Creating a Network to Study the Effect of Genomics on Clinical Outcomes: The View from FDA

Group Health Cooperative – CDC Meeting

Seattle, WA
December 14 – 15, 2005

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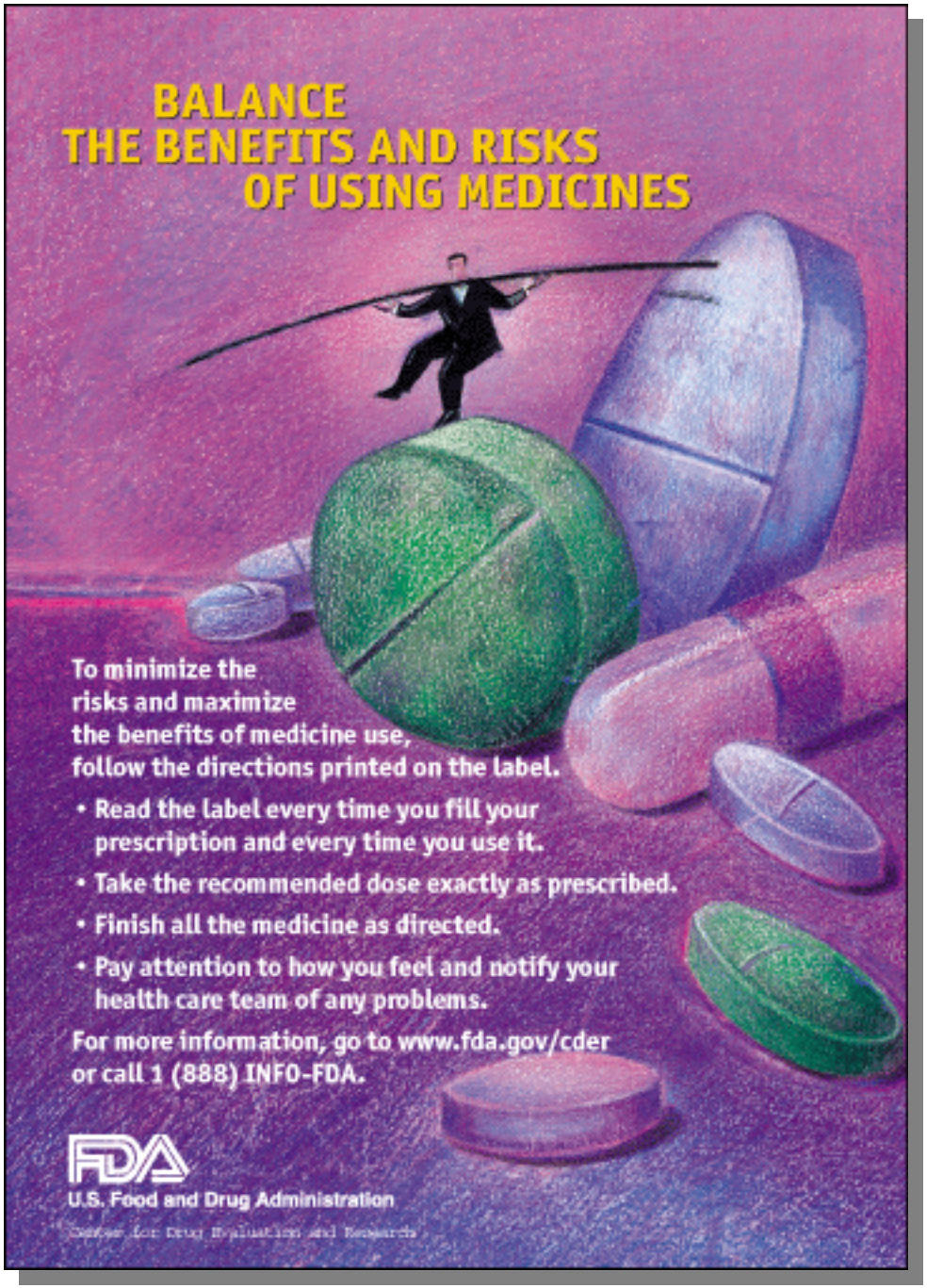
BALANCE
THE BENEFITS AND RISKS
OF USING MEDICINES
To minimize the
risks and maximize
the benefits of medicine use,
follow the directions printed on the label.
• Read the label every time you fill your prescription and every time you use it.
• Take the recommended dose exactly as prescribed.
• Finish all the medicine as directed.
• Pay attention to how you feel and notify your health care team of any problems.
For more information, go to www.fda.gov/cder
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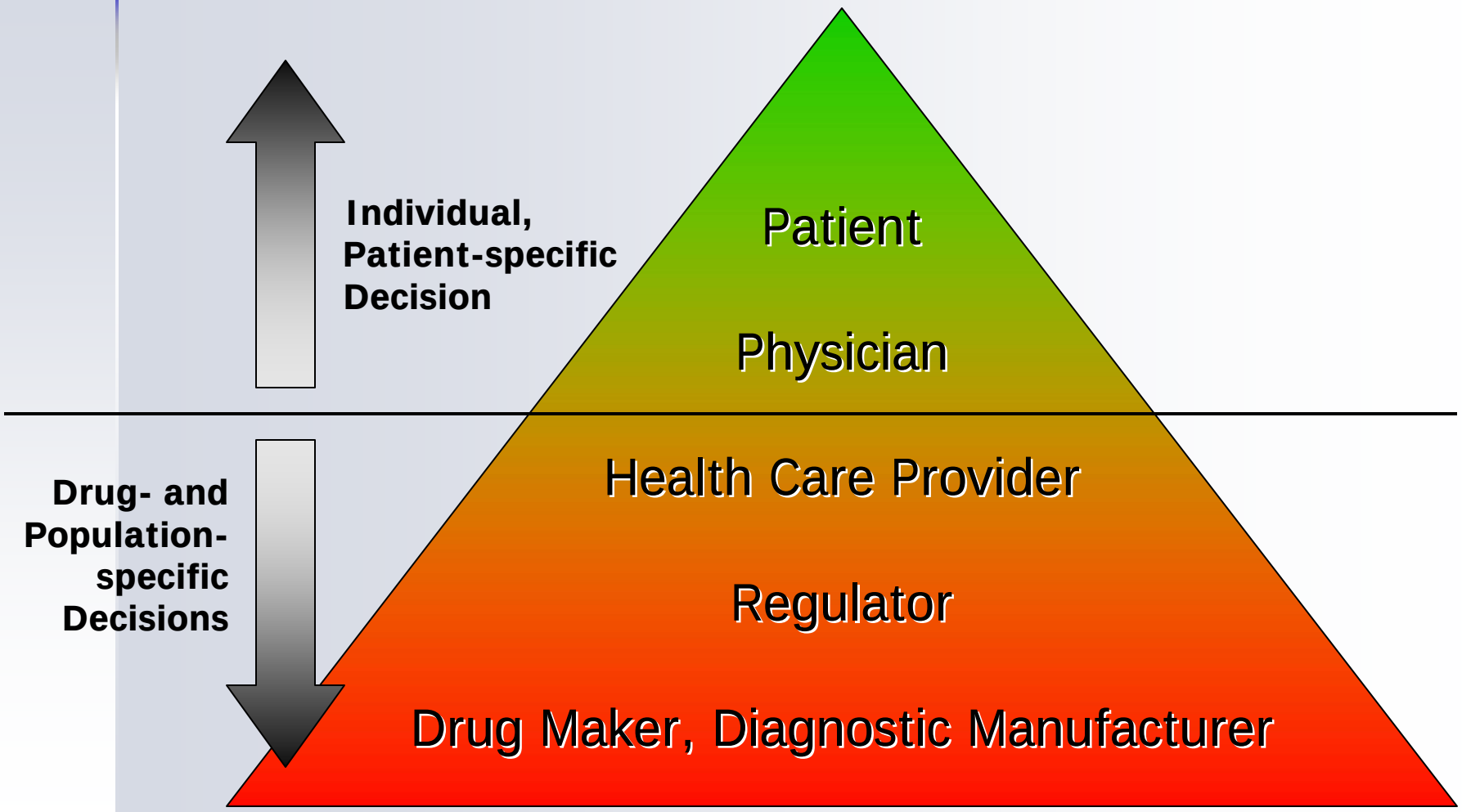
FDA
U.S. Food and Drug Administration
Center for Drug Evaluation and Research

