SESSION III: EMERGING TECHNOLOGIES

New Paradigms in Drug Discovery: How Genomic Data are Being Used to Revolutionize the Drug Discovery and Development Process – A Workshop

Pharma Perspective

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Jane Fridlyand
March 21st, 2012

Roche Pharma and Diagnostics

Pharma

Diagnostics

Roche Pharma

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CHUGAI
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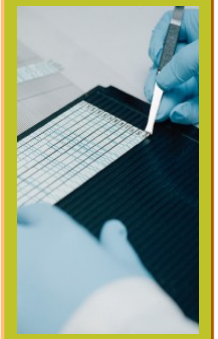
Roche Applied Science

Roche Molecular Diagnostics



Roche Professional Diagnostics

Roche Tissue Diagnostics

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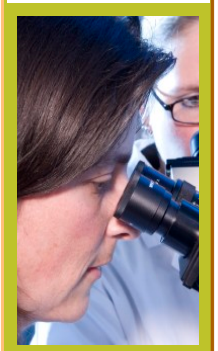
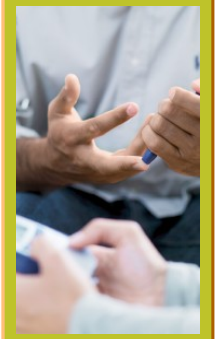


