# Pharmacogenomics: Patient Selection for Clinical Trial Participation & Enrichment Strategies

**Accelerating Anticancer Agent Development and Validation Workshop**

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# What I want to talk about:

- The fact that people differ in their risk and response to drugs,
  - Which provides an opportunity:
    - To better target therapy and
    - To utilize more efficient study designs in enriched populations.

- Objective:
    - To provide an overview of concepts and strategies, illustrate with examples, but
    - Not to provide details, e.g. statistics, etc.

# Patient Stratification, Enrichment – Why ?

- Goal: selecting patients more likely to respond (demonstration of efficacy) for a clinical trial
  - This is by no means a new idea: inclusion/exclusion criteria for clinical trials have always existed and can include patient characteristics that are believed to “enrich” the trial population towards a “responding sub-population” (e.g. age, disease state, etc.)
- Goal: exclude patients at risk (“risk stratification”)
  - Probably more difficult – often risk factors are not known in early trials

# Enrichment

- Enrichment is the prospective use of any patient characteristic – demographic, pathophysiologic, historical, genetic, and others – to select patients for study to obtain a study population in which detection of a drug effect is more likely.

  This occurs to a degree in virtually every trial and is intended to increase study power by:

  - Decreasing heterogeneity
  - Finding a population with many outcome events, i.e., high risk patients
  - Identifying a population capable of responding to the treatment

# Enrichment Strategies

- These approaches are virtually universal
  - Find (prospectively) likely compliers
  - Choose people who will not drop out
  - Eliminate placebo-responders in a lead-in period
  - Eliminate people who give inconsistent treadmill results in heart failure or angina trials
  - Eliminate people with diseases likely to lead to early death
  - Eliminate people on drugs with the same effect as test drug

- In general, these enrichments do not raise questions of generalizability (i.e. they do not stratify the patient population).

# From Enrichment to Stratification

- Often, enrichment characteristics are not well understood – trial and error, mixed with instinct and experience
- Problem is that trials are not designed to look at individual responses, but at group effects
- However, there is an increasing knowledge about mechanisms of action, e.g. drug targets etc.
- This is particularly true in oncology (e.g. EGFR, Her2/neu receptor status, etc)
- Once these specific characteristics are known, the patient population can be stratified (requires test)

# From Enrichment to Stratification: The Use of Pharmacogenomics

- Pharmacogenomics is the science that allows us to predict a response to drug therapy based on an individual's genetic makeup (molecular level)
- This assessment is based on the measurement of a biomarker; therefore, we must know the marker and possess a tool (test) to measure the marker
- Pharmacogenomics influences both, PK and PD of drugs, and can be important during all phases of drug development to assess drug safety and efficacy
- There is also pharmaco –proteomics, -metabolomics, etc. For the sake of simplicity, we will embrace all of these technologies and call them "PGx"

# PGx Biomarkers – Are They Different from Traditional Markers ?

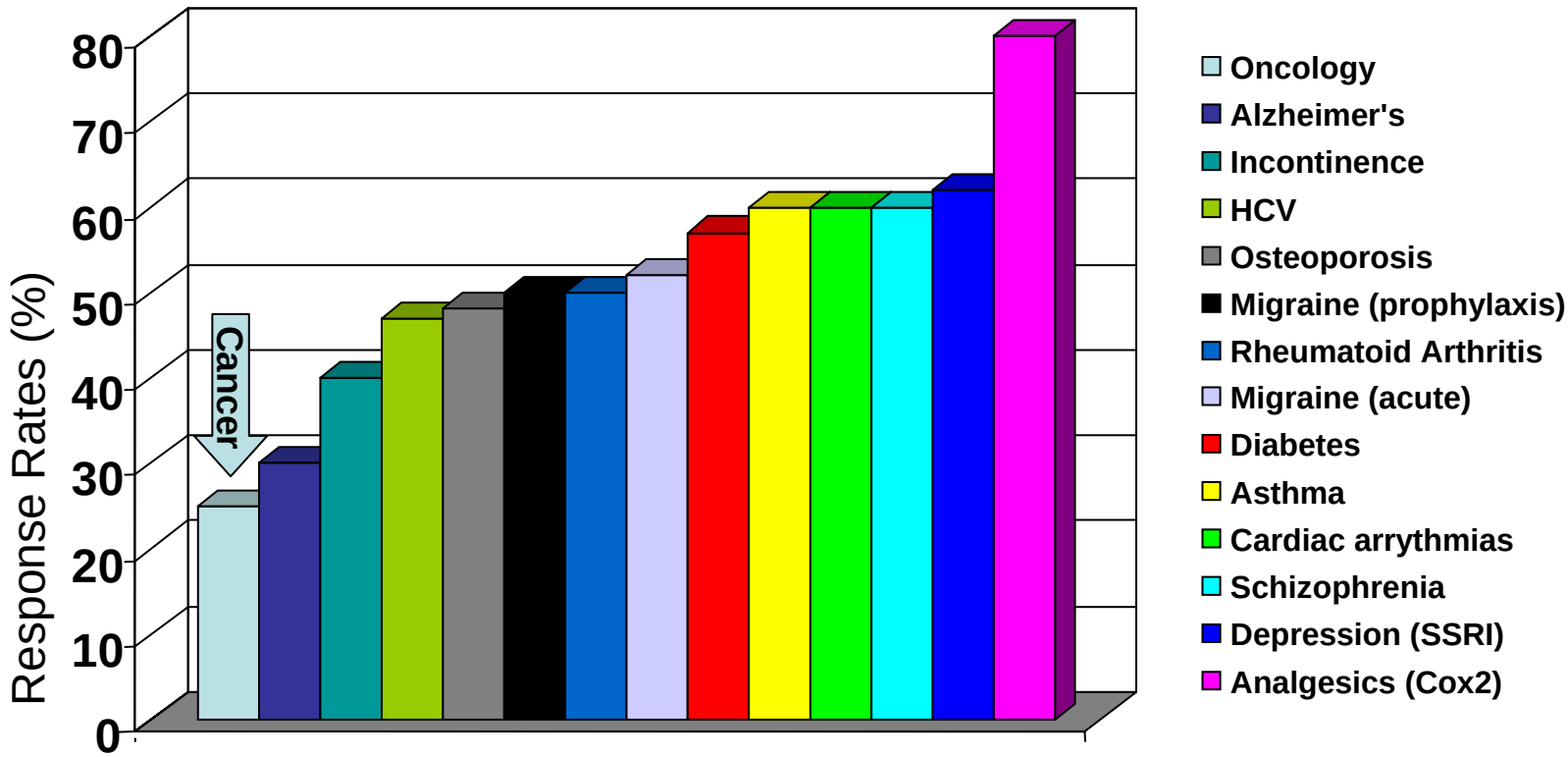
- No, not conceptually: A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic or pathogenic processes or pharmacologic response to a drug
  - This applies to both, genomic and non-genomic biomarkers
- In general, a biomarkers is valid if:
  - It can be measured in a test system with well established performance characteristics
  - Evidence for its clinical significance has been established