Where to Focus: Population vs. Individual Interest



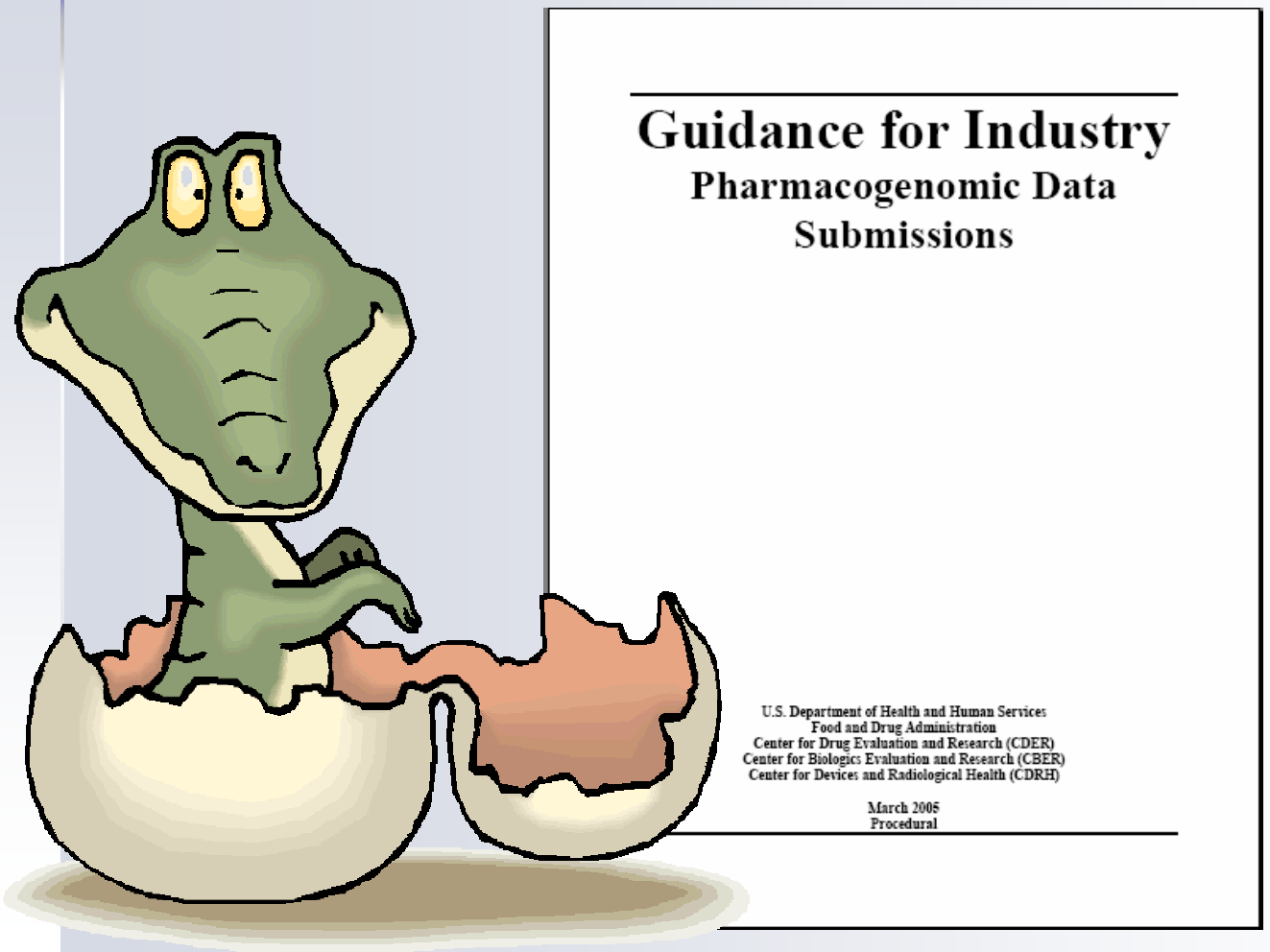
Population vs. Individual Benefit/Risk: Personalized Medicine

