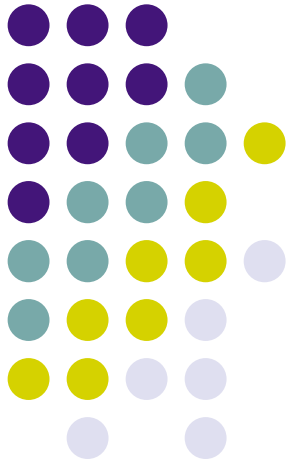
Right Drugs for the Right Patients



Jane Fridlyand
Genentech

PhUSE SF SDE
Aug 31, 2011

Personalized Health Care – Fantasy or Reality?

Here's my DNA sequence

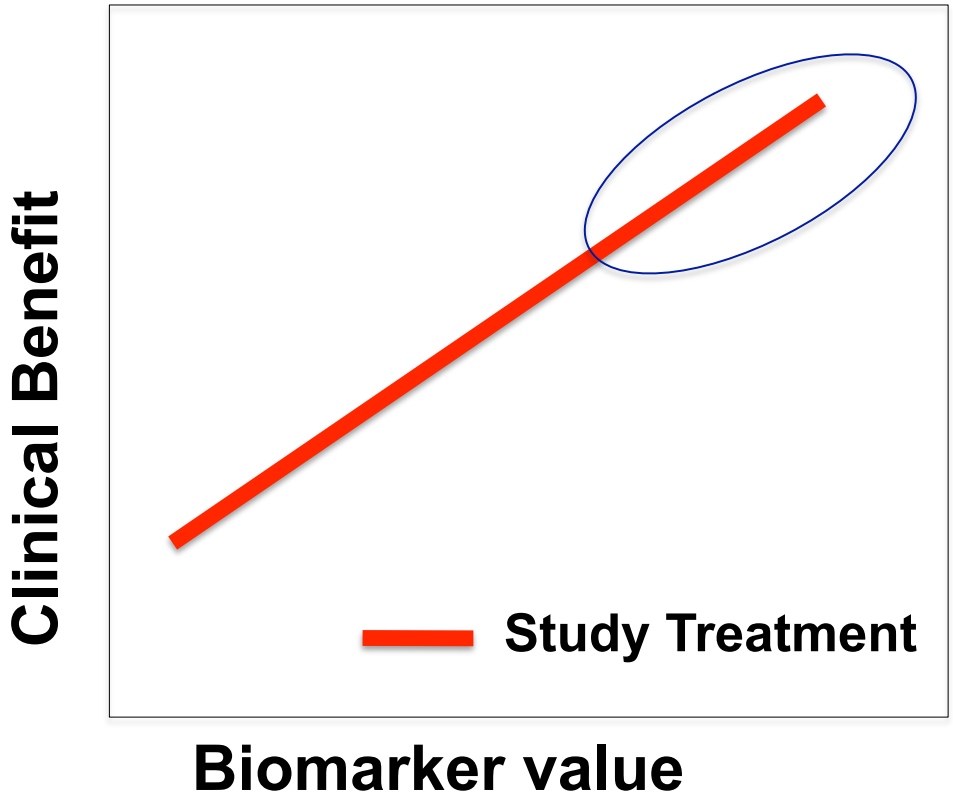
Personalized Health Care – Fantasy or Reality?

Here's my DNA sequence

Personalized health care describes medical practices that are targeted to individuals based on their specific genetic code in order to provide a tailored approach. These practices use preventive, diagnostic, and therapeutic interventions that are based on genetic tests and family history information. *The goal of personalized health care is to improve health outcomes and the health care delivery system, as well as the quality of life of patients everywhere.*

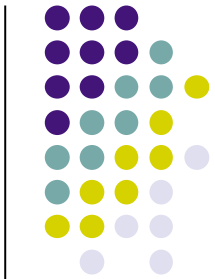
Source: HHS

PHC question –
Is the Biomarker "Predictive"?



Goal: identify a treatment-sensitive biomarker subgroup based on value of a pre-treatment biomarker.