Roche Diabetes Care



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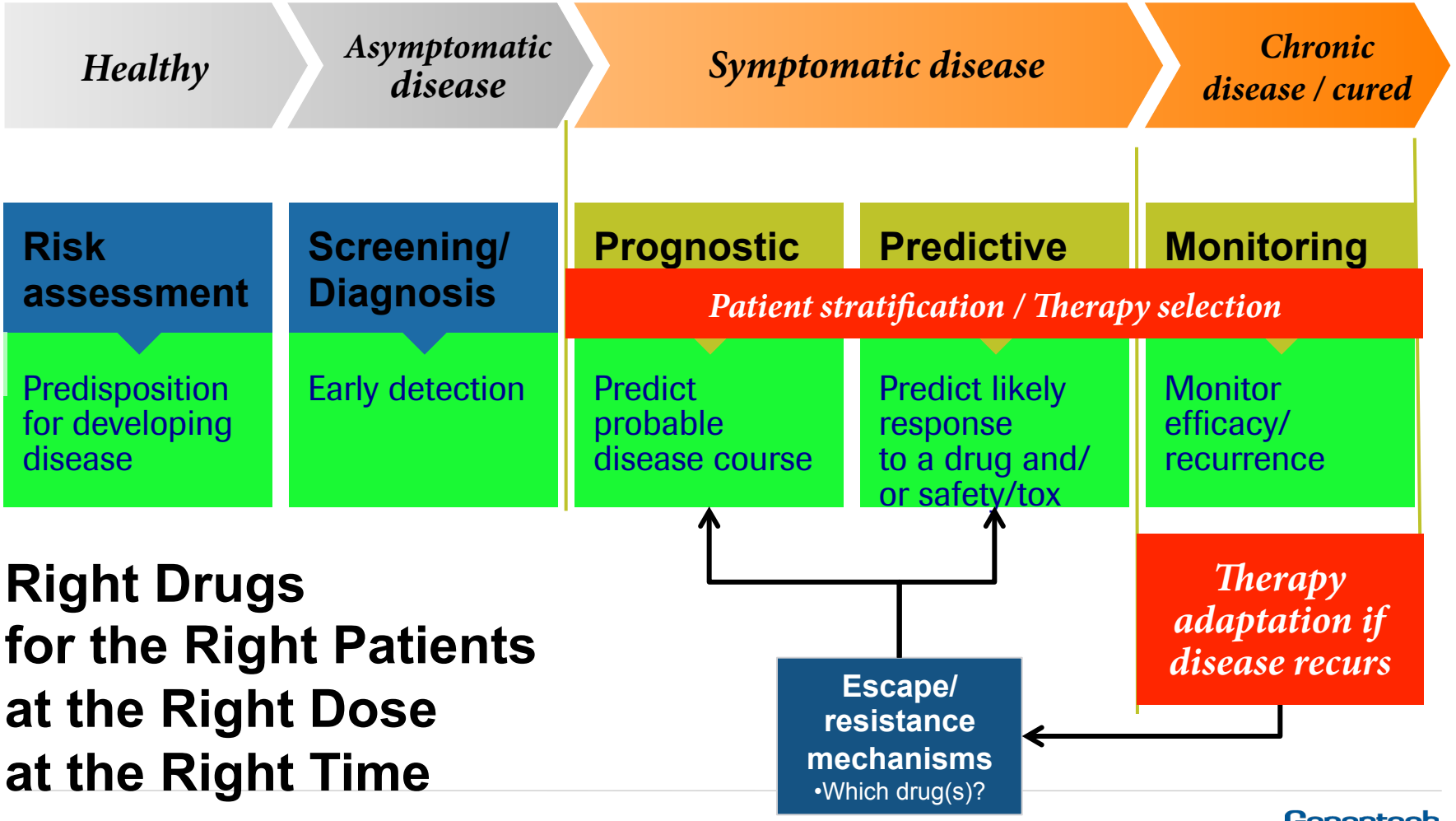
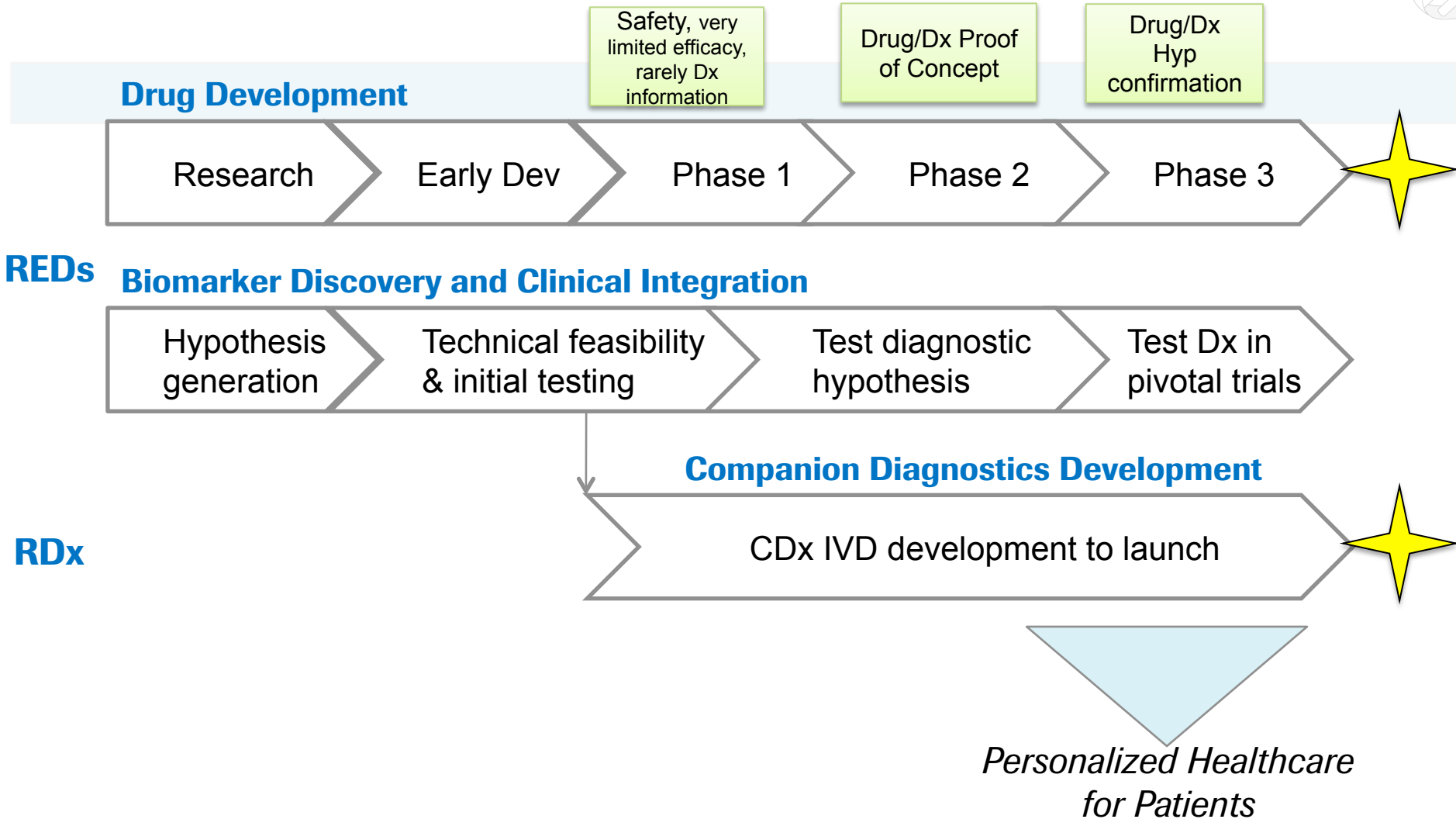
Biomarker development – why ?