- For the most part, drugs have been developed and approved based on overall assessments of risks and benefits: what is wrong with this?
  - Example:
    - Drug X shows response in 45% of patients compared to placebo
    - Drug X has serious, rare adverse event (1 in 10,000)
    - Of 1,000,000 patients, only 450,000 benefit - serious adverse event is experienced by 100 patients of which 55 do not benefit
- Ability to predict the 100 patients at risk (or even more importantly the 55 who are at risk without benefit) would be useful, as would the ability to predict the 450,000 responders even if no predictor of safety were available

FDA Areas of Relevant Activities

1. Regulation of Medical Products: Guidances and concept papers: inform stakeholders about current thinking and provide guidelines
    a. Drugs: Pharmacogenomics
    b. Devices: to “measure” genomics
    c. Drugs and Devices: drug-test co-development
2. Voluntary Genomic Data Submissions
3. Research
4. Education

Guidance for Industry: Pharmacogenomic Data Submissions



March 22, 2005

What Does the PG Guidance Do?

- Clarifies what type of genomic data needs to be submitted to the FDA and when
- Introduces a classification for genomic biomarkers
- Introduces a new data submission pathway to share information with the FDA on a voluntary basis
- Encourages the voluntary submission of exploratory genomic data
- Introduces new agency-wide PG review group (IPRG)
- Clarifies how the FDA will review genomic data submissions

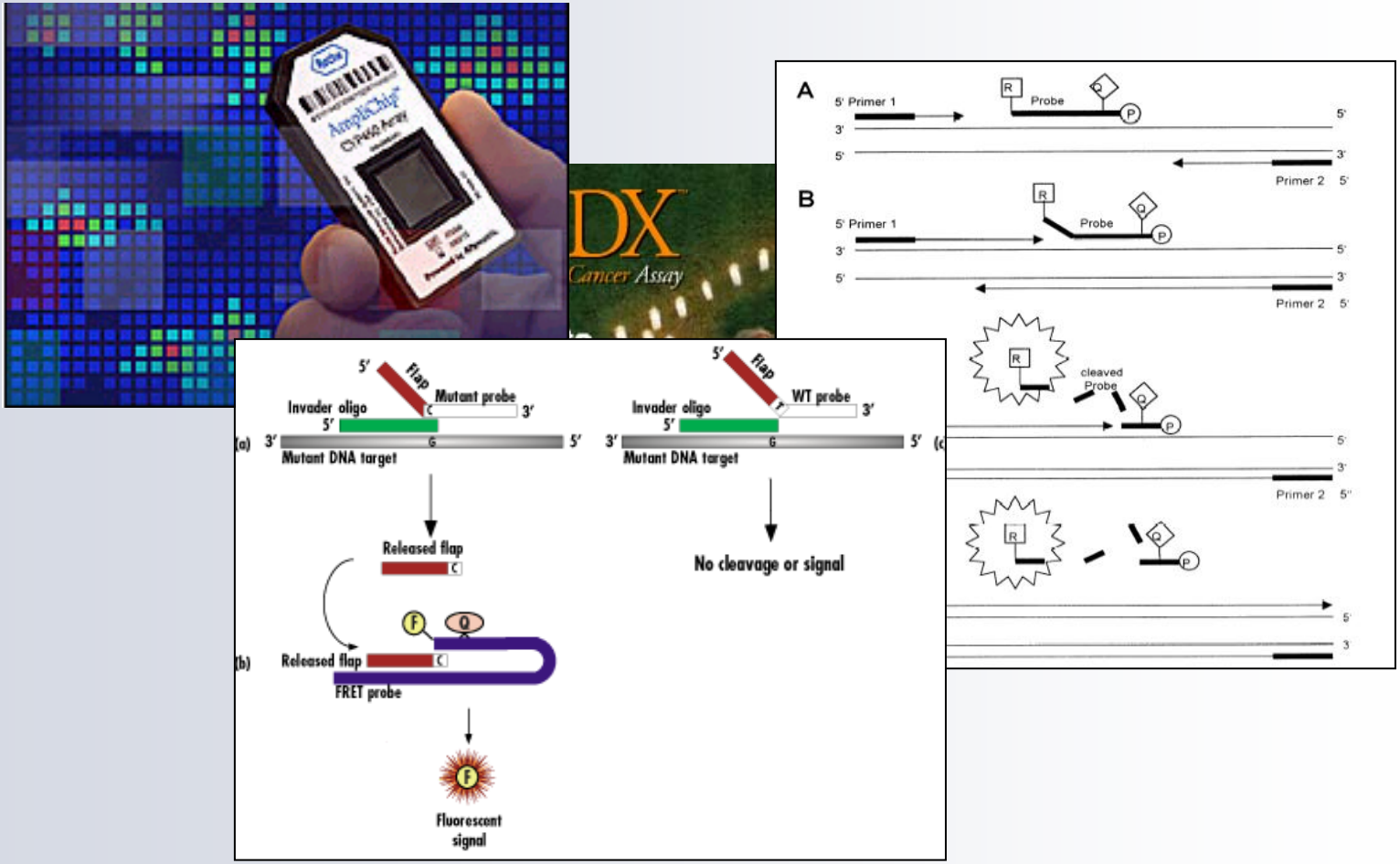
What Does the PG Guidance *Not* Do?