# What We Have Is Not Good Enough

- 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

# *Why do we need better predictive markers?*

**Because the average response rate to drug treatment is poor:**






**Slide: Paul Waring, Genentech (modified)**

# Vision and Impact

- "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*)
- Identify who benefits from a treatment – who does not, and/or identify who is at risk
- PGx biomarkers have the potential to be used as key decision tools in drug development (and review). They can have significant value in how we practice medicine. Particularly in oncology.

# Classification of Valid Biomarkers

- **Known valid**
  - Accepted by scientific community at-large to predict clinical outcome
- **Probable valid**
  - Appears to have predictive value but not yet replicated or widely accepted

- Classification leads to specifications for validation in the context of **intended use** for biomarker

# A Word of Caution: Biomarkers and Surrogate Endpoints

- A biomarker is a measured attribute: therefore, a change in the biomarker MAY be a useful predictor or measure for outcome, and in some cases be used as a surrogate endpoint
- However, biomarkers per se ARE NOT surrogate endpoints:
  - A surrogate endpoint is a measurement or a physical sign that can be used as a substitute for a clinically meaningful endpoint that represents how a patient feels, functions, or survives
  - Therapy-induced changes on the surrogate endpoint are expected to reflect changes in a clinically meaningful way
  - The effect on the surrogate itself has no value to the patient – it is a valid surrogate however if the effect on the surrogate does lead to a clinical benefit
  - Most biomarkers cannot do this

# Biomarker Validation

"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*

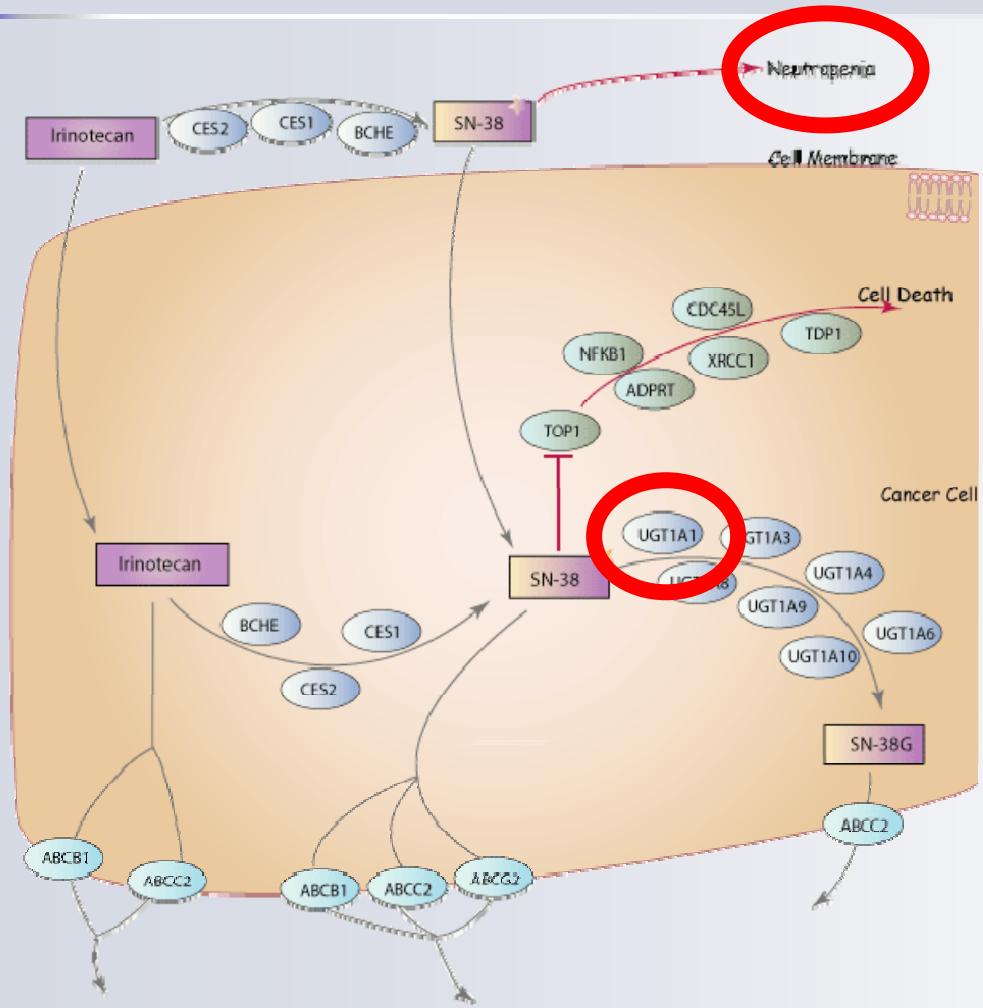
# Getting to Know… Biomarker Validation

- There are basically two distinct ways to qualify (or validate) a biomarker:
  - To wait long enough until ample evidence has accumulated (e.g., cytochrome P450 enzymes)
  - To follow a “validation path”, which consists of defined criteria
- Let’s take a look at:
  - What (we think) we know we know
  - What we know we don’t know

# Examples

- Known Valid Biomarkers (we know):
  - Irinotecan (Camptosar®) and UGT1A1 *polymorphisms*
  - Trastuzumab (Herceptin®) and Her2/neu *overexpression*
- Probable Valid Biomarkers (we think we know):
  - EGFR-inhibitors and EGFR *expression* and *genetic variations*

# The Role of UGT1A1 in Irinotecan Therapy




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)

