Pharmacogenomics: New Directions in Regulatory Strategies

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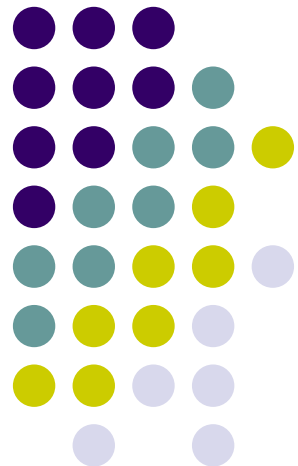
CAPRA Symposium
November 21, 2006



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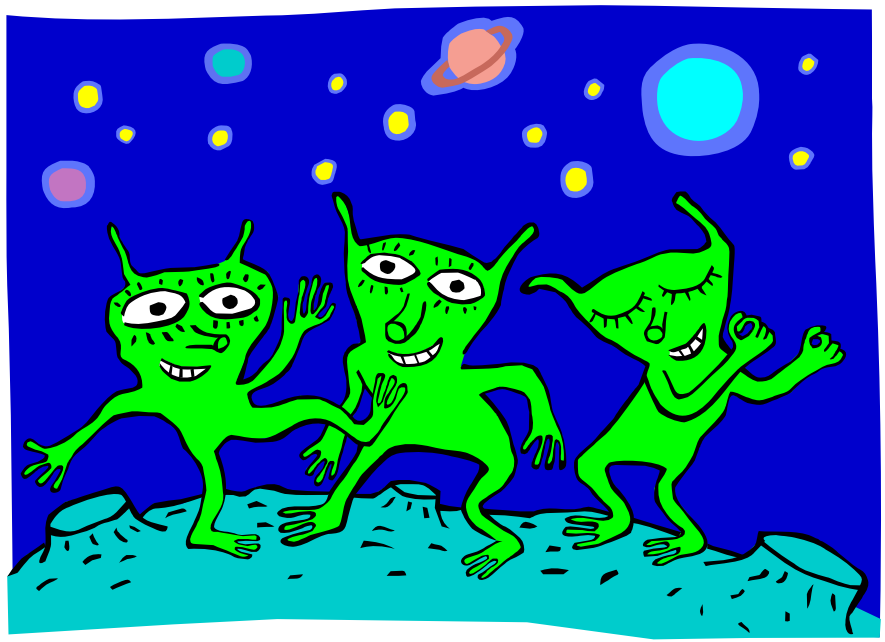
Today's Talk

- Why Personalized Medicines ?
  - Pharmacogenomics and Biomarkers
- Where are we now ?
  - How biomarkers are being used.
- Moving Forward Around the World
  - Update on FDA Guidance
  - Update on Regulatory Guidance in the EU, and Canada
  - PG initiatives in ICH

Think Ahead…to medicines of the future



- Recent headline in the New York Times:

  “Blockbuster drugs are so last century”

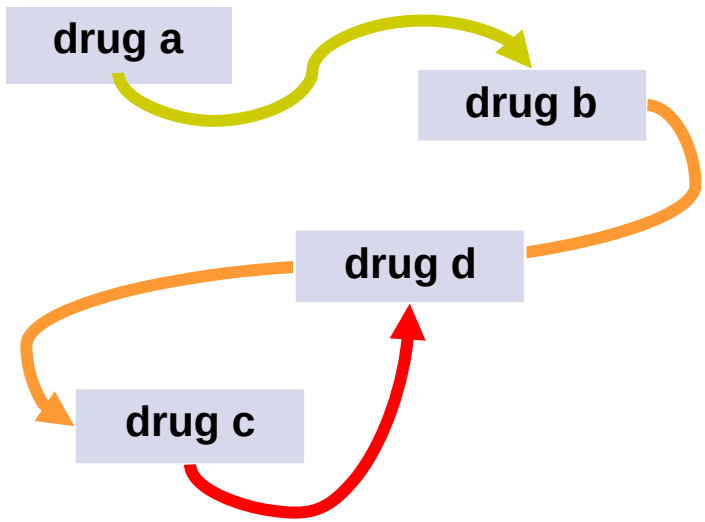
Standard versus Targeted Therapies

Today

empirical prescription

"mass market"