Right Drugs
for the Right Patients
at the Right Dose
at the Right Time

Adapted from Stefan Scherer BRG

Co-development of drugs and diagnostics at GNE / Roche



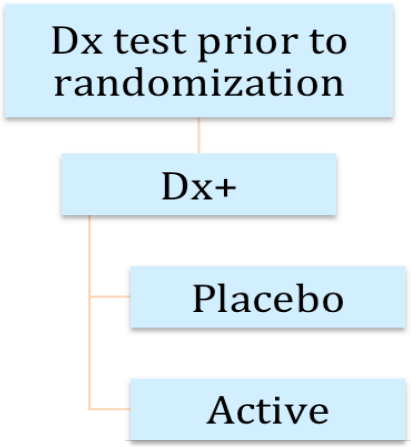
Adapted from FDA draft concept paper on drug diagnostic co-development, April, 2005

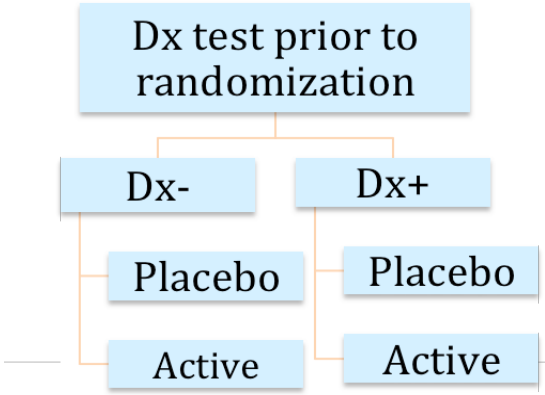
PHC Assessment

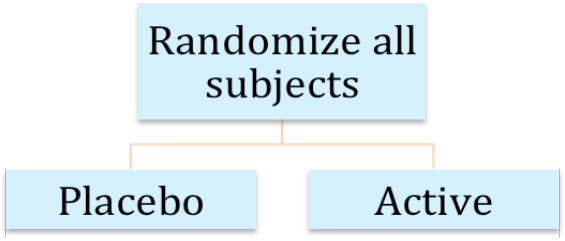
• Strong Dx hypothesis • No activity in Dx-	• Strong Dx hypothesis • Some activity in Dx-	• No strong Dx hypothesis • Exploratory Stage

Development Strategy

• Patient selection through all phases of development	• Complex, larger phase IIs with stratification • Complex phase IIIs	• No selection or stratification • Retrospective data exploration







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Key challenges for drug-diagnostic co-development

- Label-enabling trials design and analysis
- Biomarker cutoff selection and refinement
- Multiple biomarkers and multi-marker tests

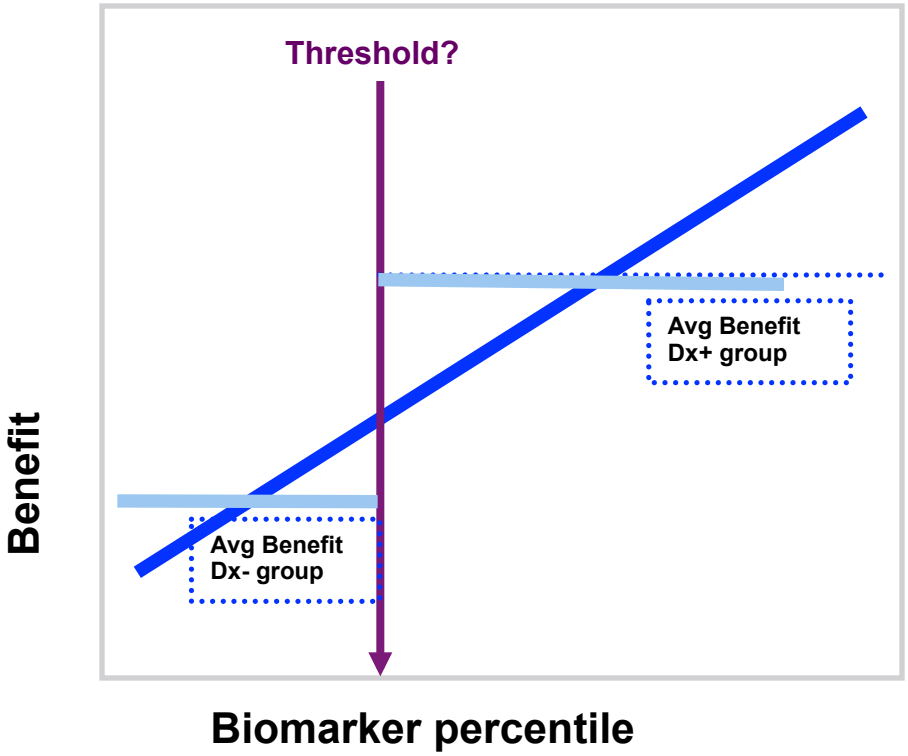
Design and Analysis: what is the target population for evaluation?