# UGT1A1*28

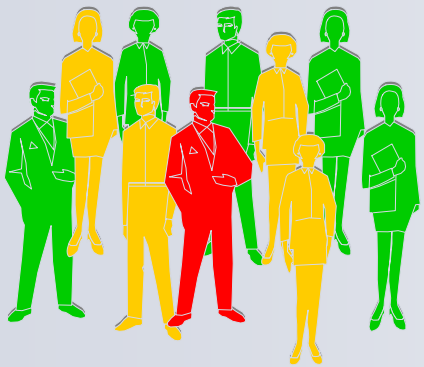
| Group | Prevalence | Risk of Toxicity |
|---|---|---|
| All Patients | ----- | 10% |
| Patients That Are 7/7 | 10% | 50% |
| Patients That Are 6/7 | 40% | 12.5% |
| Patients That Are 6/6 | 50% | 0% |

***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

# Test Result: An opportunity for making a better informed treatment decision (Risk assessment)

All Patients with Same Diagnosis (10 % risk)



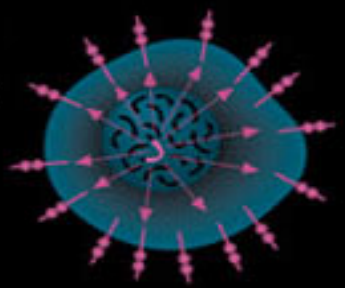
PGx profile for *high risk* treat with alternative drug or dose

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

PGx Profile for *low risk* treat with conventional dose

# 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: Value for Business and Public Health from Patient Stratification

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

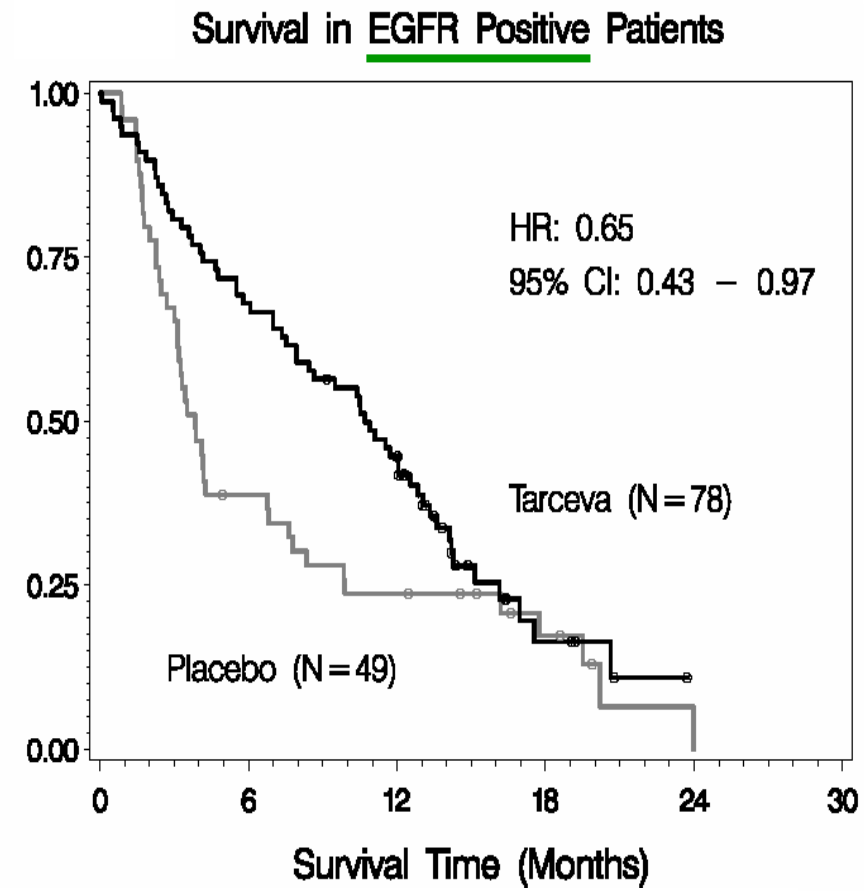
- **Savings in clinical trial costs ~ $35 million**
- **Income from 8 year acceleration of product ~ $2.5 billion**
- **Access to drug from acceleration ~ 120,000 patients**

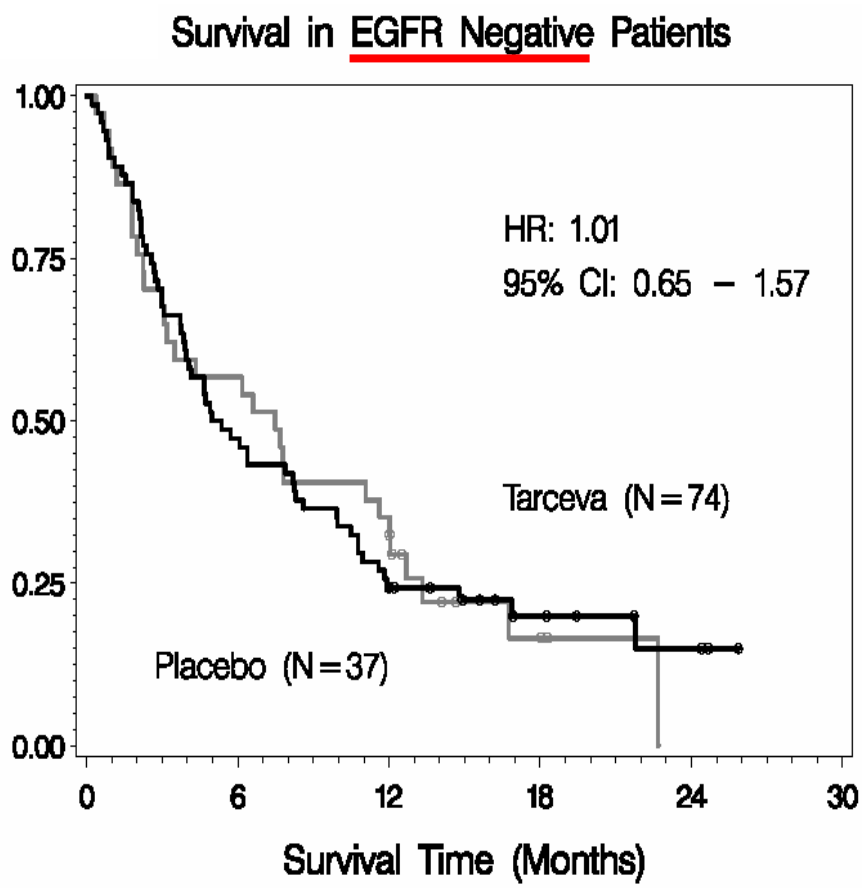
** From Press and Seelig, Targeted Medicine 2004, New York, November 2004*