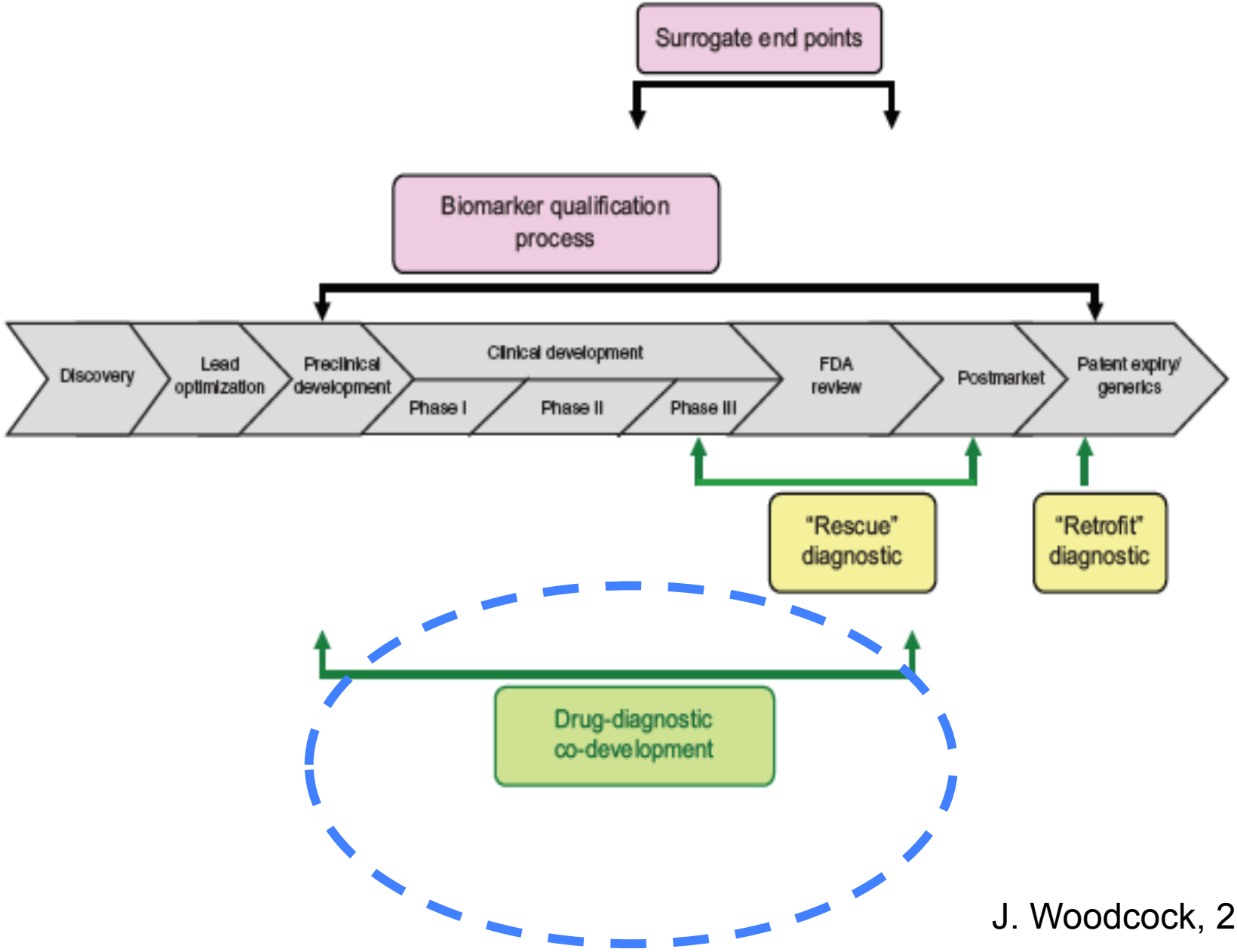
The Company's 2014 PHC Goal



- The Company's 2014 PHC is focused on incorporating biomarkers into clinical development plans with impact on:
  - Defining clinical and regulatory strategies
  - Target Product Profiles
  - Phase II and III study designs
  - LIP
  - Exploratory analyses

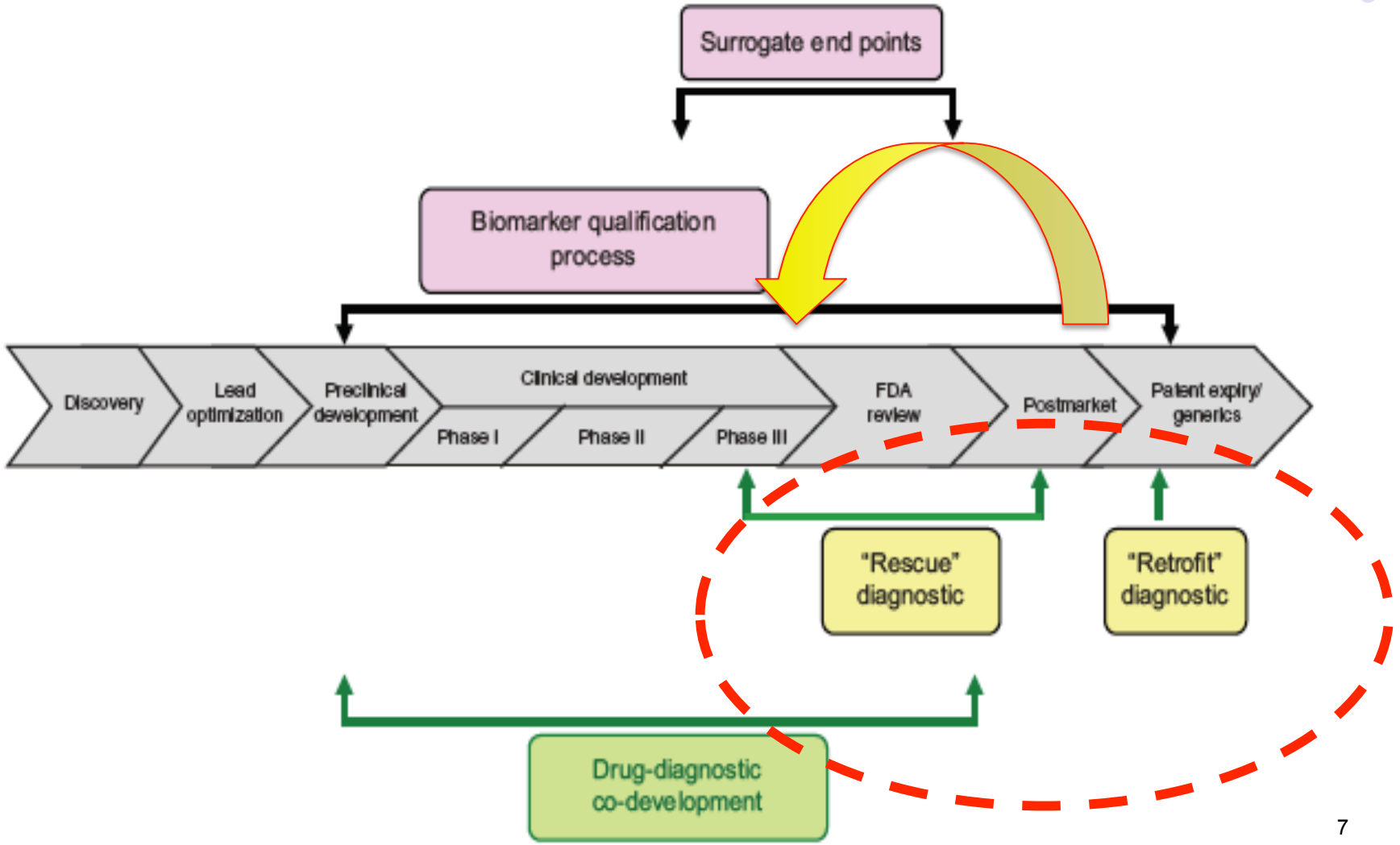
  Expect > 30% of NMEs to enter pivotal trials with the companion Dx.

Ideal PHC drug development process



J. Woodcock, 2010

PHC drug development process is often non-linear

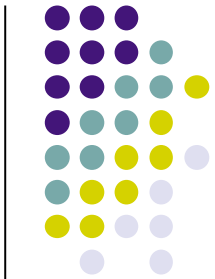


J. Woodcock, 2010

PHC Assessment ⟺ Development Strategy

PHC Assessment		
• Strong Dx hypothesis • No activity in Dx-	• Strong Dx hypothesis • Some activity in Dx-	• No strong Dx hypothesis • Exploratory Stage
Development Strategy		
• Patient selection through all phases of development	• Complex, larger phase IIs with stratification • Complex phase IIIs	• No selection or stratification • Data exploration
Selected	**Stratified**	**AllComers**

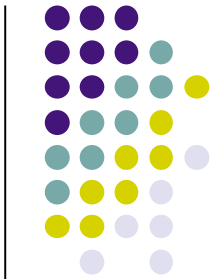
PHC – impact on drug development



- Target Product Profile (TPP)
  - Parallel development of companion diagnostic
- Phase I trials
  - Selection for Dx for quick signal seeking
- Phase II (POC) trials
  - Complex issues become more complex
  - More unknowns, more questions to answer
- Phase III trials
  - Clinical Validation of Dx
  - Design depends on Phase II outcome
    - Selection, stratification or all-comers