Scenario	Effect in Dx-	Evaluation of Dx- in Ph III	Primary endpoint
Selected	Negative	Exclude or limit patients	Dx+ only
Stratified	Minimal Benefit	Limited, adaptive stopping, or include all comers?	Dx+ first Dx- if success in Dx+
Stratified/ All-comers	Positive Benefit	Enroll all Dx- patients	Dx+ or all-comers

Considerations:

- Adequate evaluation of Dx- subgroup depends on scenario and clinical context
- Key factors in determining Dx+ vs. all-comers label (Stratified)
  - Clinically meaningful treatment benefit level
  - Magnitude of difference in Dx+ vs. Dx- treatment benefits
  - Risk/benefit evaluation in Dx- patients and unmet need
- If all-comers label pursued in the 3rd scenario, include Dx results in Clinical Studies section of label if clinically meaningful

Biomarker Cutoff Selection and Refinement



Often, no clear best threshold:

Appropriate threshold will depend on:

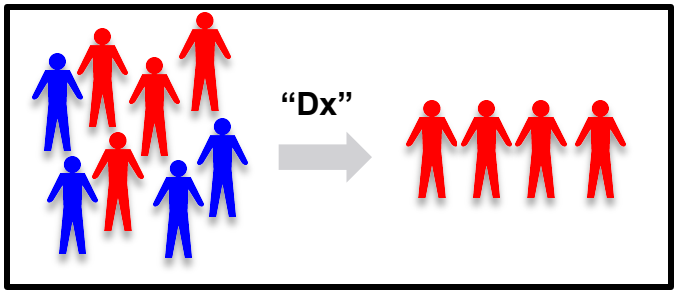
- **clinical benefit/risk**
- **scientific rationale**
- **biomarker distributional properties (e.g. bimodal)**

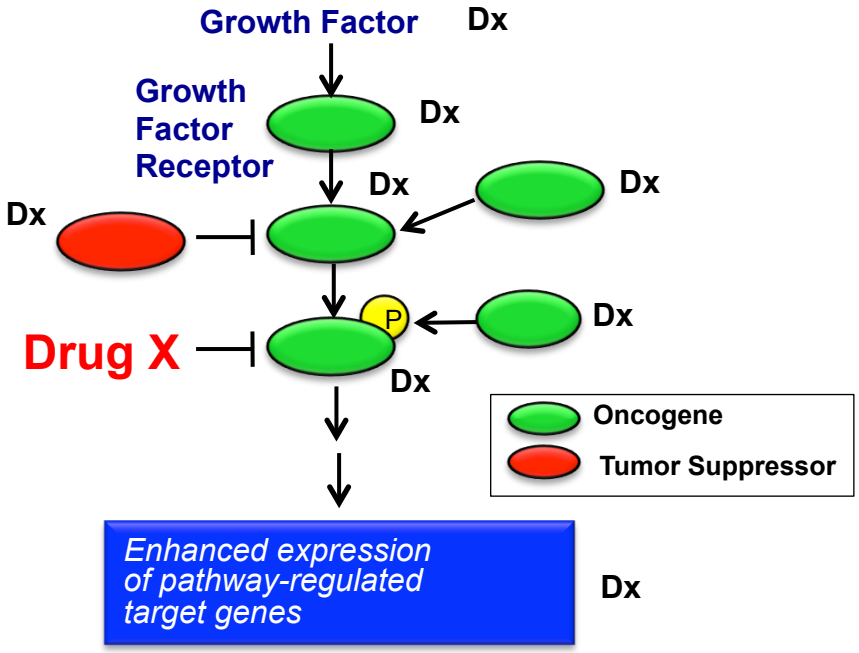
Note the population size vs effect size trade-off

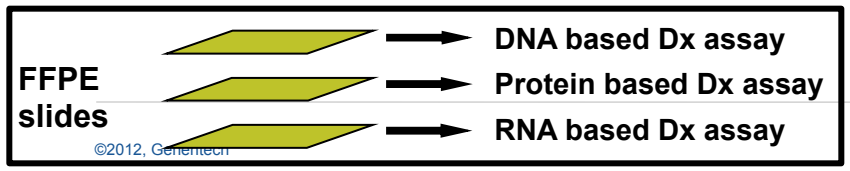
Proposed Strategy

Pre-specify Dx+/- threshold prior to Ph III unblinding, and adjust threshold in label based on Ph III results and discussions with HA (assuming positive results based on pre-specified threshold)