# Erlotinib (Tarceva®)

- **Erlotinib, like gefitinib (Iressa®), is blocking the epidermal growth factor receptor (EGFR) found on the surface of cells of non-small cell lung cancer (NCSLC).**
- **Clinical trials with erlotinib showed a 2 months survival benefit (mean) of patients treated with erlotinib when compared to placebo.**
- **However, on a second look, only a subset of patients had this benefit.**
- **Why ?**

# Erlotinib (Tarceva®)




- **Survival benefit correlates with EGFR status**
- **Approximately 50% of patients are EGFR positive**

# What Does this mean? How valid is valid?

- Biomarkers must be evaluated in the context of their use – which depends on the specific drug itself as well as on gathering enough information in both, marker positive and marker negative groups:
  - For example, cetuximab (Erbitux®), an antibody used in colorectal cancer inhibiting EGFR activity, has been studied (and approved for use in) EGFR+ patients only;
  - However, new studies seem to demonstrate that cetuximab is also efficacious in EGFR- patients.
  - (I guess this is what we don't know we don't know...)

# Gefitinib (Iressa®)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

## Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

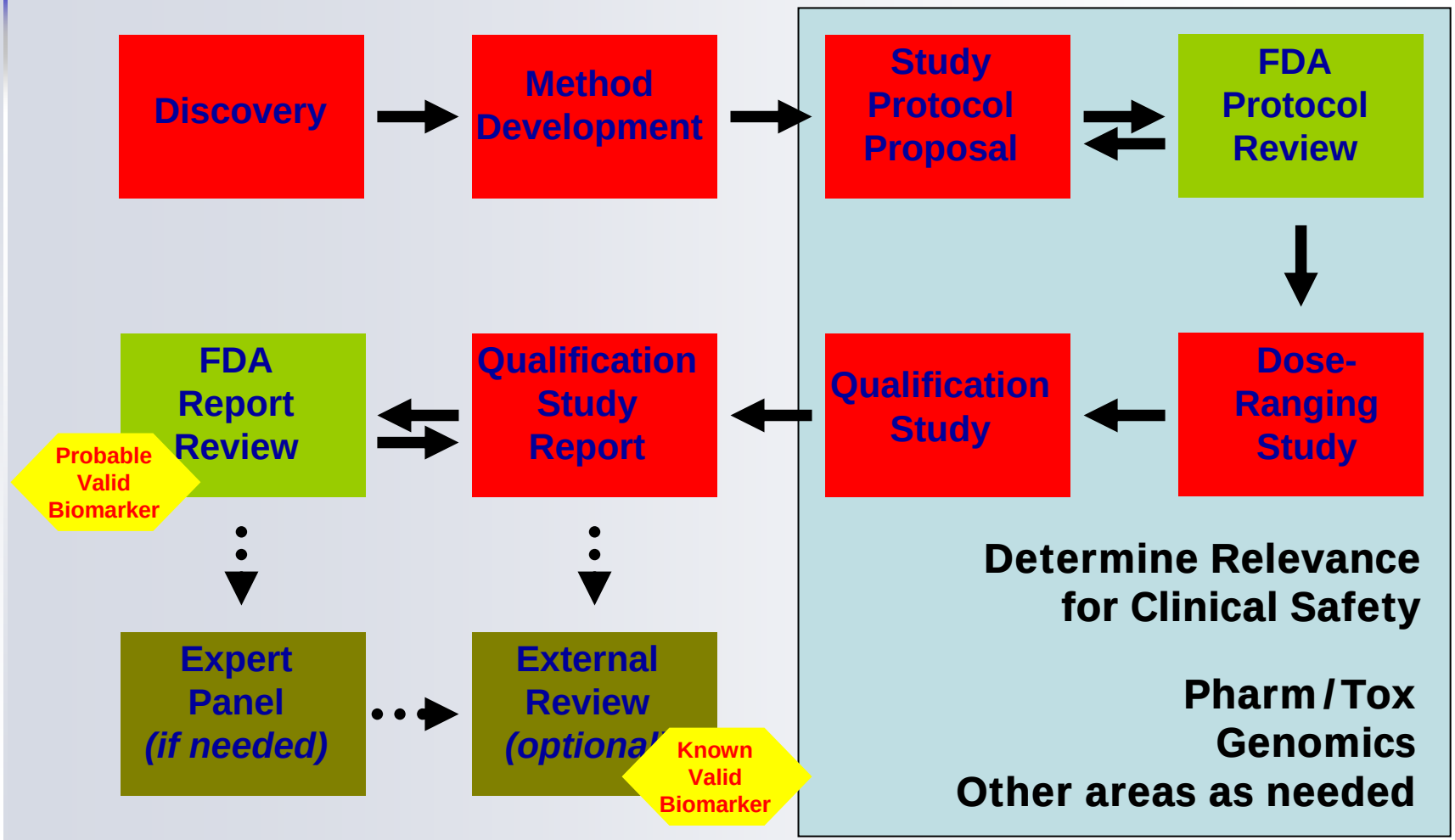
# EGFR Mutations and Response to Gefitinib: We know we don't know

- Size of published studies are small: response in carriers of mutations could be coincidence.
- How does it compare to placebo? Mutations could be predictors for better outcome (disease prognosis) regardless of drug treatment
- What about the spectrum of mutations: is the simple presence of a mutation good enough or does it need to be at a specific location?
- ... unless we have prospective, placebo controlled data, we cannot conclude that this finding is real
- So, is it worth using a test and stratify the patient population? – Some think yes, but what is really needed is a "pathway" to qualify biomarkers (here, EGFR mutations) for their use:

# 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)

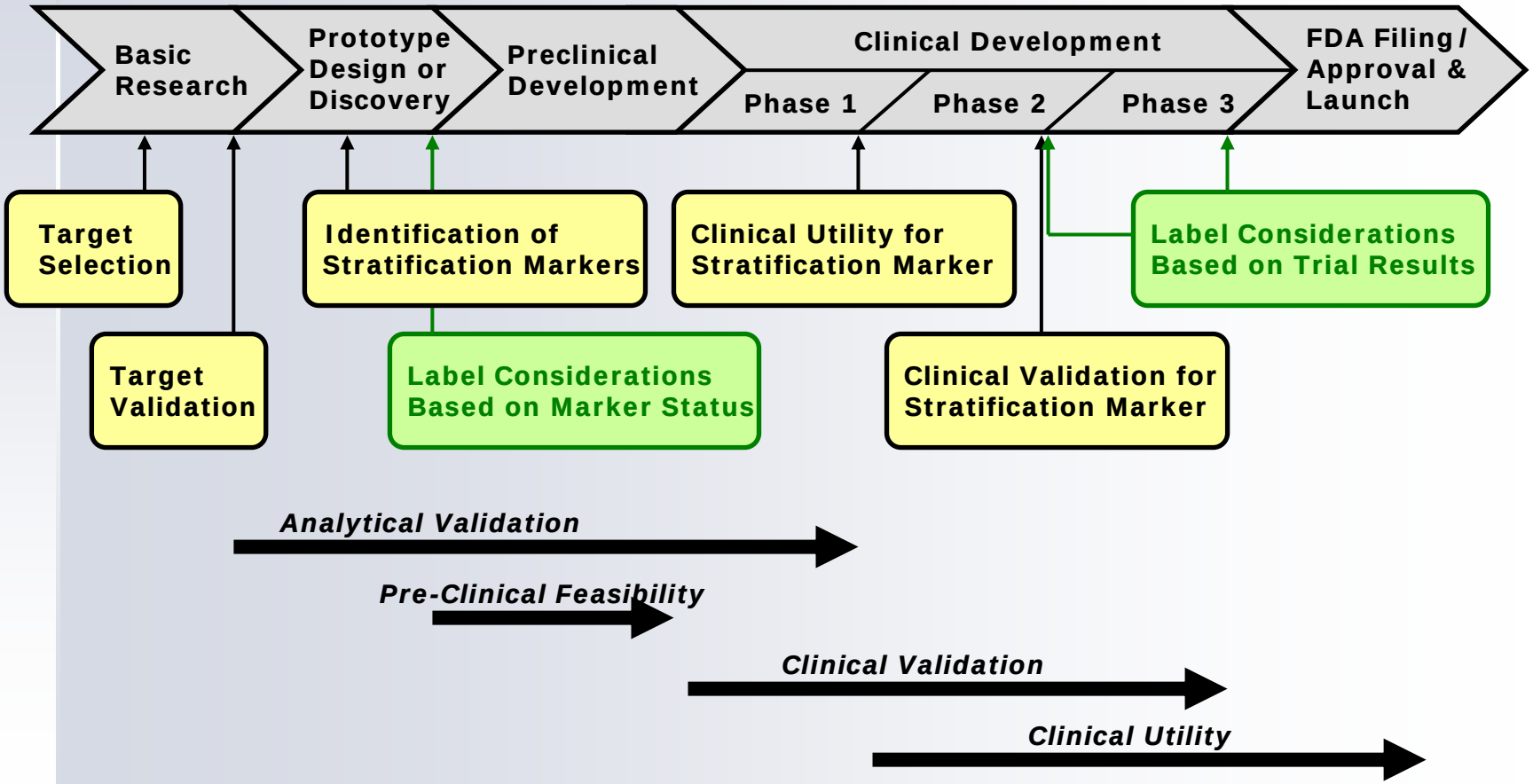
# Proposed Pathway for Validation of Preclinical Genomic Biomarkers



# Example:
# Drug-Test Co-Development – "Pathway for Validation" of Clinical Genomic Biomarkers

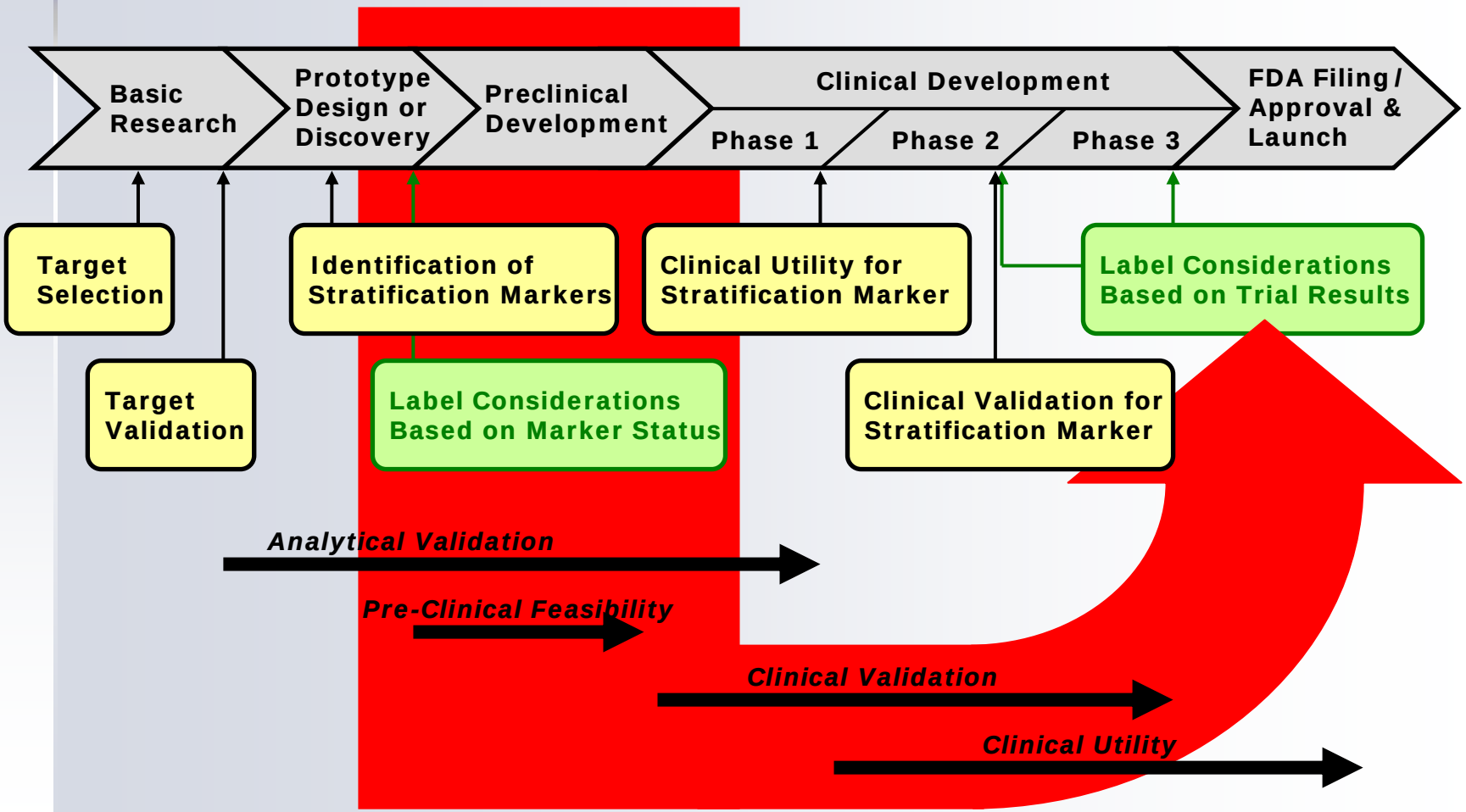
- Drug and test are developed simultaneously
- Knowledge of a PGx biomarker exists and can help to better develop drug (e.g. responder stratification)
- Ideally, early use and integration of marker in drug development program
- Coordinated effort between the development of the drug and the test, e.g. trial data will support both drug and test approval
- Test (use of marker) required
- Examples: Herceptin, Erbitux, Gleevec