trial & switch



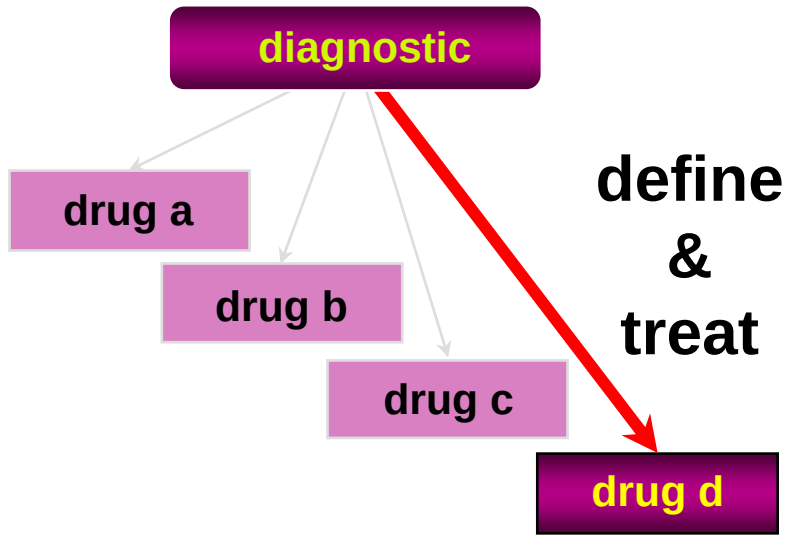
individual physician experience

Cost: time, money & well-being

Future

rational prescription

"differentiated"



define & treat

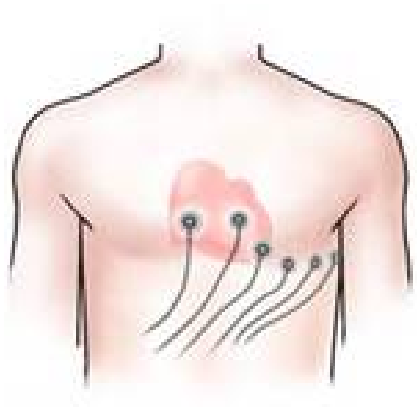
informed physician diagnosis

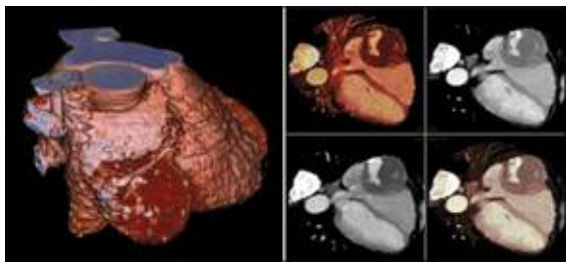
Savings: time, money & illness

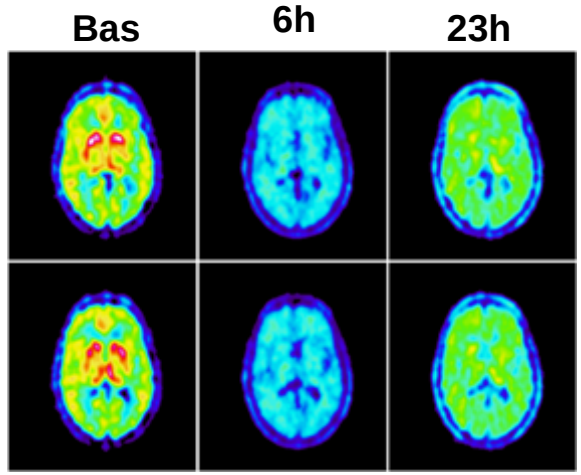
A Critical Tool for Personalized Medicine – Identify a Biomarker

Biomarker: Broad definition

- The broad definition includes all diagnostic tests, imaging technologies and any other objective measure of a person's health status and all pharmacodiagnostic tests