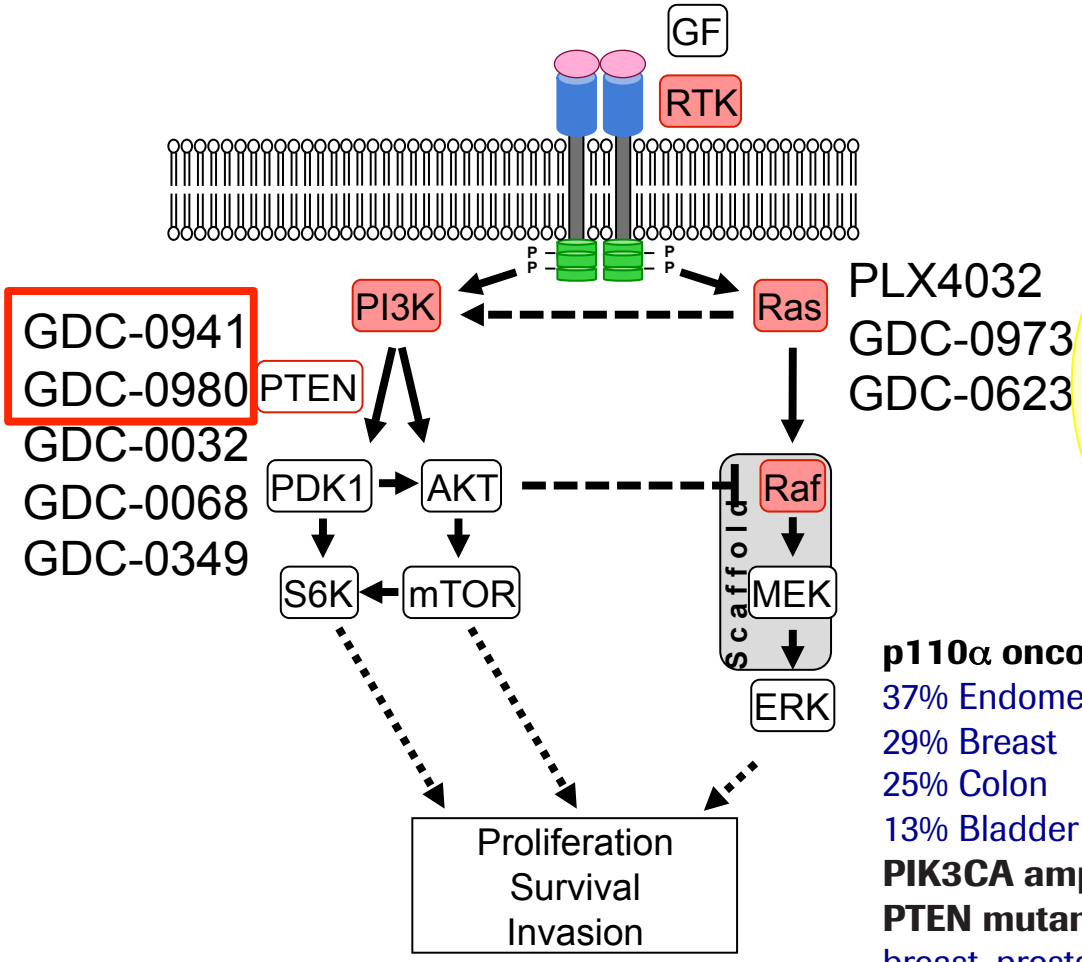
Added complexity but this is reality!

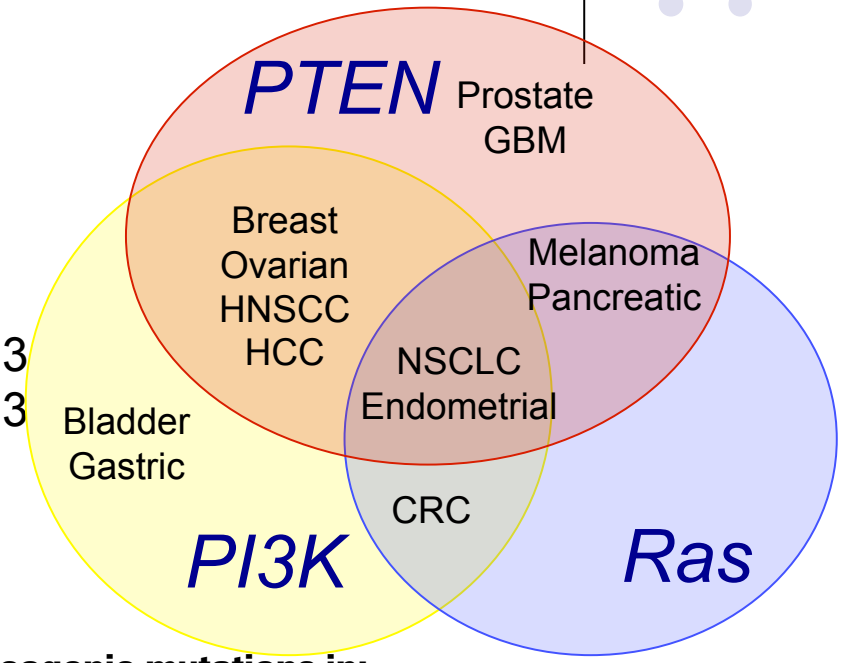
Basic Principles



- Retrospective Analyses are only considered “hypothesis” generating.
- Prospectively Defined Dx markers are required for any label enabling action.
- Dx markers must be defined prior to pivotal trials and hence planned for in a Clinical Development Plan (CDP).
- Dx. Marker evaluation often in phase II.