# Drug-Test Co-Development: The Use of Biomarkers along the Drug Development Timeline



# Strategic Thinking

## Target Product Profile (TPP)



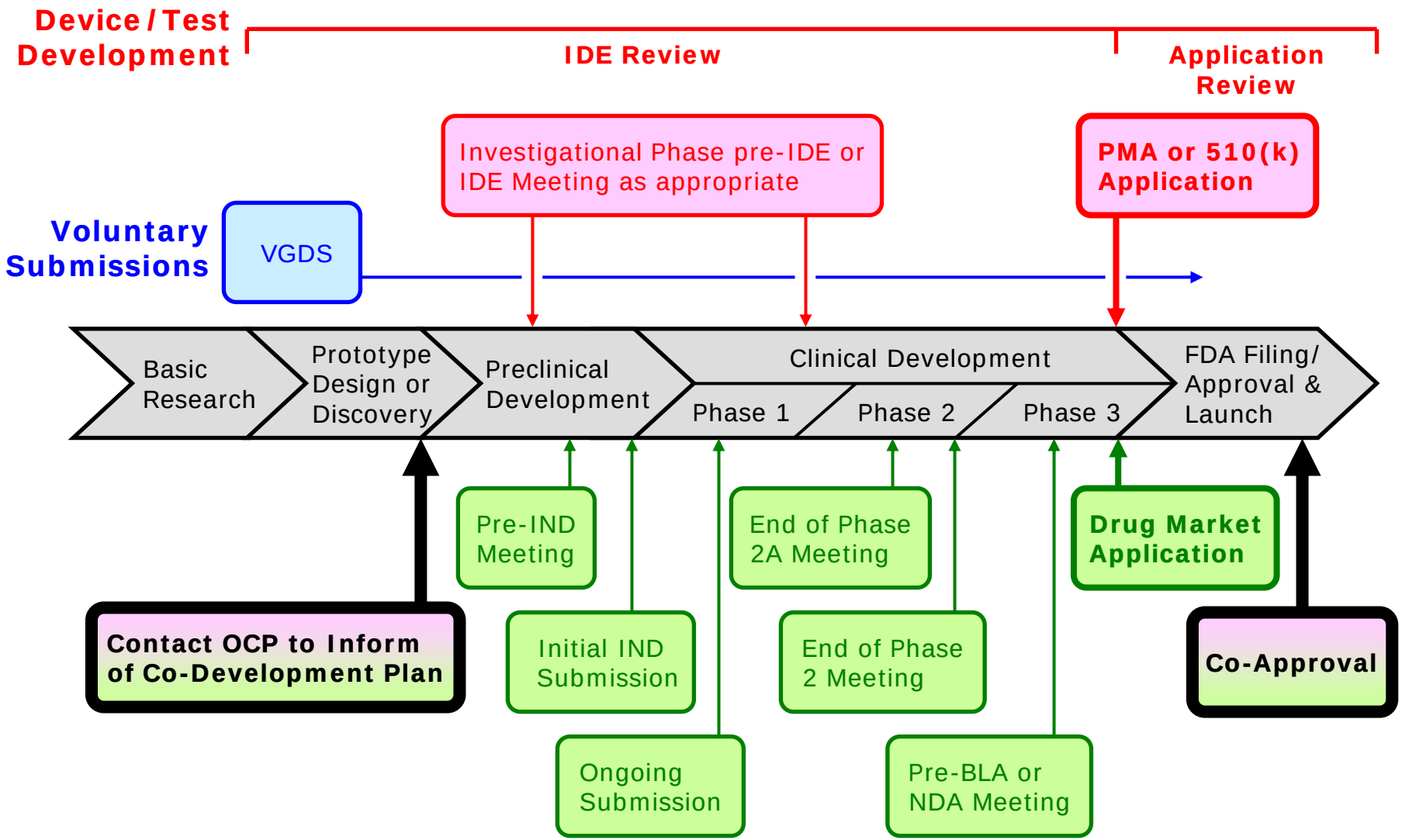
# Target Product Profile: What's the Benefit?