- Does not equal genomic data with voluntary data
- Does not provide information on how to validate genomic biomarkers
- Does not provide information on how to use genomic biomarker during drug or device development process (scientific vs. regulatory guidance)
- Does not expand into other "-omics' areas such as proteomics or metabolomics
- Does not create new processes for the review of required data submissions

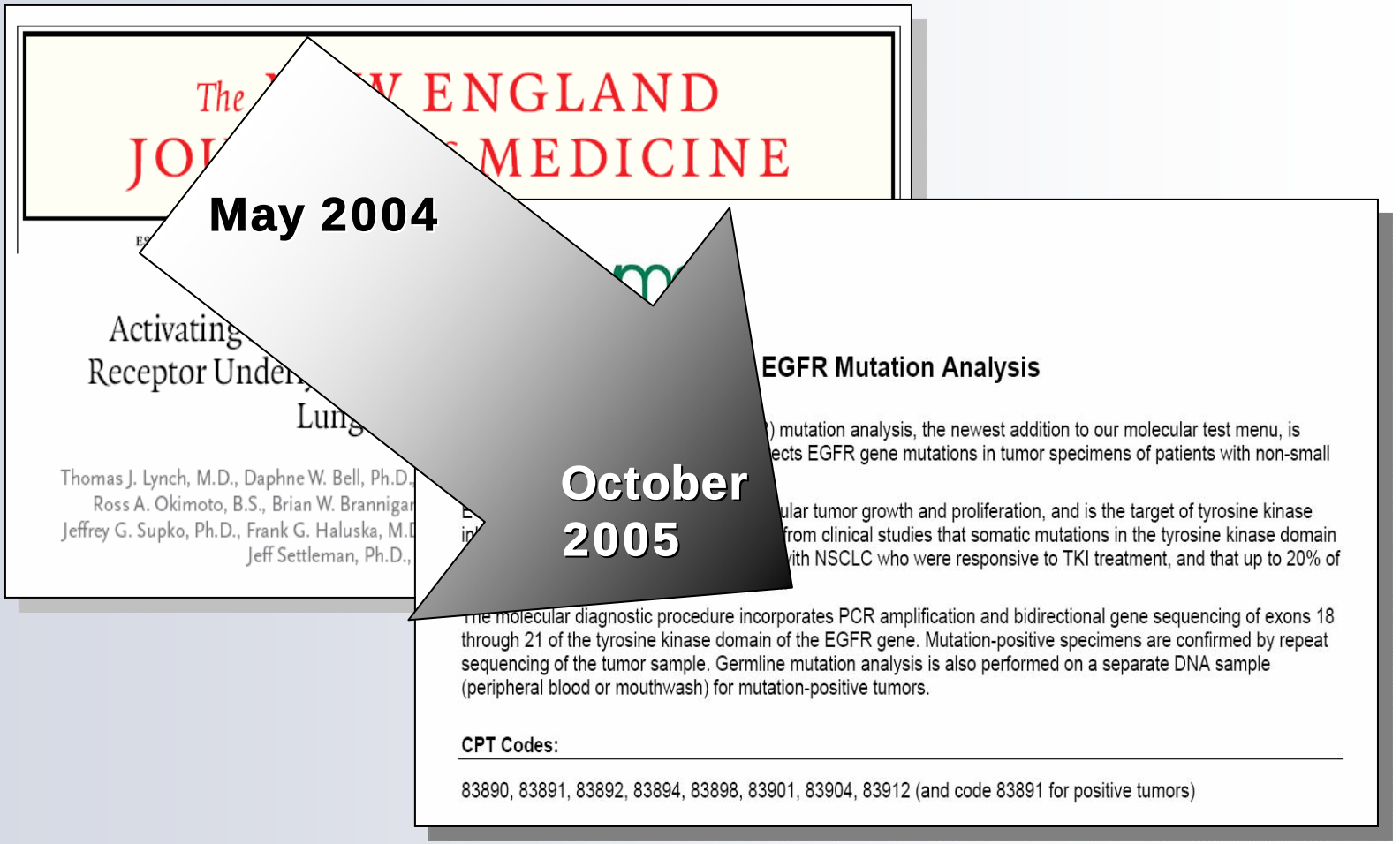
Opportunity !

- Network could conduct clinical trials for genomics-based, new drugs.
- Could address critical issues, e.g. diverse populations, statistics (large studies), ...
- Study of orphan drugs (small number of cases in single location)
- Integrated databases: more efficient mining options, coherent data sets → disease models
- Share information with FDA through VGDS process