Multiple molecules targeting core oncogenic pathways: Potential broad application, combinations, with strong biomarker hypotheses





p110α oncogenic mutations in:

37% Endometrial

29% Breast

25% Colon

13% Bladder

PIK3CA amplified in 30% ovarian, lung

PTEN mutant/lost in:

breast, prostate, glioblastoma, melanoma, pancreatic, endometrial, ovarian, lung, head and neck, hepatocellular, thyroid

Developing PI3K Inhibitors: *Follow the Tumor Genetics*

–Which target: selective or multiple

–Which disease

- Reliance on different nodes in the pathway (RTKs, PI3K mt, mTOR)
- Translatability of Proof Of Concept (POC) across diseases, line, combinations

–Which patient (role of diagnostics)

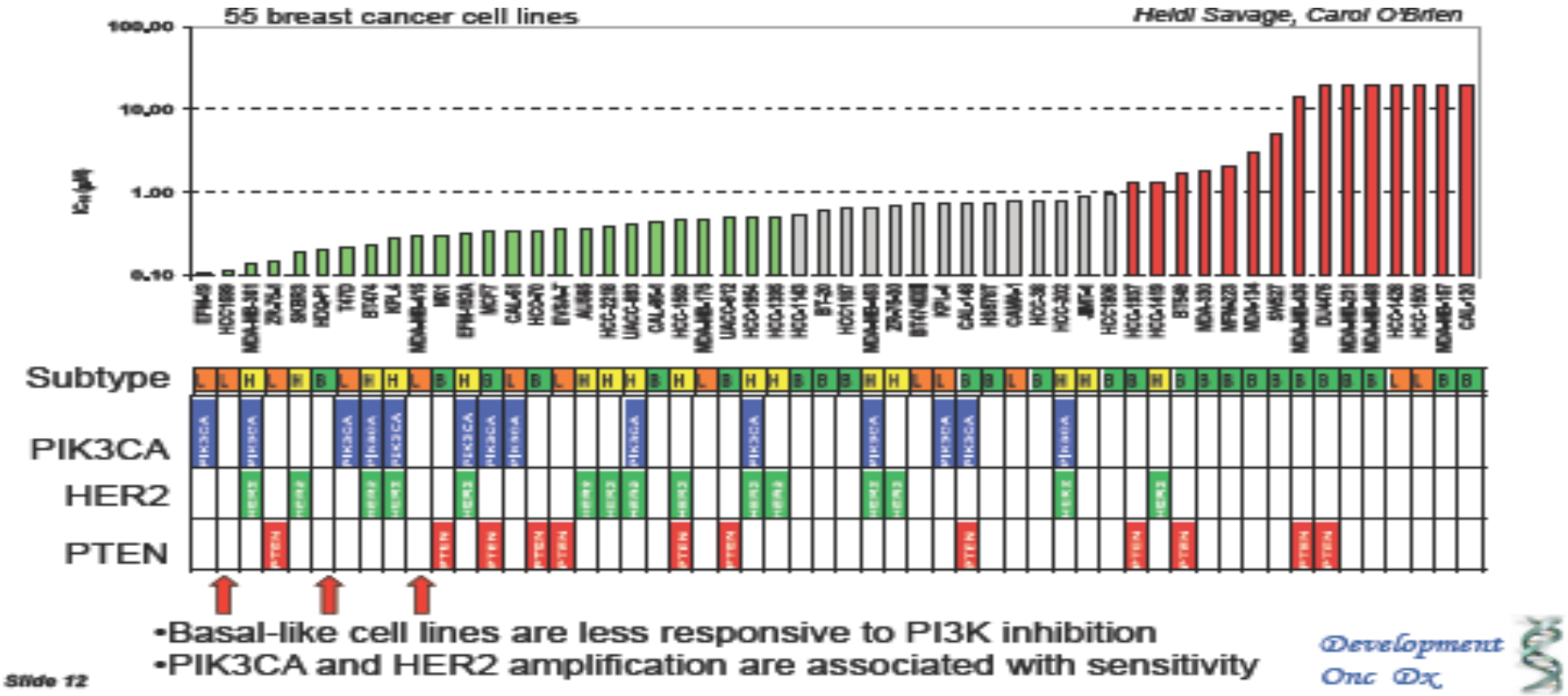
- Putative Dx markers have strong links to tumor biology
- Are pathway alterations predictive of target dependence
    - Can we select patients based on any of them?

–Single agent vs. combination

- Chemotherapy, EGFR, MEK, VEGF…..

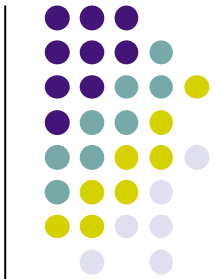
–How hard to hit the target (dose and schedule)

PHC assessment to guide development strategy



- Preclinical data in mBC suggests that cell lines harboring PI3K/PTEN alterations are highly sensitive to the pathway inhibitors

Phase II Considerations



- Objective: simultaneous Rx/Dx evaluation
- Scientific rationale and pre-clinical data - main determinants of the scenario prior to Phase II
- Statistical considerations
  - Co-primary endpoints
  - Value added and feasibility of stratification
  - Defining cut-offs for continuous biomarker
  - Go/No Go decision algorithm
- Dedicated studies to investigate assay or biomarker properties
  - Reproducibility, prevalence, prognostic value

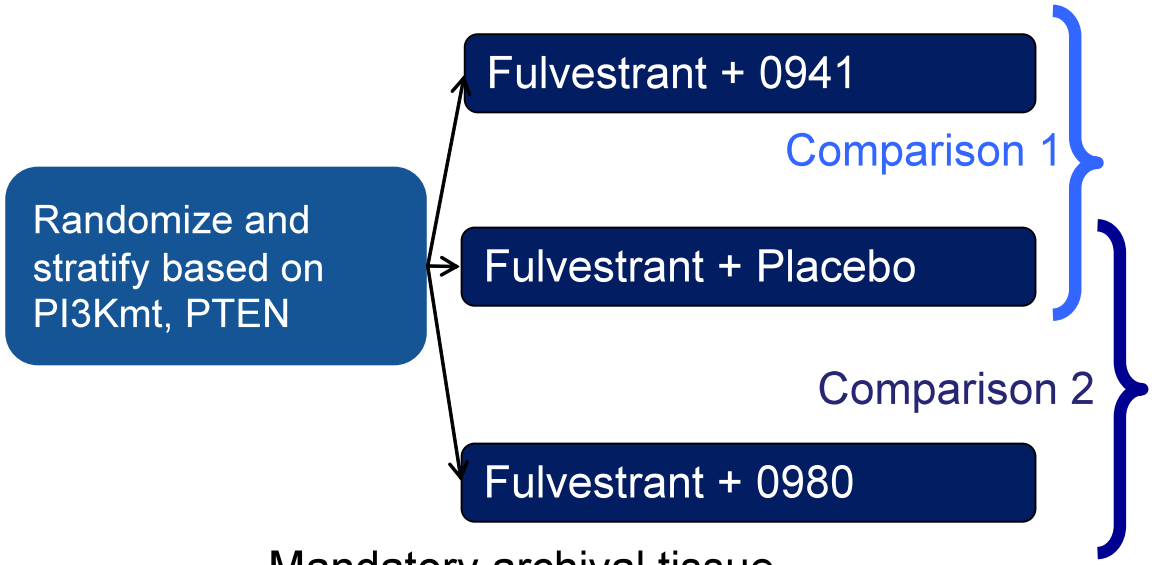
Possible POC Plans for GDC-0941 and GDC-0980