- Ideally: *Statement of what to go to the market with* (desired outcome)
- Can include, e.g. optimal labeling
- Provides grounds for discussion during pre-IND or IND phase, (or later)
- Important to revisit the profile characteristics over the period of development
- Genomic biomarkers provide good opportunity to create TPP

# PGx Biomarkers – the Holy Grail ?

- Genomic biomarkers provide:
  - "progressive reduction of uncertainty" about effects
  - "increasing level of confidence" about outcomes
- They are part of a bigger picture
  - Many other markers are useful as well – in a combined use, the benefit will likely be much higher
  - Perhaps some will become surrogates for endpoints
  - Most will remain a factor in a multidimensional set of information along the drug development process
  - The use of some markers will remain questionable over some period of time (better validation protocols needed)

# Regulatory Tools



# Use of FDA's Tools to Support Drug Development at EARLY Stages

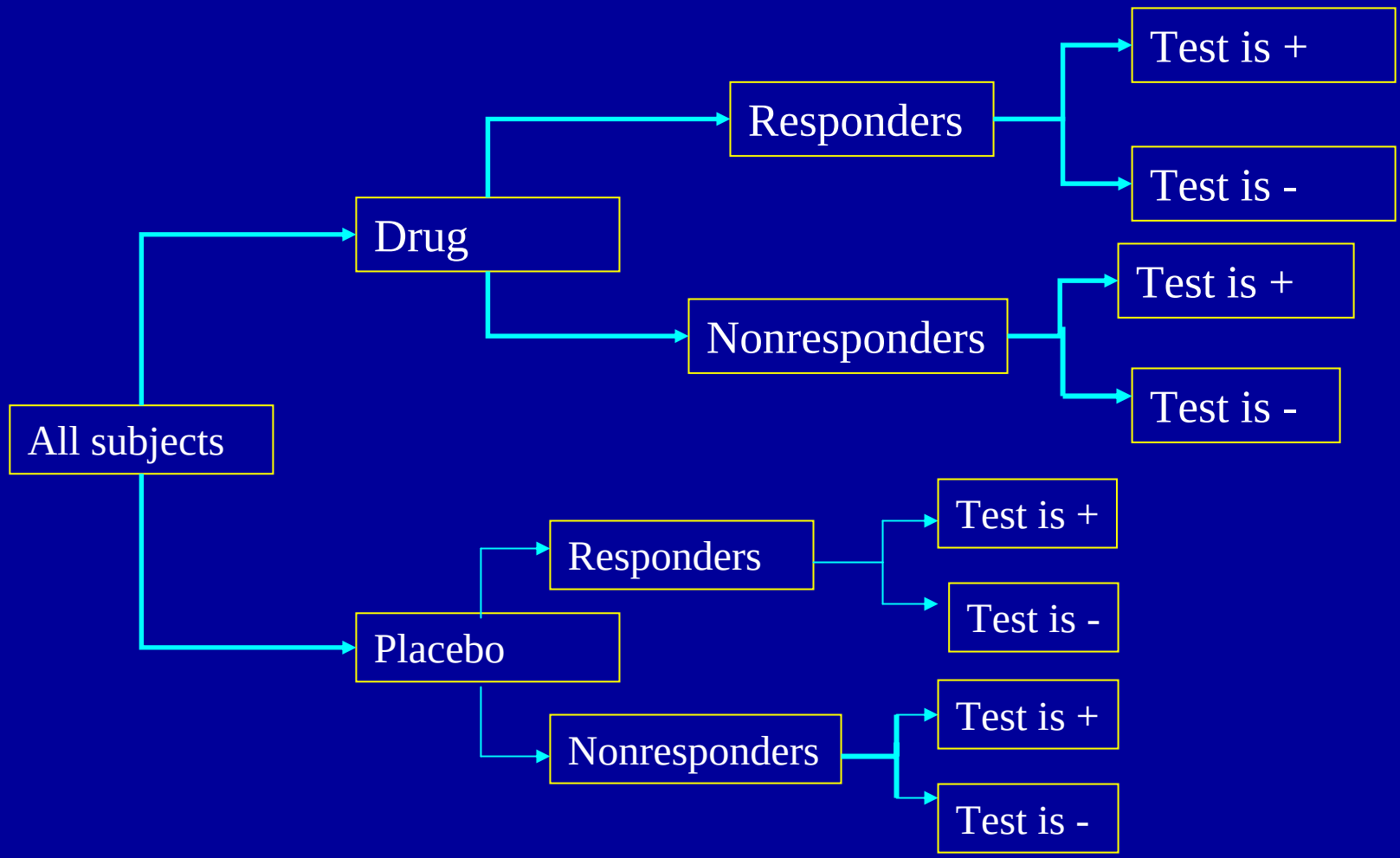
- Pre-IND
- Pre-IDE
- EOP2A
- VGDS


- FDA guidance documents, concept papers, publications, websites, etc.

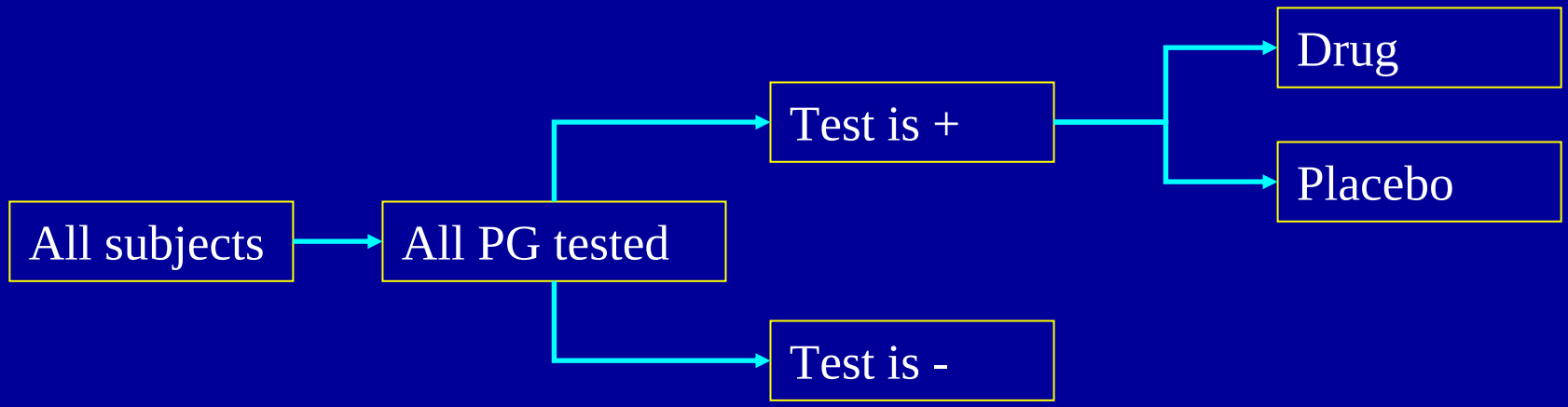
# A Look at Three Common Designs

1. Retrospective
   - Hypothesis generating; usually needs confirmatory clinical trial(s)
2. Prospective
   a. No possible effect in marker negative group
      - Test must be available
   b. Possible effect in marker negative group
      - If test not available, benefit/risk must be acceptable for whole population, even if efficacy is driven by marker positive group