Complex Biomarker World Today

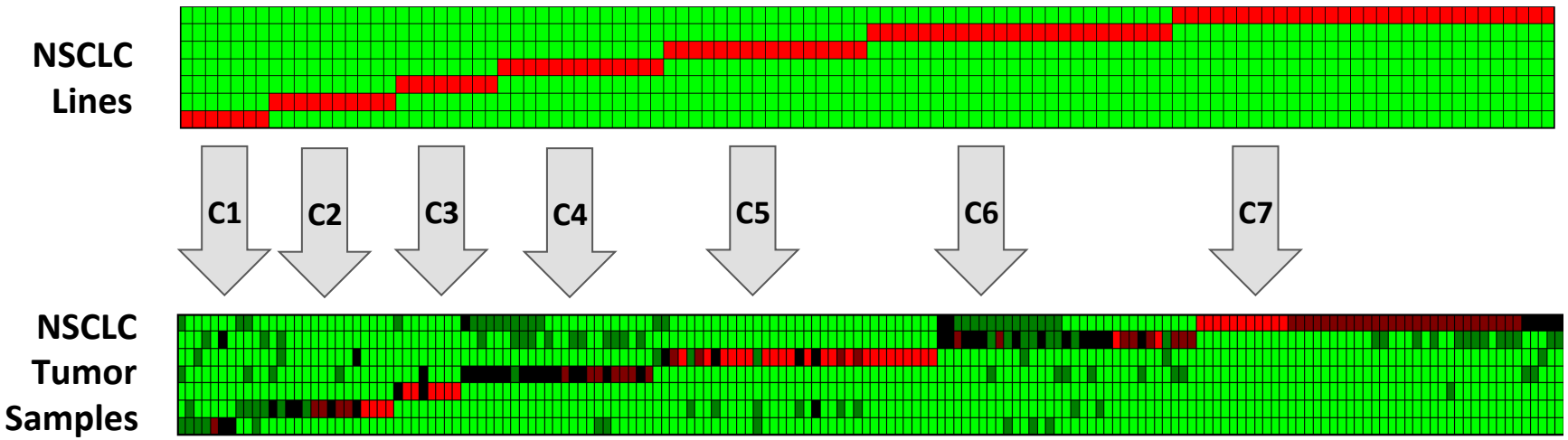


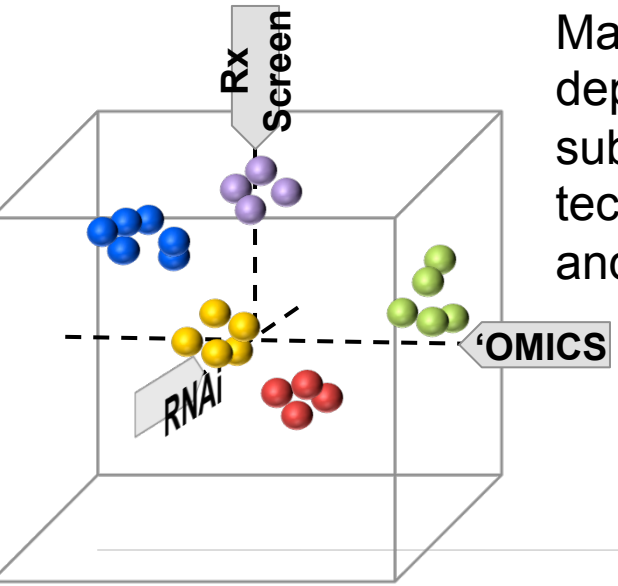




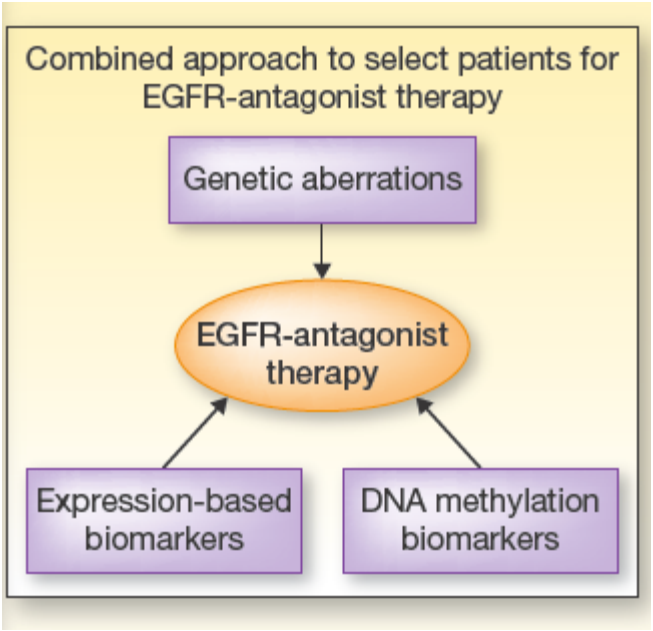
- Increasingly complex companion diagnostic
  - Driven by disease biology
- Full clinical validation of each biomarker may not be feasible (ex. infrequent mutations)
- For multiplex biomarker signatures no expectation that individual biomarkers will be predictive
- Alternative clinical and analytical validation should be considered depending on the situation

Next generation technologies: Matching drug to disease





Matching druggable dependencies with disease subtypes,
technically robust biomarkers and pipeline drugs



Biomarkers for EGFR-antagonist response: In the genes, and on the genes!

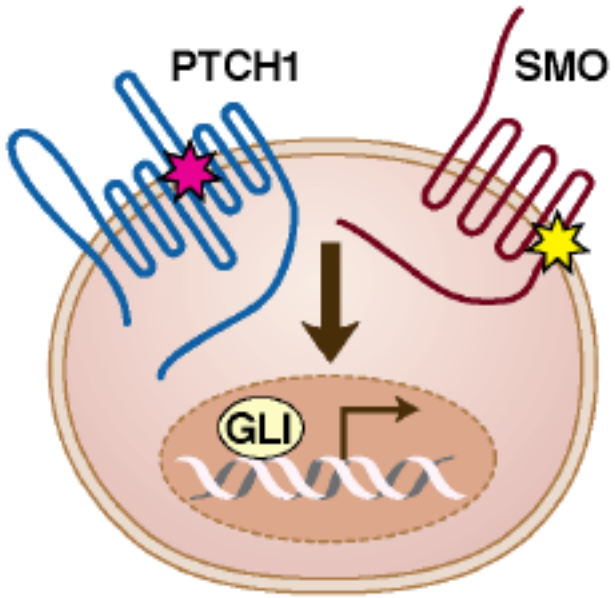
Hariharan Easwaran and Stephen B. Baylin

Clin Cancer Res Published OnlineFirst February 27, 2012.