- Selected expansion cohorts in ongoing phase Ia studies
  - Expansion in patients with PIK3CA mutations
  - Separate breast cancer-only and multi-indication expansions
  - Both GDC-0941 and GDC-0980

- Randomized 3-arm Phase II Trial in ER+ Breast Cancer

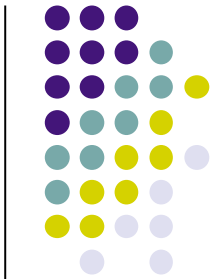
Key Elig	•prior AI in adjuvant (PD<6mo) or metastatic breast CA •HR+ and HER2- •Measurable and evaluable disease

Primary endpoints:
- PFS in all comers
- PFS in Dx selected
- 350 pts



Mandatory archival tissue
Multiple exploratory Dx assays

Proof of Concept (POC) Designs - *Overall, Operational and Statistical Considerations*



- **Overall:** Rank Speed, Probability of Technical Success (PTS) and Cost
  - Strategic context - company portfolio and competitive landscape
  - Single vs randomized controlled trial
  - Diagnostic TPP

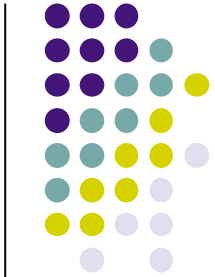
- **Operational:** Feasibility of the proposed trial with the biomarkers
    - Enrollment rate
    - Site choice
    - Dx prevalence

- **Statistical:** Enable a joint Rx/Dx evaluation to inform Phase III design
  - Ordinal markers with pre-defined cutoffs
  - Continuous biomarker

Exploratory Analyses: Scope & Key messages

Topic	Key Messages
1. Planning, Documentation & Communication	Biomarker analysis plan (scope control, priority); good statistical practice
2. Data generation	good understanding on sample & assay data generation processes
3. Fit-for-purpose statistical analysis & criteria	Project objectives/TPP to guide; predictive vs prognostic; consider effect size + statistical significance criteria;
4. Assessing & interpreting statistical significance and clinical meaningfulness	Statistical significance and clinical meaningfulness most useful for ranking/filtering candidates; cautions for interpreting nominal stat significance values
5. Cutoff selection for continuous biomarkers	Common approaches are data driven (convenience cutoffs; optimization); challenging
6. Developing a complex predictor	No regulatory precedent; complex process, often overfit; validation important; set realistic expectation
7. Validation strategy	Independent dataset; internal validation by CV, bootstrapping

Example: Retrofit Diagnostic



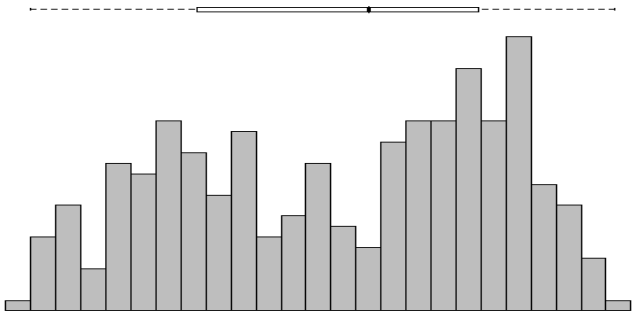
Objective: Are there biomarkers which predict benefit from approved drug Y?

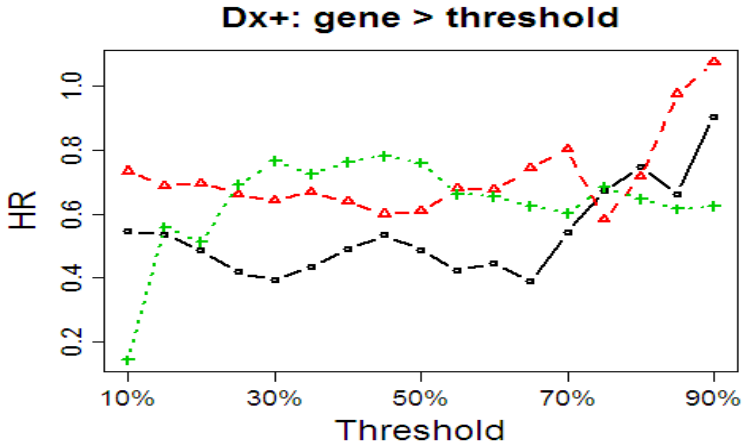
- Hypothesis generation for drug Y: MOA and resistance
- To inform early development molecules targeting the same pathway
- Publications

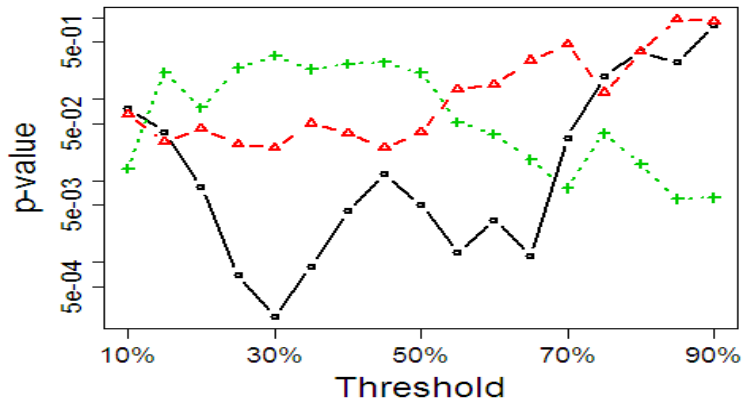
Data: n=500 samples from a Phase III trial

Assays	#probes	# features	# relevant features
Affymetrix WT ExonST 1.0	~5M	~1.4M exons ~300,000 transcripts	278162 core exons; 17952 RefSeq genes
Affy U133plus2	~1M	54675 probesets	54675 probesets/genes
DiscovArray	~28000	14000 probesets	582 known human miRs
Illumina 1M HapMap	~2M beadtypes	~1M SNPs +38000 CN probes	~1M genotype calls; Unknown # Inferred CNVs

Very involved, platform-specific processes for data preprocessing, QC, annotation



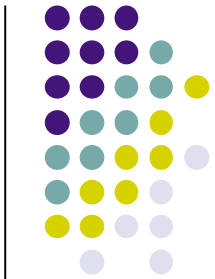




Some considerations:

- Biologically Meaningful Cutoffs
- Effect Maximization
- Subset size

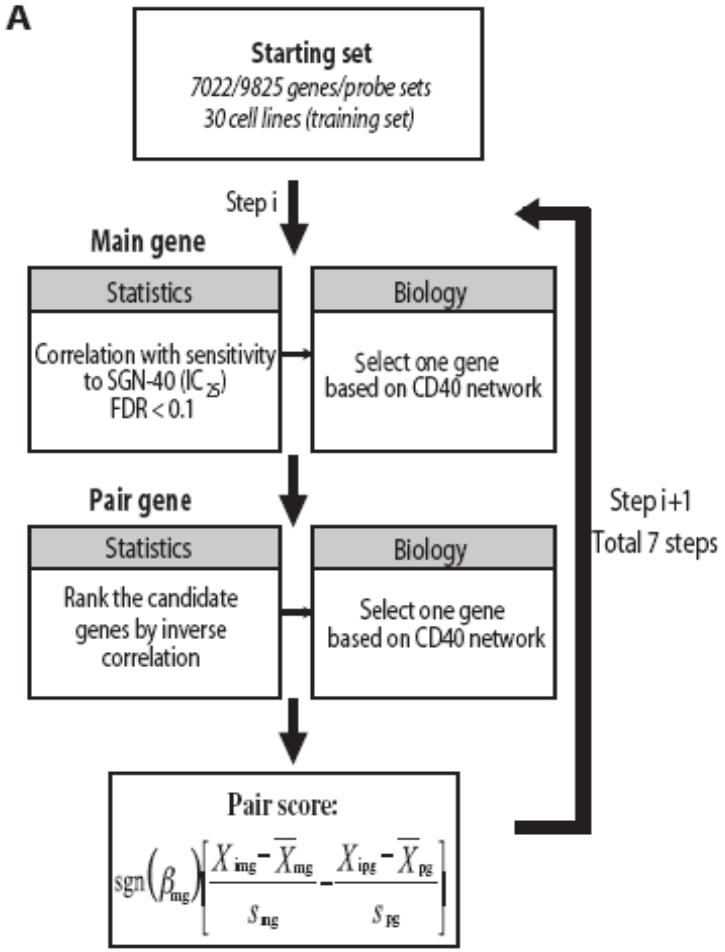
VI. Developing a Complex Predictor

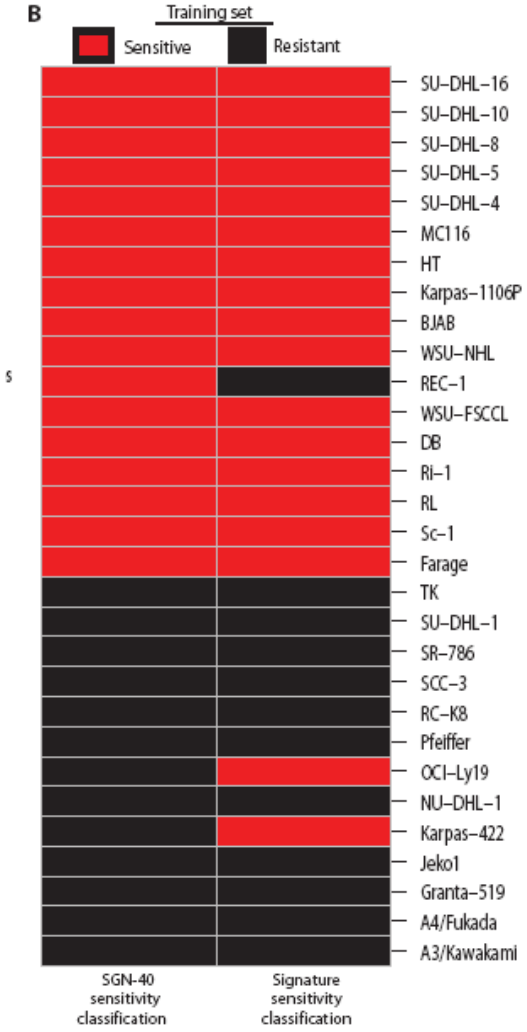


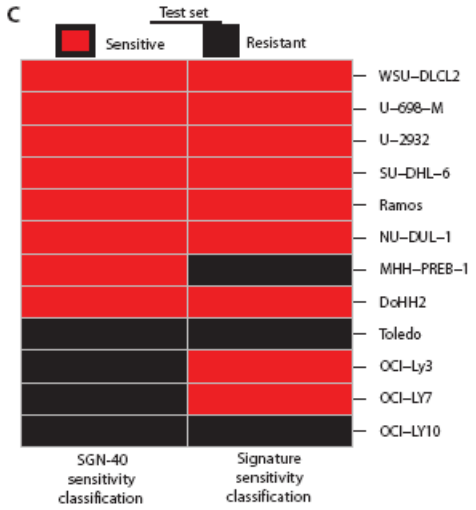
- Uncharted area for predictive application:
  - No HA-approved examples of complex predictor-based companion diagnostics predictive of a specific drug
  - Only related examples: FDA-cleared tests for prognosis of breast tumor recurrence: Oncotype DX (21-gene qPCR), MammaPrint (70-gene array)
- Multi-step processes involving many decisions & tuning:
  - Feature selection, model building, performance evaluation
  - Choice of options & algorithms, especially the performance metric, should be guided by the clinical objective and the nature of dataset
  - Major concern: high variance & overfitting due to large p (features), small n (sample size)
  - Validation strategy important
- Reality check: Set realistic expectation on the feasibility given the sample size, data quality and potential impact

Example: SGN-40

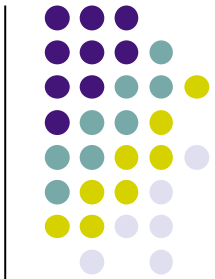
Burington et al. Sci Transl Med 16 March 2011. 3(74), p.74ra22