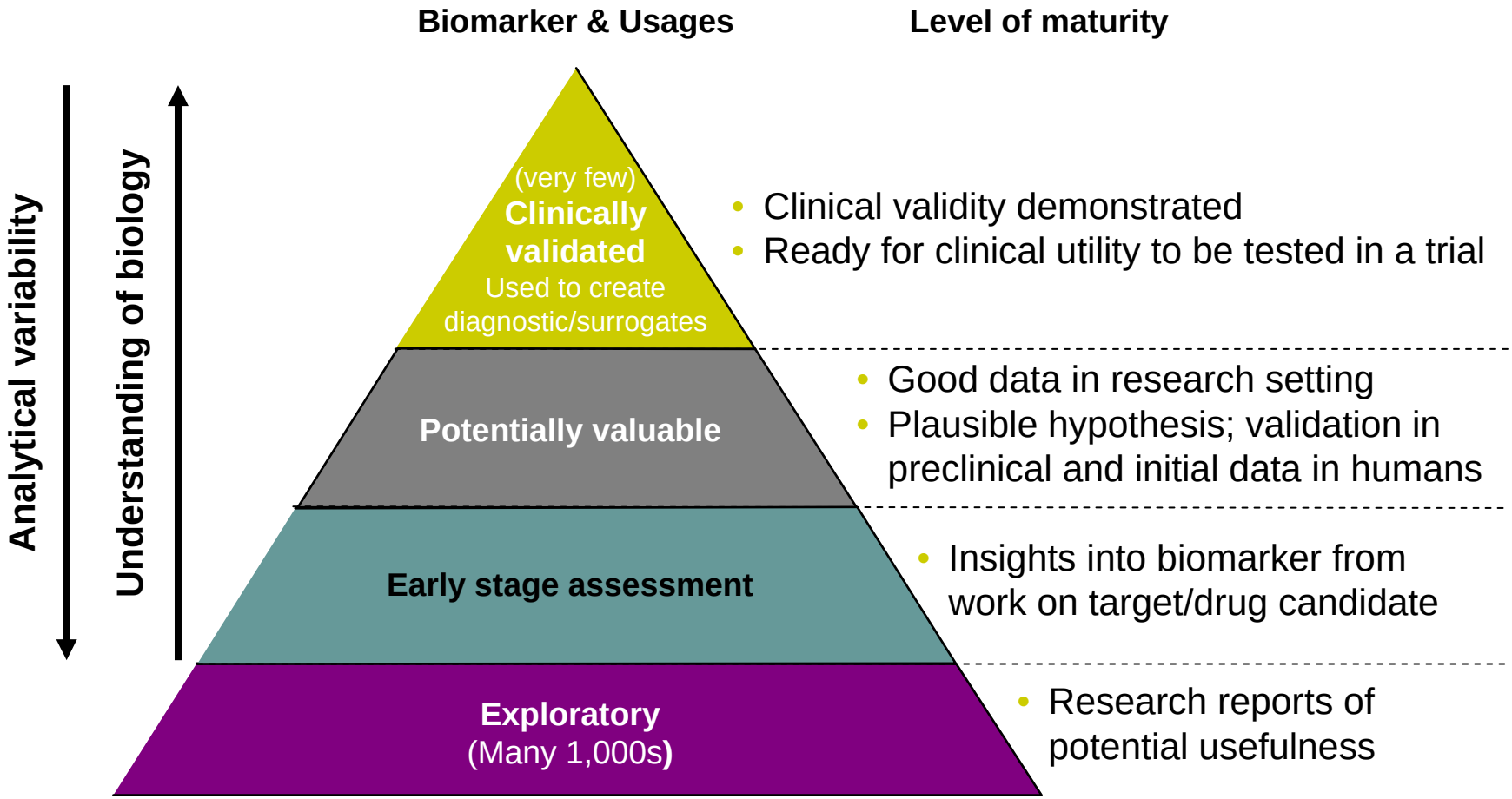






Biomarkers similar to drug candidates

Both have to be evaluated for their usefulness



The Pharmacogenomic Proposition

Safety
‘Pgx for Individual’

Increased risk of serious adverse event

No increased risk of serious adverse event

Efficacy
‘Pgx for Group’

Predict increased response

Predict reduced response

Using genes to predict response to medicines

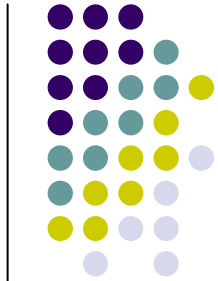
Need DNA + Relevant Clinical Data

Pharmacogenomics (PGx) and Pharmacogenetics (PGt)

New ICH Definitions (Step 2 Guidance)

- **PGx: Investigation of variations in DNA and RNA characteristics as related to drug response.**
- **PGt: A subset of PGx and defined as the influence of variation in DNA sequence on drug response**
  - **PGt and PGx are applicable to activities in drug discovery, development and clinical practice.**
  - **Drug response includes drug disposition (PK) and drug effects (PD)**
- **Measured by changes in a genomic biomarker**

Genomic Biomarkers



- A measurable DNA or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes, and or response to therapeutic of other intervention
- A genomic biomarker
  - could reflect expression, function or regulation of a gene
  - may consist of one or more DNA or RNA characteristic
  - is not limited to human samples

Incorporating These Exploratory Strategies into Early Clinical Development is Complex