Adapted from David Shames OBRF presentation, 2012

Everidge(Hedgehog Pathway Inhibitor)–
Follow the Tumor Genetics

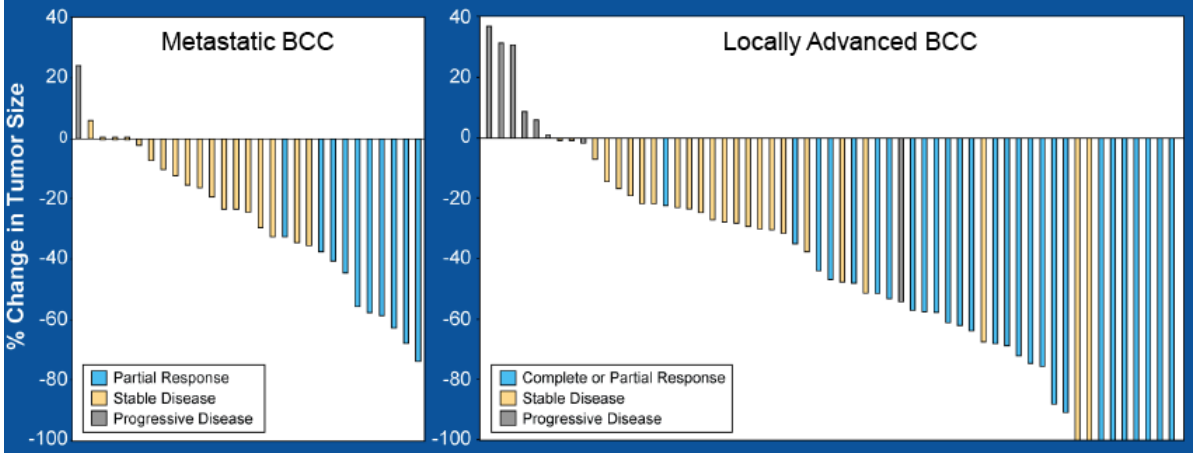
Mutation-associated



Basal Cell Carcinoma (BCC)

Medulloblastoma

Pivotal Phase 2 Study of Metastatic and Locally Advanced BCC Patients



	mBCC (n=33)	laBCC (n=63)
ORR by Independent Review	30.3%	42.3%
PFS by Independent Review	9.5 m	9.5 m

ORR= Objective response rate; PFS= Progression-free survival

Disease (BCC) = Diagnostic, hence no companion Dx (nearly all BCCs have mutations in PTCH1 or SMO)

Adapted from Nov1 2011 ODAC

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Molecular Classification of Medullablastoma

- Mutation-based test NOT feasible to identify Hedgehog-driven medullablastoma
  - Multiple genes involved, no hotspots
  - Non-mutation changes possible (e.g. epigenetic silencing, gene inversion)