Tools to Identify Genetic Variations



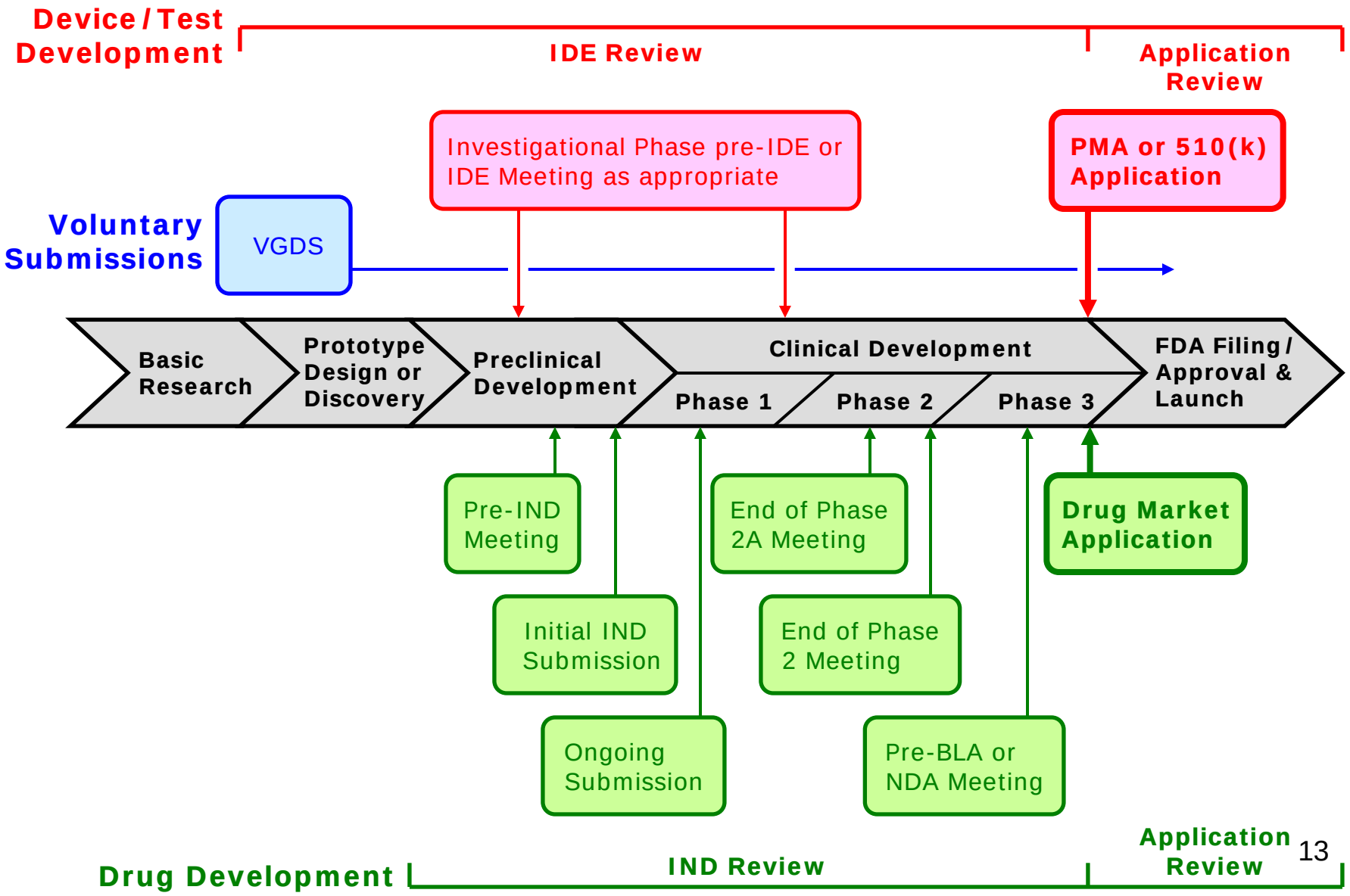
Advances in Science



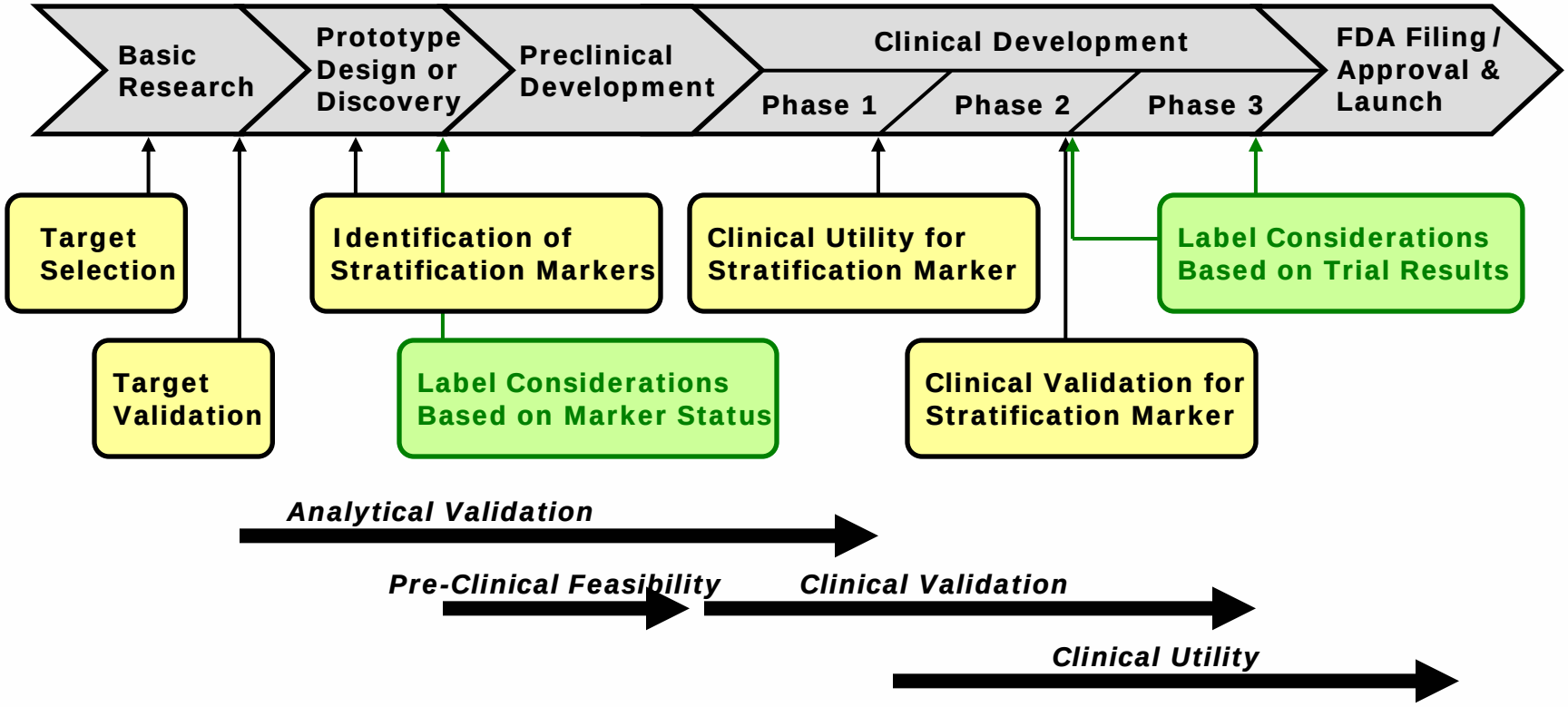
Opportunity !