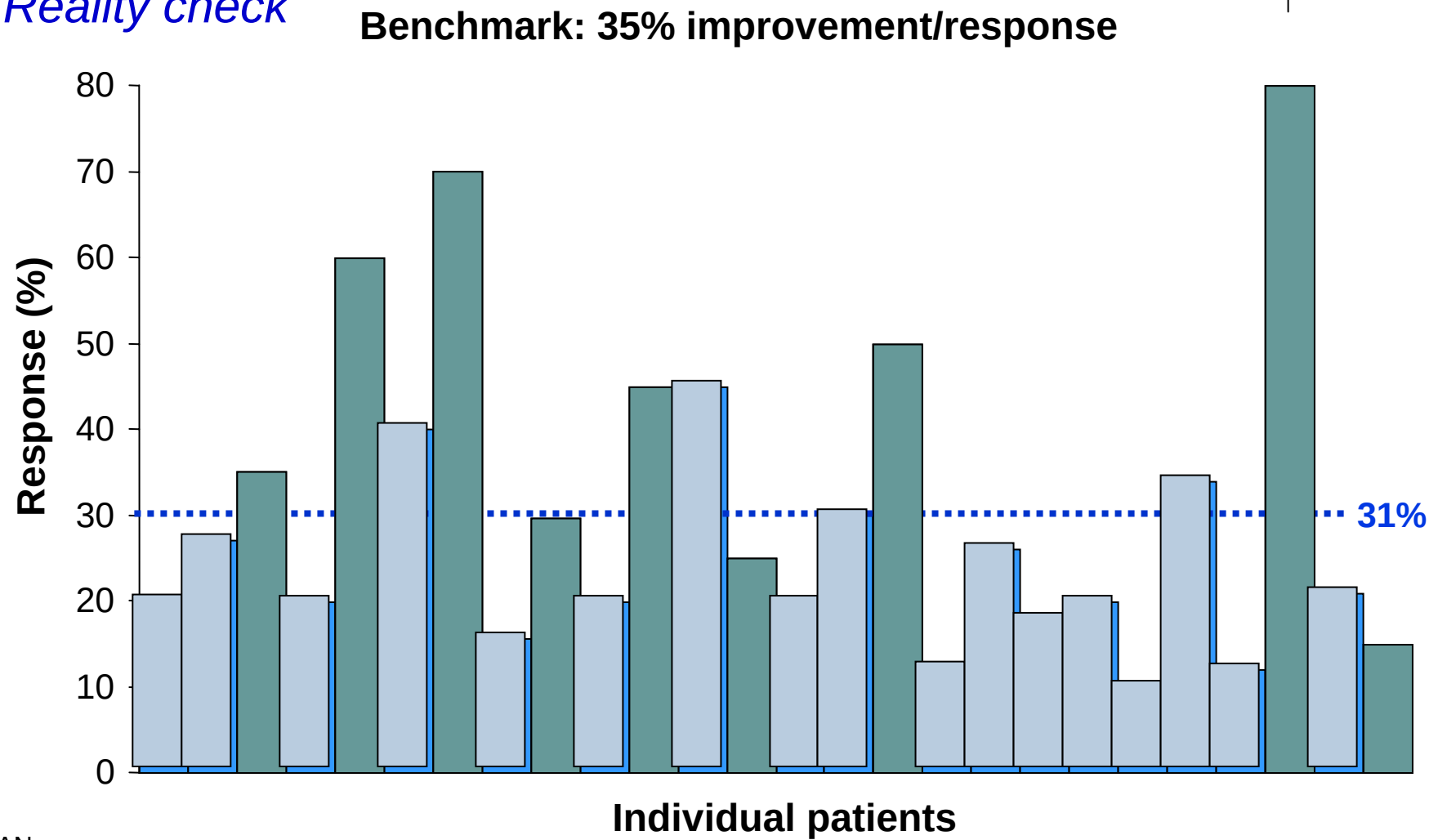
- Ethical Issues on Sample Collection and Coding
  - How are samples coded or anonymized?
  - Who should have access to the genetic information?
- General Considerations for Regulators:
  - How to provide a pathway for the identification of genomic biomarkers in a timely manner?
  - How to smoothly integrate the identification and validation of markers into the drug development process?

Drug Developers and Regulators See a Pipeline Problem

- Major Drug and biologic submissions to FDA are declining
- Biomedical research spending is on the increase.
- PG and Biomarker Strategies are important component- allows predictive approach to treatment, a new paradigm.
- Allow for selecting of the right patient population and the right drug
- How will PG help?