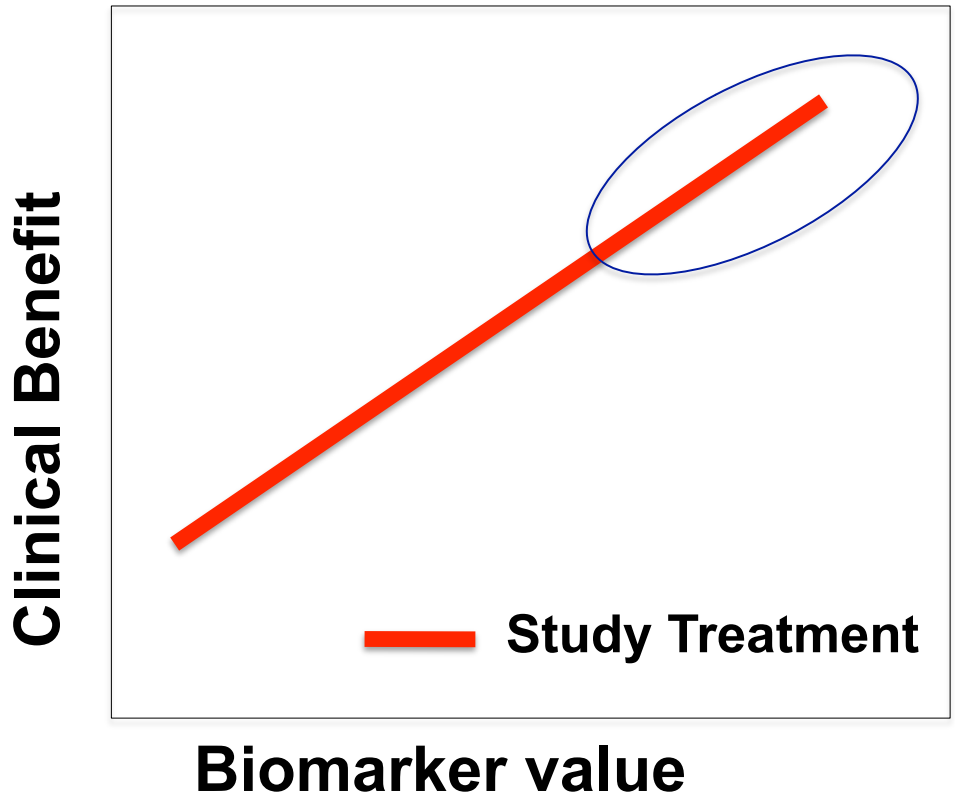


VII. Validation Strategy



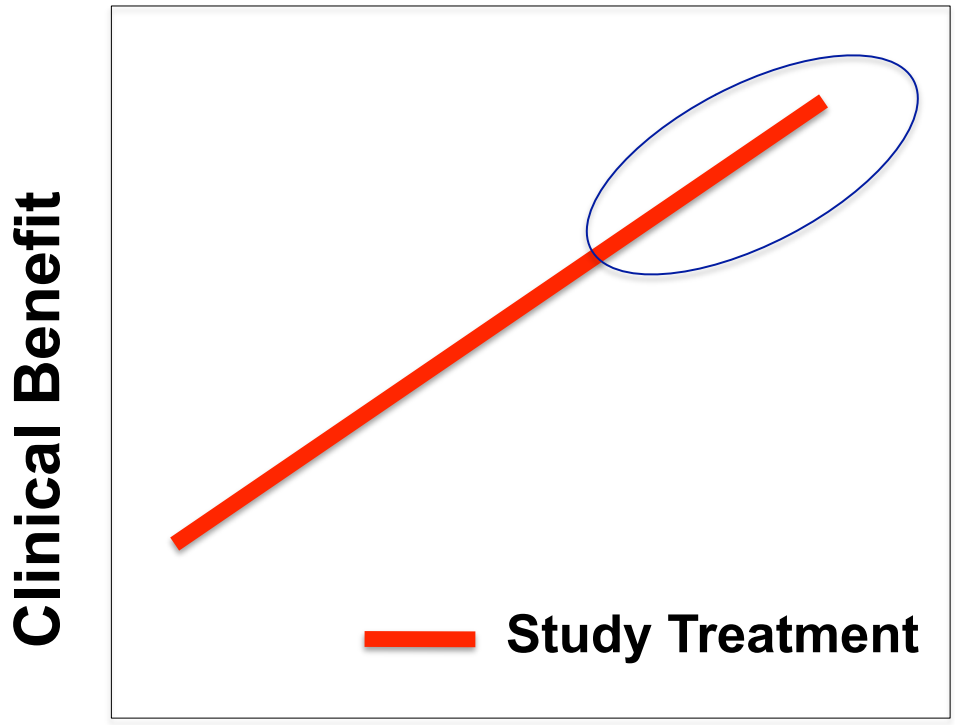
- Validation & resource allocation strategy at the molecule program level to increase overall program PTS:
  - one bigger biomarker study with more power for discovery vs. two (or more) small studies, one for discovery and the other for independent validation.
- “External” validation with independent datasets
- “Internal” validation: cross-validation or bootstrapping
  - Very easy to make mistake by ignoring some aspects of predictor training or the discovery process inside the CV loop, leading to incorrect estimates (usually optimistically biased) of prediction errors.

PHC question –
Is the Biomarker "Predictive"?



Goal: identify a treatment-sensitive biomarker subgroup based on value of a pre-treatment biomarker.

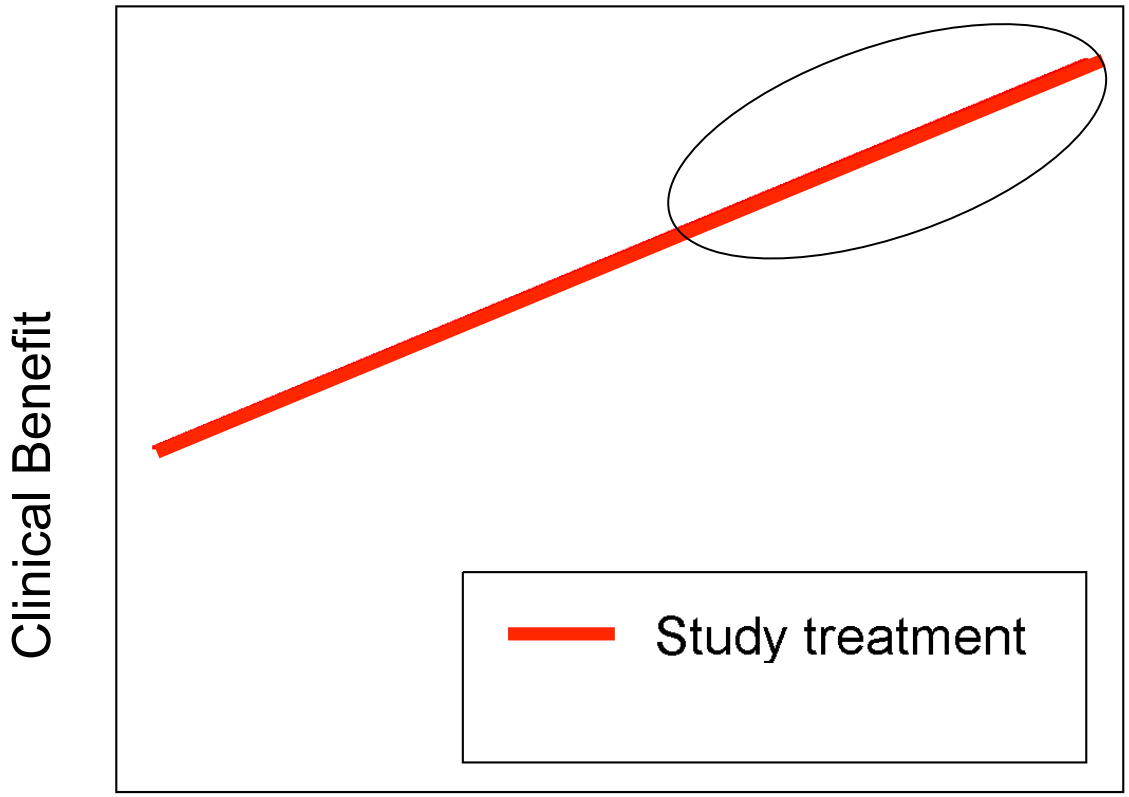
PHC question –
Is the Biomarker "Predictive"?