- Analytical and clinical validation for new genomic tests
- Work with stakeholders:
  - Patients, clinicians
  - Tool developers, industry
  - Patient advocacy groups
- Evaluate risk – benefit profile for test
- Evaluate pharmacoeconomic impact
- Become “early-adaptor”

Drug-Test Co-Development Process:



Drug-Test Co-Development Process:



Drug-Test Co-developed Products: Issues

- Strategy (use during drug development only)
- Competitive advantage (i.e. ID responders)
- Timing (development, approval)
- Cost (development, reimbursement)
- Availability of alternative therapy (what if none?)
- Platform (platform change)
- Complexity (point-of-care vs. service laboratories)
- *Clinical usefulness* (i.e. therapeutic area, marketability)

Opportunity !

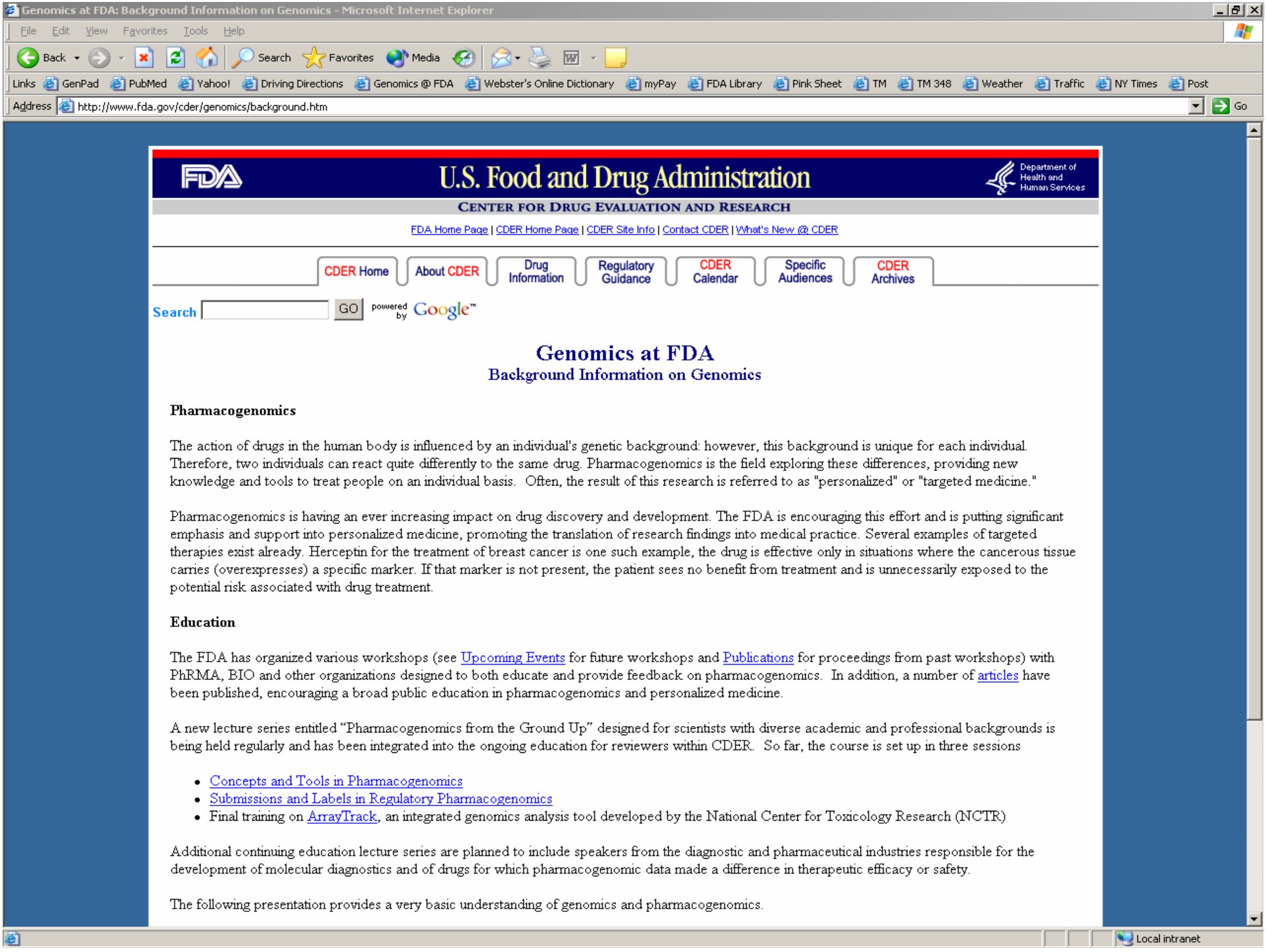
- Provide optimized setting for conduct of complex pharmacogenomic studies
- Real-life setting for clinical trials ~ optimal setting for evaluating clinical utility
- Evaluate risk – benefit profile for test
- Evaluate pharmacoeconomic impact
- Identify and determine impact of confounding factors ~ continued optimization of therapy
- Become “early-adaptor”

