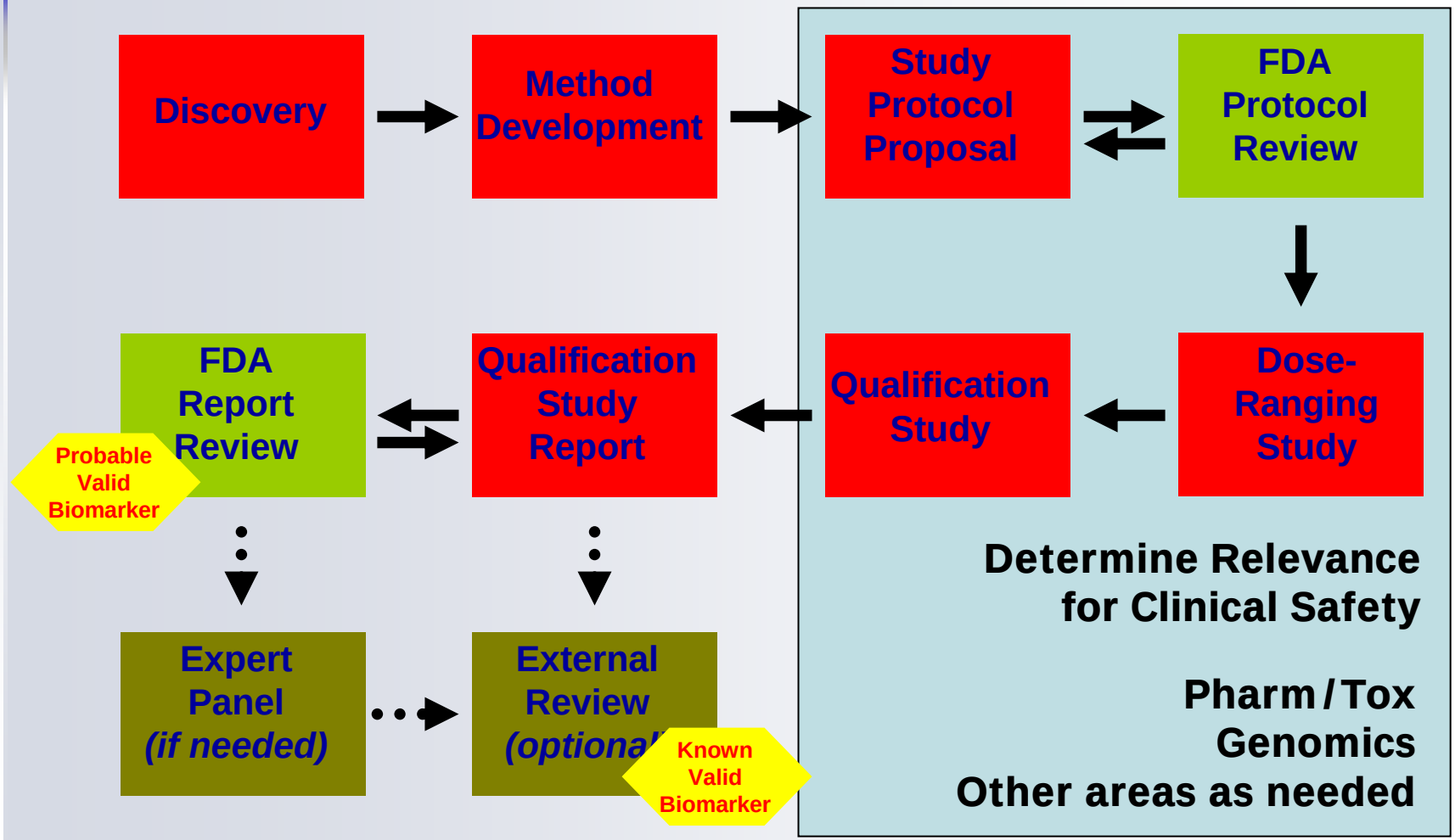
From Good to Great: New Biomarkers are Needed

- Historically, successful markers are linked to single effects in large populations (e.g., surrogate markers such as BP, HIV mRNA, etc.)
- This framework needs to be expanded because:
  - It does not recognize multidimensional quality of clinical response
  - It does not include possibility of multiple biomarkers providing useful information in aggregate
  - Therefore, this framework is at odds with our current goals for individualized therapy
- How do we make sure new markers are fit for purpose?
  - Biomarkers need to be qualified in the context of their use – but we lack a generalizable qualification scheme...