“Responders” and “Non-Responders”

Reality check



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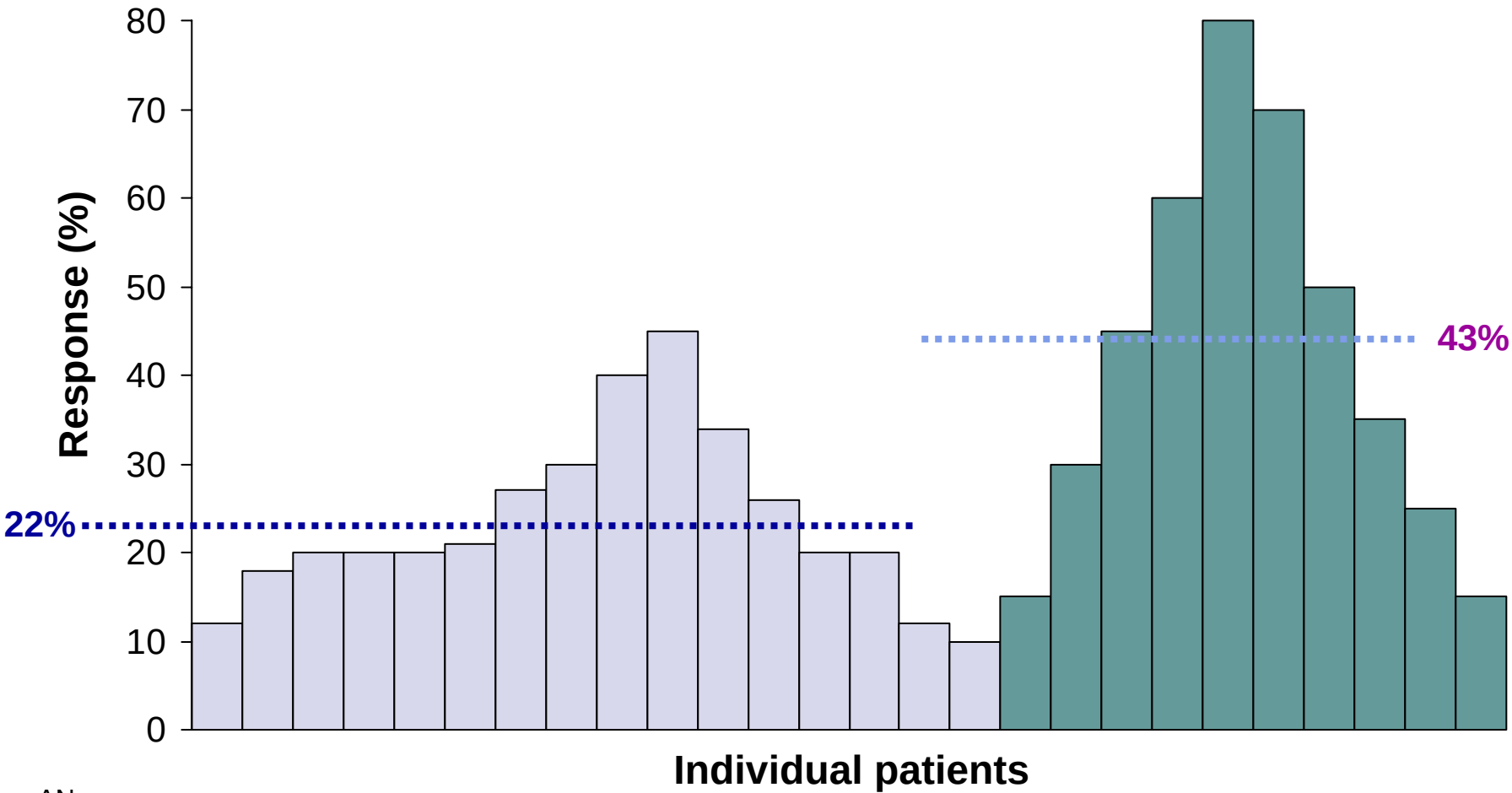
“Responders” and “Non-Responders”