Education

- Internal Education:
  - Pharmacogenomics 101, three parts
  - VGDS, briefings
  - Seminars, lectures, ...
- External Education:
  - Publications, workshops
  - Website (www.fda.gov/cder/genomics)
  - Online course (in development)

Online Course: Personalized Medicine – From Theory to Practice

- Co-developed with American Medical Association
- CME credits
- Sponsored by Roche via unrestricted educational funding
- Background information on, e.g.:
  - Genetics, human genome
  - Concepts and tools in pharmacogenomics
  - Drug metabolism
  - Clinical examples, drug labels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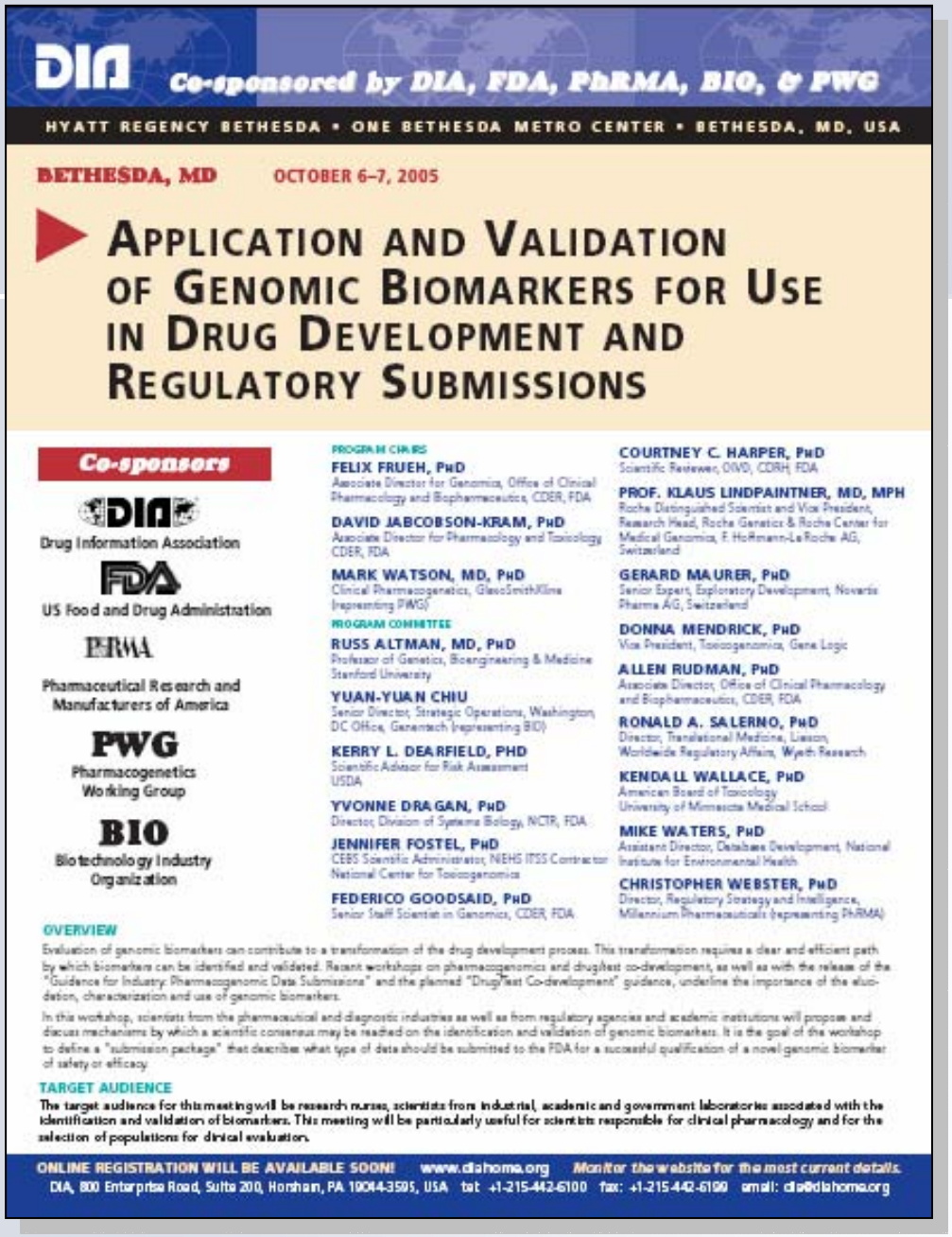
Background Information on Genomics
Pharmacogenomics
The action of drugs in the human body is influenced by an individual's genetic background: however, this background is unique for each individual. Therefore, two individuals can react quite differently to the same drug. Pharmacogenomics is the field exploring these differences, providing new knowledge and tools to treat people on an individual basis. Often, the result of this research is referred to as "personalized" or "targeted medicine."
Pharmacogenomics is having an ever increasing impact on drug discovery and development. The FDA is encouraging this effort and is putting significant emphasis and support into personalized medicine, promoting the translation of research findings into medical practice. Several examples of targeted therapies exist already. Herceptin for the treatment of breast cancer is one such example, the drug is effective only in situations where the cancerous tissue carries (overexpresses) a specific marker. If that marker is not present, the patient sees no benefit from treatment and is unnecessarily exposed to the potential risk associated with drug treatment.
Education
The FDA has organized various workshops (see Upcoming Events for future workshops and Publications for proceedings from past workshops) with PhRMA, BIO and other organizations designed to both educate and provide feedback on pharmacogenomics. In addition, a number of articles have been published, encouraging a broad public education in pharmacogenomics and personalized medicine.
A new lecture series entitled "Pharmacogenomics from the Ground Up" designed for scientists with diverse academic and professional backgrounds is being held regularly and has been integrated into the ongoing education for reviewers within CDER. So far, the course is set up in three sessions
Concepts and Tools in Pharmacogenomics
Submissions and Labels in Regulatory Pharmacogenomics
Final training on ArrayTrack, an integrated genomics analysis tool developed by the National Center for Toxicology Research (NCTR)
Additional continuing education lecture series are planned to include speakers from the diagnostic and pharmaceutical industries responsible for the development of molecular diagnostics and of drugs for which pharmacogenomic data made a difference in therapeutic efficacy or safety.
The following presentation provides a very basic understanding of genomics and pharmacogenomics.
Local intranet