Biomarker Qualification – Example: "Pathway for Validation" of Preclinical Genomic Biomarkers for Drug Safety

- Good toxicogenomic data is difficult to create:
  - Which compounds to test, how many, controls
  - Dose range and time points, replicates
  - Which genes to include (mechanistic vs. empiric)
- Cross-validation: will move biomarker to "known valid" status
- Goal of exercise: regulatory acceptance of genomic biomarker(s) for a particular purpose (e.g. nephrotoxicity)

Proposed Pathway for Validation of Preclinical Genomic Biomarkers



Predictive Safety Testing Consortium

FDA News

FOR IMMEDIATE RELEASE
P06-40
March 16, 2006

Media Inquiries:
301-827-6242
Consumer Inquiries:
888-INFO-FDA

FDA and the Critical Path Institute Announce Predictive Safety Testing Consortium

Consortium Will Share Tests to Understand Safety of Potential New Drugs Earlier

The Food and Drug Administration (FDA) and The Critical Path Institute (C-Path) today announced the formation of the Predictive Safety Testing Consortium between C-Path and five of America's largest pharmaceutical companies to share internally developed laboratory methods to predict the safety of new treatments before they are tested in humans. The FDA, while not a member of the Partnership, will assist it in an advisory capacity. This unprecedented sharing of potential early indicators of clinical safety may streamline the cost and time of preclinical drug safety evaluation and better inform the use of "personalized medicine". The Consortium was announced today at a press conference detailing the release of the Critical Path Opportunities List – 76 initial research priorities that, if accomplished, will modernize the drug development process by 2010 and help get new medical discoveries to Americans faster and at a lower cost.

Timeline of Predictive Safety Consortium

- Initial discussions in March 2005 at the SOT Meeting in New Orleans
- Structural framework proposal by C-Path in July 2005
- Legal framework completed in March 2006
- Four working groups initiated in March 2006 at the SOT Meeting in San Diego
  - Nephrotoxicity
  - Hepatotoxicity
  - Vasculitis
  - Genotoxic and Non-Genotoxic Carcinogenicity
- Launch by Secretary of Health and Human Services on March 16, 2006

PTSC: Current Membership

- Bristol-Myers Squibb Company
- GlaxoSmithKline
- Johnson & Johnson Pharmaceutical Research & Development, LLC
- Merck & Co., Inc.
- Novartis Pharmaceutical Corporation
- Pfizer Inc.
- Roche Palo Alto, LLC
- Schering-Plough Research Institute, a division of Schering Corporation
- 5 more companies interested

Opportunities for Other Biomarker Qualification Efforts

- Consortia-driven:
  - Biomarker for predicting adverse events (common, and, perhaps, idiosyncratic – depends on what we learn)
  - Biomarkers in specific therapeutic areas (e.g. oncology: development of tests for pathways, etc.)
  - Markers that cut across indications ("biomarker trials")
- Individual companies/ organizations:
  - Clinical trials and Drug-Test Co-Development
    - Ideally, early use and integration of marker in drug development program
    - Coordinated effort between the development of the drug and the test, e.g. trial data will support both drug and test approval
    - Test (use of marker) required

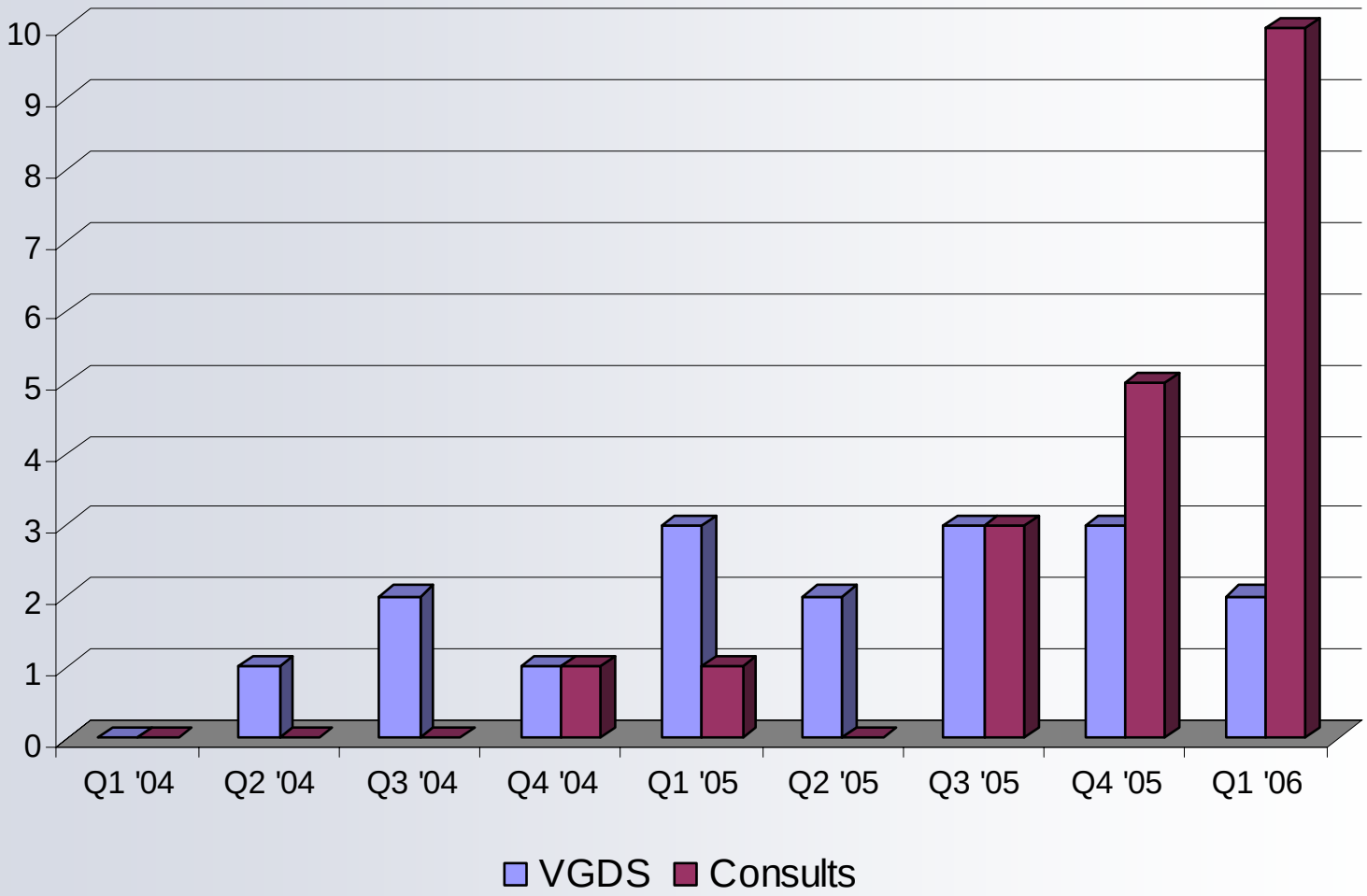
Qualification of Clinical Biomarkers: A Need for More Informative Trial Designs