# 1. Retrospective



# 2.a. Prospective, Screened



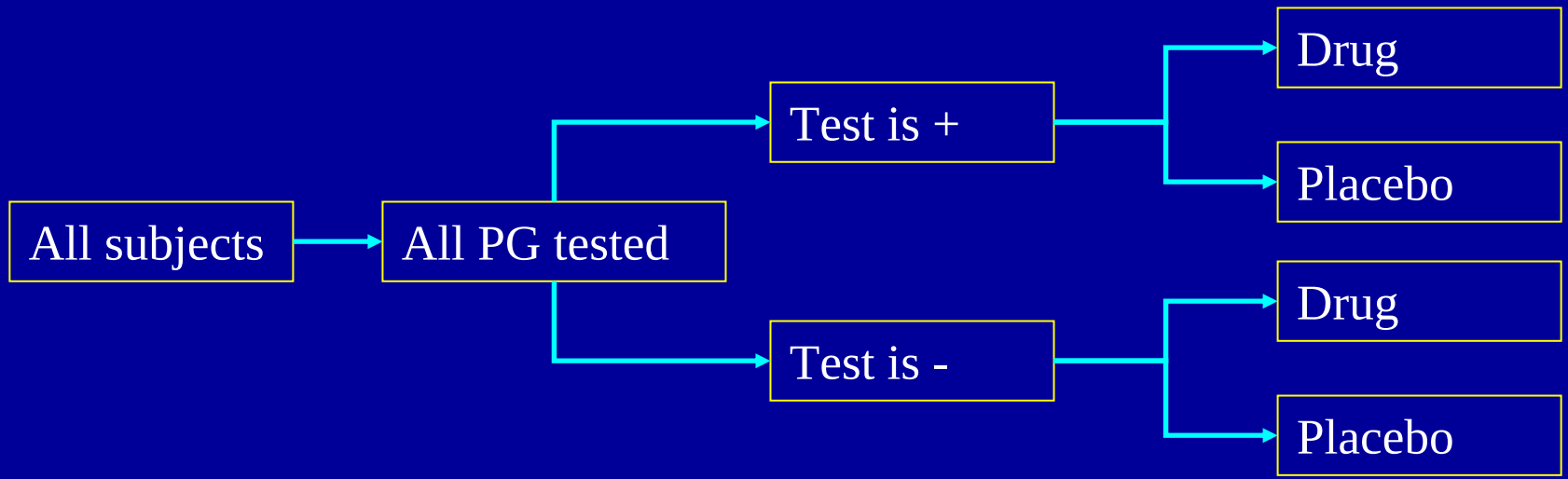

No possible effect in (-) group

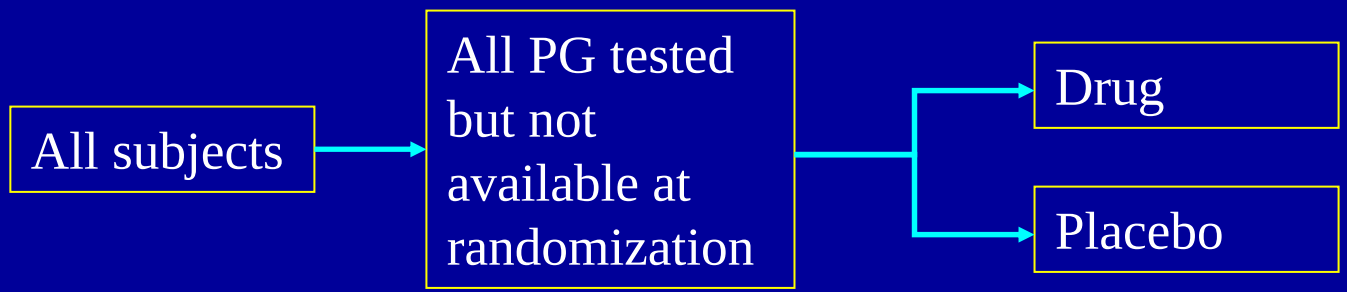
# 2.a. Prospective, Screened: Considerations

- Enrichment strategy for efficacy
- True signal of efficacy of drug - proof of principle
- Overestimate of effectiveness in an unselected population; therefore distorts B/R in that population
- Will be proof of principle and effectiveness but only if the test is available
- PGx test must be available if marker negative group is not studied, because:
- Safety must consider all patients [(+) and (-)] if selection is not possible

# 2.b. Prospective, Stratified

Possible effect in the (-) group and/or toxicity in the (-) group needs to be evaluated because pre-treatment selection is not possible




Analyze PG+ as primary analysis

Analyze toxicity in all

# 2.b. Prospective, Stratified: Considerations

- Will test efficacy and safety in both, marker positive and marker negative subgroups
- Provides proof of principle: effect in marker positive group can be the primary endpoint. If the test is not available however, one needs to analyze the whole population for benefit/risk. Benefit/risk must be positive for the whole population, even if only the marker positive group is analyzed for effectiveness.
- This design is particularly important in cases where sensitivity of marker cannot be assumed to be very high

# Summary

- PGx = biomarker + tool to measure it
- This can be the pre-requisite for a personalized or targeted drug treatment (but there are more than genomic biomarkers!)
- Validation of biomarker is a critical step with scientific as well as regulatory implications – new “validation pathways” are needed
- There are many trial design possibilities that use biomarkers for enrichment or stratification, and there is no general recipe: choosing the right strategy can make or break a trial
- Drug-test co-development makes sense and needs to be explored more (and oncology is one of the main focus areas)
- In the future more emphasis will be put on the identification of responders/non-responders or patients at risk (true for drug development AND regulation)

# How to Get It Done ?

**"The secret to getting ahead is getting started. The secret of getting started is breaking your complex, overwhelming tasks into small manageable tasks, and then starting on the first one.“**

***Mark Twain***

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# www.fda.gov/cder/genomics

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