Reality check

Benchmark: 35% improvement/response



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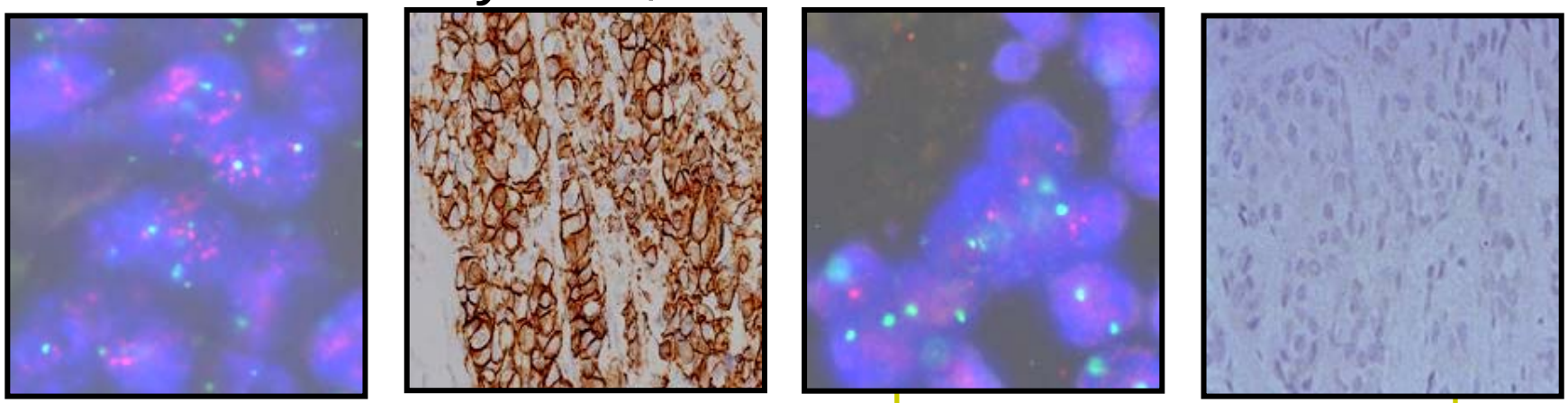
Can the Use of a PGx Marker Improve Response or Safety ?

- Two key areas where progress has been made:
  - Oncology
    - an acceptance of biomarkers and their correlation with response
  - Safety – CYP 450 Isozyme Status
    - differences in drug metabolism can be linked to sensitivity to certain drug and response
    - common safety concerns (i.e. liver tox)

In Oncology, Herceptin® is a lead example of Biomarker-driven therapy

Eligibility for Herceptin® therapy - HER2 status

- Determined by IHC, FISH or CISH

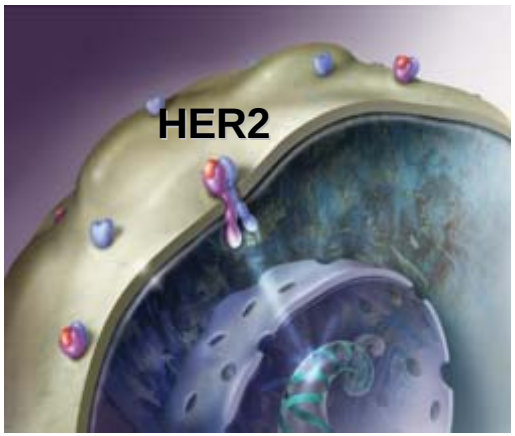


Eligible for Herceptin®

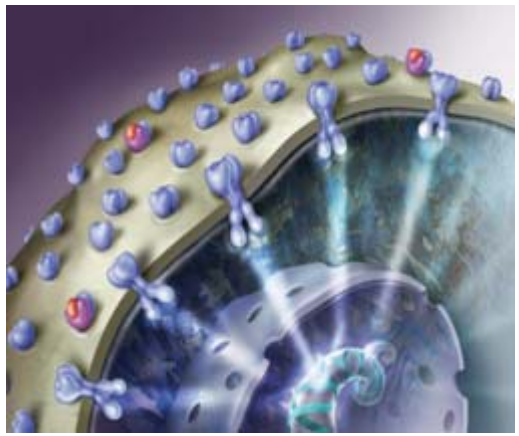
NO BENEFIT from Herceptin®

HER2 as a target – a strong rationale

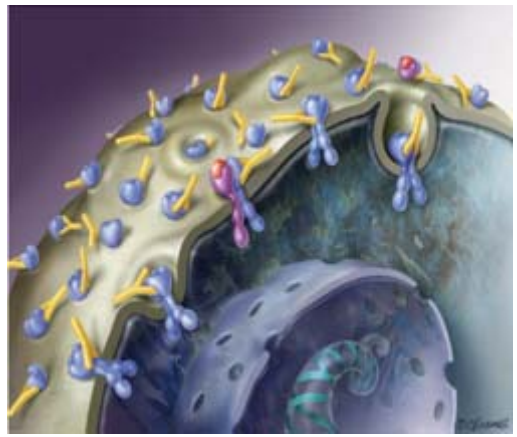
Normal cell



Tumor cell



Tumor cell +



Key Messages:

- Strong over-expression of HER2 is observed in 20-25 % breast cancer
- Clinical development focused on patients with HER2 over-expression, patients with HER2 IHC 3+ (test scoring) had greatest clinical benefit

Key Learnings:

- Herceptin would not have reached market without patient stratification in phase II, III
- Herceptin becomes a blockbuster, though only 25% of breast cancer patients are treated