Goal: identify a treatment-sensitive biomarker subgroup based on value of a pre-treatment biomarker.

Unable to answer unless …

PHC question – Is the Biomarker "Predictive"?



What is the scale of the response?

How does observed effect relate to the PHC TPP? Is Rx-Dx effect clinically meaningful?

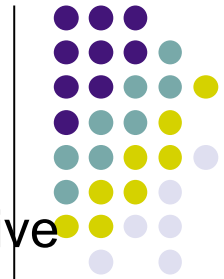
Is biomarker prognostic in the control group?

What is biomarker prevalence in the relevant population?

Does the trial design allow us to make appropriate inferences (e.g. Rx-Dx interaction)?

How was the biomarker identified?

Summary



- Developing drugs is hard (long, expensive and risky) – co-developing them with the Dx is long (slower speed) and expensive (higher cost) but more likely to succeed (PTS)
  - Making clinical decisions early based on pre-clinical data
  - Regulatory path is complex and not always clear at the present time
  - Operational issues are difficult
- Exploratory strategies for either retrofit or rescue require
  - Planning
  - Communication
  - Standardization
  - And most importantly, clear stopping rules

True strategic partnership of all functions is paramount to program success.

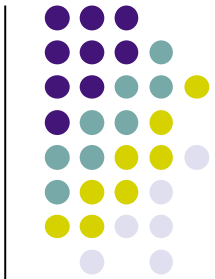
Acknowledgments

- Predictive Biomarkers Biostatistics Guidance 2010 Team

- PI3K Development Team

Predictive Biomarkers Biostatistics Guidance, 2010, Team

Overall Goal Lead is Gracie Lieberman



The 2010 Biostatistics Predictive Biomarker Initiative has generated a Biostatistics guidance document that outlines

- Critical issues related to incorporating biomarkers into the clinical plans
- Possible analytical and strategic approaches to address the above issues

Proof of Concept Designs:

Onco: Jane Fridlyand, Paul Delmar, Thomas Bengtsson, Daniel Coleman, Cheryl Jones, Howie Mackey, James Song

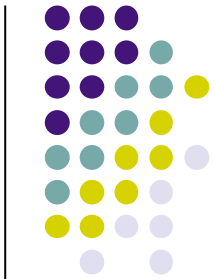
Non-Onco: Jianmei Wang, Zheng Su, Lada Markovtsova, Sarah Williams, Rohit Kulkarni, Sofia Mosesova, Nadejda Mudie, Paul Jordan

Guiding Principles:

Greg Spaniolo, Lada Markovtsova, Jane Fridlyand

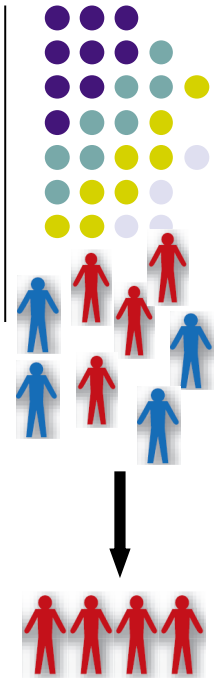
Exploratory:

Ru-Fang Yeh, Colombe Chappey, Bill Forrest, Mike Friesenhahn, Jianmei Wang



BACKUP

Drug-Dx co-development

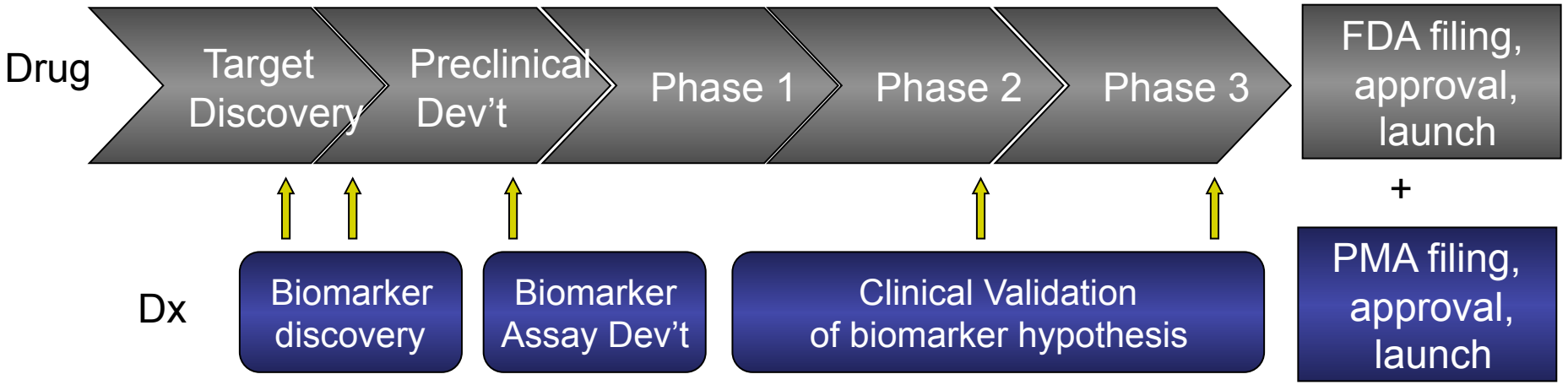


- **To maximize clinical benefit from our therapeutics:**
  - Enable patient selection
  - Informed decision making around indication choice

Predictive biomarker: a test that can be done before treatment to predict whether a particular treatment is likely to be beneficial

Pharmacodynamic biomarker: a test that can be done pre- and post-treatment to confirm target modulation

- **Current regulatory paradigm requires early biomarker discovery**



FDA draft white paper on Drug-Dx co-development

Prognostic?
Predictive?