DIA
Co-sponsored by DIA, FDA, PhRMA, BIO, & PWG
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OCTOBER 6–7, 2005
APPLICATION AND VALIDATION OF GENOMIC BIOMARKERS FOR USE IN DRUG DEVELOPMENT AND REGULATORY SUBMISSIONS
Co-sponsors
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US Food and Drug Administration
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PWG
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OVERVIEW
Evaluation of genomic biomarkers can contribute to a transformation of the drug development process. This transformation requires a clear and efficient path by which biomarkers can be identified and validated. Recent workshops on pharmacogenomics and drug/test co-development, as well as with the release of the "Guidance for Industry: Pharmacogenomic Data Submissions" and the planned "Drug/Test Co-development" guidance, underline the importance of the elucidation, characterization and use of genomic biomarkers.
In this workshop, scientists from the pharmaceutical and diagnostic industries as well as from regulatory agencies and academic institutions will propose and discuss mechanisms by which a scientific consensus may be reached on the identification and validation of genomic biomarkers. It is the goal of the workshop to define a "submission package" that describes what type of data should be submitted to the FDA for a successful qualification of a novel genomic biomarker of safety or efficacy.
TARGET AUDIENCE
The target audience for this meeting will be research nurses, scientists from industrial, academic and government laboratories associated with the identification and validation of biomarkers. This meeting will be particularly useful for scientists responsible for clinical pharmacology and for the selection of populations for clinical evaluation.
ONLINE REGISTRATION WILL BE AVAILABLE SOON! www.diahome.org Monitor the website for the most current details.
DIA, 800 Enterprise Road, Suite 200, Horsham, PA 19044-3595, USA tel: +1-215-442-6100 fax: +1-215-442-6199 email: dia@diahome.org

Workshop on Genomic Biomarker Validation: Call To Action

- Issue: Increasing complexity of biomarkers
  - DME → Molecular Targets → Tissue Injury Model → Pattern Recognition
  - Ideally: combine multiple markers
- New guidances
  1. Drug-Test Co-development
  2. Statistical Considerations
  3. Biomarker Qualification
- List of genomic biomarkers on website

Workshop on Genomic Biomarker Validation: Call To Action (cont'd)

- Need for consortia:
  - Validation of biomarkers is too complex for individual entity to perform, requires cross-validation
- Biomarker performance is about risk management:
  - quantitative risk models
  - decision making
  - redefining disease

Opportunity !

- Network could provide guidelines, manuals for use of genomic test in clinical practice, publish “Best Practices”
- Educate physicians and patients about benefit and risk of genetic testing
- Biomarkers:
  - Electronic records → retrospective data mining →
  - Test and validate new biomarkers
  - Explore new trial designs (stratification, enrichment, adaptive designs)
  - Low-hanging fruit: e.g. EGFR mutations and Iressa ~ large study needed to (prospectively) confirm importance of mutations

Re-Labeling of Drugs Based on New Genetic Knowledge

- Azathioprine, 6-MP
  - TPMT
  - Avoid toxicity, testing recommended
- Irinotecan
  - UGT1A1
  - Avoid toxicity, testing recommended
- Warfarin
  - CYP2C9, VKORC1
  - Avoid toxicity, ensure efficacy

Example: Warfarin

- Anticoagulant ~ one of the most often prescribed drugs in U.S. and worldwide
- Problem:
  - Inter-individual variability in dose requirement
  - Major risk is bleeding: frequent and severe
  - 10-24 bleeding episodes per 100 patients
- Some of the variability in dose requirement can be attributed to genetic variations in CYP2C9 (metabolism, PK) and VKORC1 (mode of action, PD)
- Relabeling recommended in 8:2 vote at CPSC advisory committee meeting (Nov. 14, 2005)

Entry into Model	Variable	Coefficient	Effect on Warfarin Dose	R^2 after entry
1	Caucasian * VKOR6853	-0.319	-27% (–25% to –30%)	22%
2	BSA, per 0.25 m2	0.454	12% (10% to 14%)	32%
3	2C9*3	-0.408	-33% (–29% to –38%)	39%
4	2C9*2	-0.218	-20% (–16% to –23%)	43%
5	Age, per decade	-0.007	-7% (–6% to –9%)	47%
6	African American * VKOR5808	-0.395	-33% (–19% to –44%)	48%
7	Target INR, per 0.5 increase	0.161	8% (5% to 12%)	49%
8	Amiodarone	-0.277	-24% (–15% to –32%)	51%
9	African American	-0.126	-12% (–1% to –17%)	51%
10	Smokes	0.085	9% (2% to 16%)	52%
11	Simvastatin or fluvastatin	-0.053	-5% (0 to –10%)	52%

Opportunity !

- Provides access to large number of patients ~ necessary to conduct statistically meaningful studies
- Collect patient data in a coherent and coordinated fashion ~ data formats, standardization
- Disease modeling → develop dosing algorithm
- Test feasibility for genotyping in clinical setting
- Evaluate pharmaco-economic impact

- Benefits patients, clinicians ~ but also any other stakeholders

www.fda.gov/cder/genomics

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