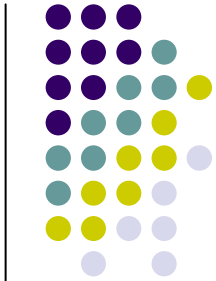
Current thoughts on PG in safety

- Targeting patients based on genetic make-up
  - An improved approach to drug safety
  - Test in advance to assess who should and should not be taking a drug
  - Recent example:
    - revision of Tamoxifen® label to recommend Cytochrome P450 2D6 testing prior to treatment for adjuvant breast cancer
      - increased risk of BC recurrence in poor 2D6 metabolizers
- Safety biomarkers a topic for a number of Industry/Academic/FDA Consortia being established.

The Regulatory Dilemma: How fast to move forward with Guidance?

- FDA is marching forward with guidance
  - Genomic Data Submission
    - Draft Guidance (VGDS): Nov. 03
      - docket comments received from many companies
    - Final Guidance (GDS): March 05
  - Concept Paper on RxDx Co-development
    - Issued: April 05
    - Discussed at PG Workshop in April 05
  - CDRH Guidances (DME Genotyping System & Mutiplex Tests for Heritable DNA markers)

FDA: Genomics Data Submission Guidance



- Guidance and Manual of Policies and Procedure (MAPP)- issued Mar05.
  - when to submit PG data to Agency
  - format and content of submissions
  - how and when this information will be used in regulatory decision making
  - examples of when submission is voluntary and when it is required.

GDS Guidance makes distinctions among a number of key points:

- PG data being used for “regulatory decision making” vs. PG data that are “exploratory or researched based” in nature.
- definitions of known valid biomarkers, probable valid biomarkers, exploratory research PG data.
  - these definitions plus role of PG in development impact the level of data submission expected.
- For early projects a “Voluntary GDS” is encouraged

A Novel Data Submission Path: VGDS

- Submission of exploratory PG data irrespective of an active IND, NDA, or BLA
- Data may result from evolving methodologies e.g.:
  - DNA microarrays
  - gene expression profiles
  - genotyping or SNP profiling
- Provides FDA access to emerging PG data so that a foundation can be built for developing scientifically sound regulatory policies
- The VGDS process provides a forum for scientific discussions with the FDA outside of the application review process.

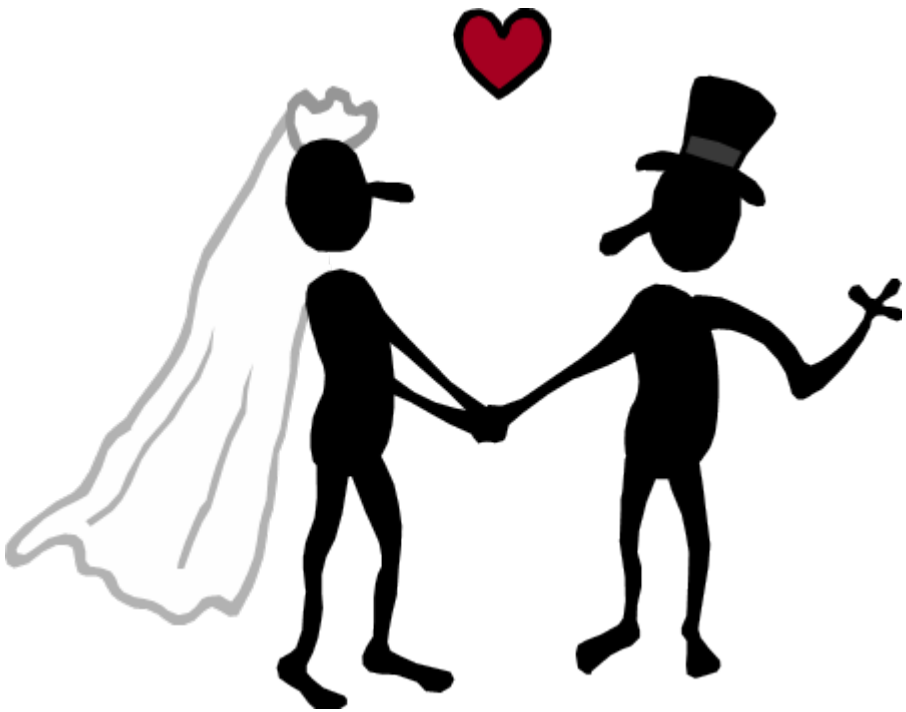
Incentives to Submit a VGDS (from Felix Frueh, FDA)

- Provides an opportunity for an informal meeting with FDA PG experts
  - Receive and benefit (?) from informal peer review of PG issues and/or questions
  - Gain insight into current FDA thinking on PG issues
  - Familiarize FDA with the company's PG experiments and approaches, with minimal regulatory impact
  - Pave the way for developing protocols and more binding discussions.