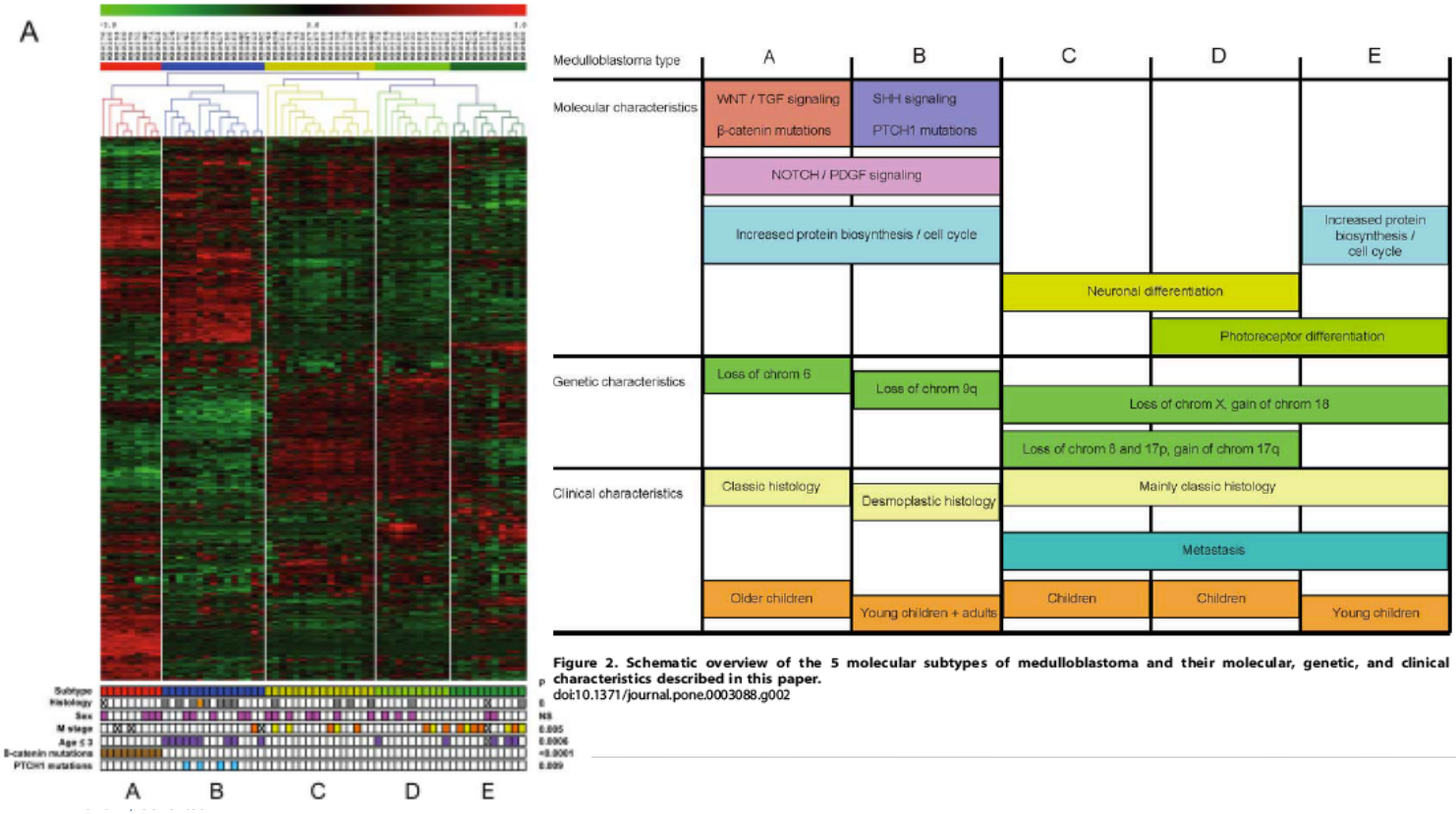

Figure 2. Schematic overview of the 5 molecular subtypes of medulloblastoma and their molecular, genetic, and clinical characteristics described in this paper.
doi:10.1371/journal.pone.0003088.g002