- Randomized controlled clinical trial addresses bias and the impact of "random" variability – basis for many advances in modern medicine
- Qualification of clinical biomarkers is dependent on clinical trial data (ideally prospective, but to some extent also possible retrospective)
- Current clinical trial designs are limiting the extent of information that can be derived from a trial:
  - However, this trial design answers only 1 questions at a time, yet there are many questions about the appropriate use of medical products – and these questions evolve over time
    - (What if wrong question is asked? – Little flexibility)
  - Binary outcome (success or failure) is determined by p-value – limits information gain

New, More Informative Trial Designs

- Approach: Pair diagnostic with therapeutic
  - Identify responders and non-responders
  - Prevent toxicity
  - Monitor response
- Flexibility using adaptive designs
  - Answer series of questions, e.g.,
  - Which dose is correct for which sub-population?
  - Which sub-population should be treated?
- Can provide recipe to success when low efficacy overall
- Can provide important information when efficacy is compared to competitor drug: which drug to use for which group?

Indicator of Change: More Genomic Data Submitted to the FDA



Fostering Knowledge Development: Voluntary Genomic Data Submissions

- Voluntary data submissions address the need for informal interaction between sponsors and regulators to evaluate exploratory data with no immediate regulatory impact
- Program was launched two years ago to discuss exploratory pharmacogenomic data sets
- A new FDA-wide, interdisciplinary review group – IPRG – has been created to ensure high-quality review of voluntary submissions, while “shielding” voluntary from non-voluntary data
- Genomics → Proteomics, Metabolomics, … (VXDS)

VGDS Program at FDA

- **VGDS statistics:**
  - 25 submissions received
  - 17 sponsor meetings held (2 bilateral with EMEA)
- **Impact:**
  - Strategic use of VGDS meetings
  - New policy development, best practices
  - Education
  - New pathway for communication
- **Success Measures:**
  - Overall feedback: 4.5 out of 5 (formal survey)
  - Multiple (and follow-on) submissions from single sponsor

VGDS Submission Types

- **Therapeutic Areas:**
  - Cancer (multiple types)
  - Alzheimer's Disease
  - Hypertension
  - Hypoglycemia
  - Depression
  - Obesity
  - Rheumatoid Arthritis

Data based on 25 submissions

- **Scientific and PGx Areas:**
  - Biomarkers
  - Genotyping Devices
  - Microarrays
  - Analysis Software
  - Databases
  - Metabolic Pathways
  - Biostatistics
  - Enrichment design
  - Registry design
  - Toxicology

Issues Remaining (a partial list)

- Clarify regulatory aspects of drug-test co-development
- More emphasis on figuring out the right dose
- Stronger labels if diagnostics are available
- Establish clear guidance on clinical utility for tests
- Eliminate ambiguity of reimbursement (FDA – CMS)
- Educational programs
- Infrastructure development for studying AEs
- Response monitoring and prevention
- Ethical, legal, and social implications
- (I’m sure you can think of more...)

Some Parting Thoughts

- We have seen some spectacular successes using biomarkers to develop better medicines – but many questions remain to be addressed
  - It is more likely for future drug development to become more, not less, complex – the use of new, innovative approaches is needed
- New information will help us to better understand who benefits, when and why, from a specific treatment
  - We need to identify and put to use appropriate measures for translating this knowledge into clinical practice: this will allow us to move from trial-and-error to evidence-based medicine
- The FDA's mission is not only to protect the public health, but also to *advance* the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable

Personalized Medicine

A mind-bending code

A desperate race

An astonishing truth...concealed for centuries...unveiled, at last.

www.fda.gov/cder/genomics

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