How is the VGDS Process Working?

- FDA Workshop (27Nov06) on the Genomic Data Submission Process.
  - Speakers from FDA and Industry to share experiences.
  - Address format for data submissions
- Some joint genomic advice meetings have been held with FDA and EMEA
  - Seen as quite successful in providing global input

Pharmacogenomics can lead to Personalized Medicines



But…..

- Building a partnership of a therapeutic and a test is essential
- it needs nurturing
- It takes time and lots of support

RxDx Partner Products- ideal for the future

RxDx Co-development

- FDA has issued a draft concept paper on drug/PG test co-development.
  - The idea is interesting, but there are many outstanding questions on how this would work.
- The concept paper focuses on a development plan where drug and Dx will be developed and approved simultaneously.
- How realistic is this as a development scenario ??

Many Questions: the RxDx Co-development Concept

- Rx and Dx development have very different timelines (basic flaw in the concept)
- The review mechanism is not clear
  - Cross-labeling considerations are not clear
- How does advice under VGDS get transferred to this more committed development pathway.
- High approval hurdles for IVD's
- How to globalize?

Status of RxDx Co-Development

- The draft concept paper comment period has recently closed.
  - PhRMA and a number of companies have commented.
- FDA is now preparing a draft guidance.
  - Expect it will be “quite different”
  - More focus on the clinical expectations than diagnostic test validation

Moving Forward in Europe

- **EMEA – Collaborative Approach with Academics and Industry**
  - Let the science lead
- **EMEA Guidance-set up CHMP PG Working Party (17Feb05)**
  - Makes recommendations to the CHMP on matters relating to PG
  - 50% academic/50% regulators
  - Hosts workshops, and review guidances, interface with EFPIA, coordinates PG Briefing Meetings
- **Guidelines on PG Briefing Meetings (27April06) prepared**
  - Similar approach to VGDS, informal, non-binding, science-based discussion.
  - Joint meetings with FDA encouraged.

Other EU PG Guidance Documents

- The Pharmacogenomics Working Party release a brief concept paper (June 06) stating their plan to develop a reflection paper of PG data evaluation in oncology.
- A draft reflection paper has been prepared on the use of PG in PK evaluation of medicinal products.

Heath Canada – Guidance Document: Submission of PGx Information

- Draft Guidance released for 60 day review period, March 15, 2006.
  - Industry comments received from both drug and diagnostic companies
  - Final Guidance is in preparation

- Guidance applies to human drug clinical trial submissions, clinical trial and medical device applications that use PGx information.

HC PGx Guidance Document provides Sponsors / MAHs with

- guidance on submission of pharmacogenomic information
  - for Clinical Trial Applications
  - for NDS, SNDS or ANDS with PGx Tests including labeling considerations
- guidance on pre-application or pre-submission consultation meetings
- advice on post-market PGx considerations

International Conference on Harmonization (ICH)

- **Expert Working Group on PG**
  - E15 guidance “Harmonization of PG Terminology”
    - Harmonize definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, and descriptions of data and sample coding categories
    - Team members from FDA, EMEA, MHLW, PhRMA, EFPIA & JPMA plus Canada and Switzerland
  - Step 2 guideline approved by steering committee (10/06) to be released for public comment by end of 2006.
- **Next Steps for ICH group** –
  - Identify additional areas for harmonization

How to Influence in this Field: Examples of PG Interest Groups

- **International**
  - OECD
  - CIOMS
  - International Society of Pharmacogenomics (ISP)
  - Pharmacogenomics Working Group (PWG)
- **United States**
  - NIH
  - American Society of Human Genetics (ASHG)
  - Personalized Medicine Coalition (PMC)
  - BIO
- **Europe**
  - European Commission Directorates
  - European Society of Human Genetics (ESHG)
  - European Scientific Networks on Genetics
  - Working Party of Patient's Organizations
  - Europa BIO
- **Japan**
  - Japanese Society of Clinical Pharmacology
  - Japan Health Sciences Foundation

Moving Forward – What's Next?

- Health Authorities are partnering with Industry on PG-driven development
  - listening to our comments
  - organizing meetings, considering guidance
  - consortia being established to address common challenges – targets and approaches
- PG represents an excellent opportunity for industry/HA partnership
- Promise of "The Right Therapy for Each Individual" has universal appeal.

Thank You

Happy to answer questions