Adapted from Kool et al, PLoS ONE 2008

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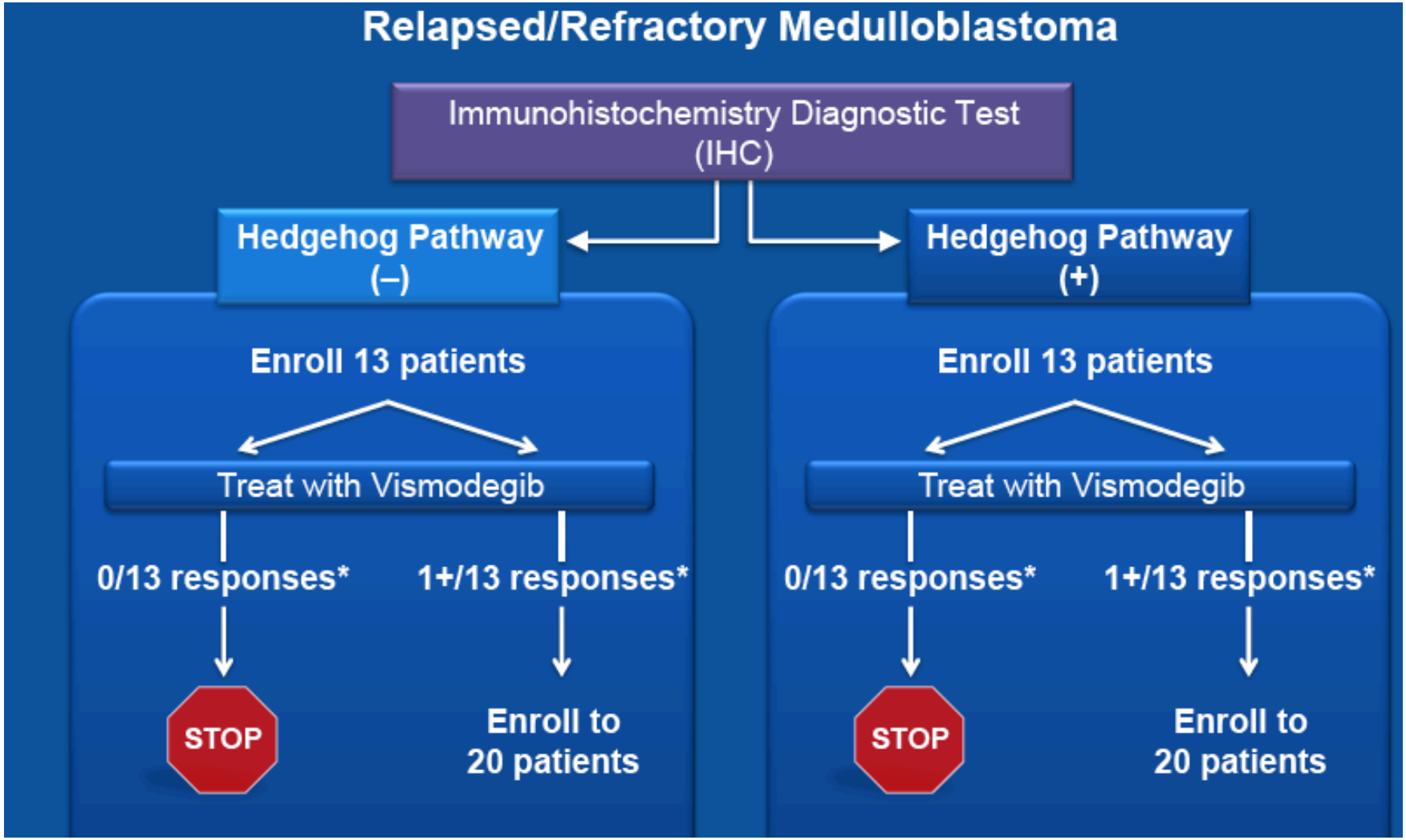
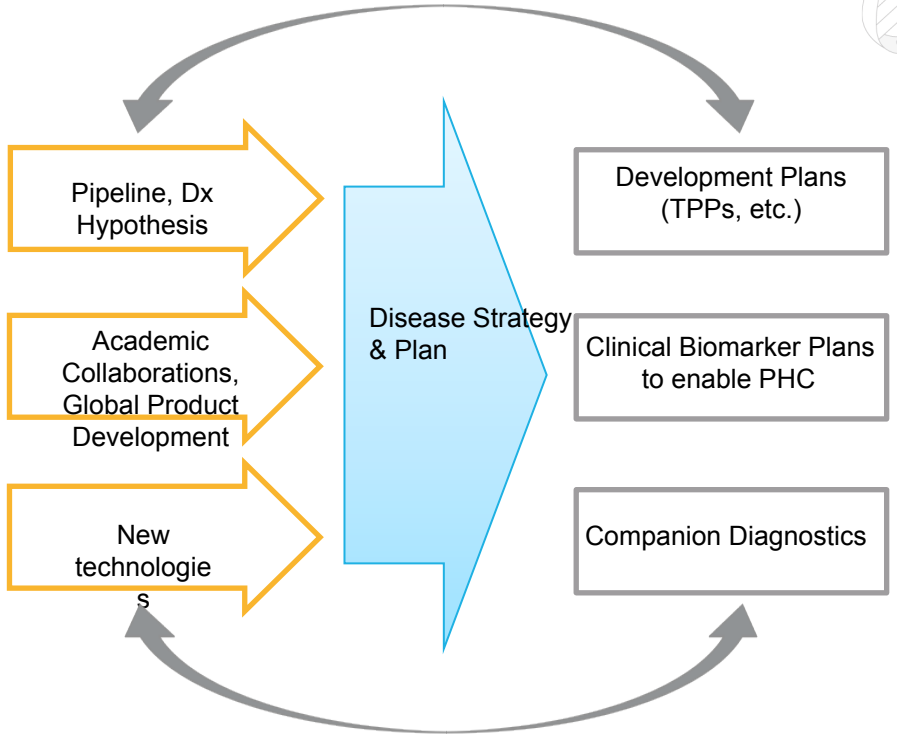
Examining Dx Hypothesis: PBTC-032 Phase II Pediatric Study



Adapted from Nov 1, 2011 ODAC

PHC: Integrating research and development

- Extensive drug and technology pipeline
- Focus on effective .EDU-.ORG-.COM collaborations
- Cross-functional teams including research and development
- Strategic information gathering to provide robust datasets for better informed efficient drug development



Adapted from David Shames OBRF presentation, 2012

Summary – Biomarkers, clinical development and next generation technologies

- **Extensive use of evolving technologies to improve disease molecular classification and biomarker hypothesis generation**
  - **Effective research-development integration**

- **Focus on established technologies for companion Dx development**
  - **Proactive discussions with the regulators to establish acceptable approaches**

Beyond companion Dx:

- Formulating strong preclinical hypothesis about effective drug combinations
- Identifying relevant early-on-treatment measures
- Steering Phase I patients to the most appropriate trials – shift in signal-seeking
- Understanding mechanisms of resistance upon progression with the aim of finding most appropriate next treatment
  - Characterizing tumors via circulating tumor cells analysis.

Acknowledgments

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- Clinical:
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- Regulatory:
  - Michelle Rohrer, Azin Shahzaman, Nancy Gerber