



The Importance of High Quality, Appropriately-annotated Specimens in the Development, Registration and Commercialization of Candidate Drugs and Diagnostics:

*Observations from the perspective of a pharmaceutical sponsor
and government consultant*

John C Bloom, VMD, PhD
President, Bloom Consulting Services, LLC
Special Government Employee, FDA

Drug and Diagnostic Co-development Workshop on the Cancer Human Biobank Biospecimen-based Reference Sets

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National Institutes of Health, Rockville, MD



What's Different Today?

- Portfolios
 - Mergers and acquisitions
 - R&D transformation and relentless downsizing in Pharma
 - Aggressive (desperate) outsourcing efforts
 - Rapidly evolving translational science and enabling (disruptive) technologies:
identification and characterization of major signaling pathways and key mutations
 - Growth in number of specialized life sciences/drug development service providers
 - Gov/Academic/Industry partnerships and cooperative groups
(ie FDA Centers of Excellence, NCI Cancer Genome Atlas Project, ADNI)
 - Integrated biomarker and diagnostic development strategies
 - Growing emphasis on personalized medicine and health outcomes
- Presents increasing challenges to stakeholders relating to the access to and use of biological specimens***

Specimen Access as a Critically Enabling Resource in Pharmaceutical and Diagnostics R&D

Appropriately collected, stored and annotated specimens provides for molecular characterization of the patient/clinical trial subject and disease, which enables:

- drug discovery
- translational medicine
- clinical development
- diagnostic development
- product differentiation
- personalized medicine

BIOSPECIMEN STAKEHOLDERS

- Drug and Dx developer
- Regulator
- CRO/ARO/ Res Cooperative Group
- Specimen provider
- Specimen banker
- Specimen analytical service provider
- Prescriber
- Payer
- Patient

*Rapidly evolving and interdependent value propositions
with strategic, technical and operational implications*

Specimen Access as a Critically Enabling Resource in Pharmaceutical and Diagnostics R&D

- Requires access to a range of biological specimens that includes **blood components, urine, CSF, tissue and extracted nucleoproteins**, among others
- May be collected fresh or (more commonly) stored temporarily or long term in biorepositories, or biobanks
- May be obtained commercially or collected from clinical trial subjects during development of a drug or diagnostic
- Requirements relating to collection process, handling and storage conditions; and level of annotation are defined by the application (ie “fit-for-purpose”)

Applications of Commercially-obtained Specimens in Drug Development

Greatest demand in oncology candidate discovery and development: used in conjunction with cell lines, xenografts and related in vivo models

- Target identification, validation and characterization:
 - target specificity
 - expression in tumor types and other tissues
 - off-target effects
 - heterogeneity of expression/polymorphisms
- Validation of animal models for efficacy and preclinical safety (ie species specificity)
- Patent claims
- Regulatory submissions

Applications of Commercially-obtained Specimens in Drug Development (Con't)

- Inform clinical development strategy
need to screen/stratify patients
- Biomarker development
informed by target characterization, expression, off-target effects, pathophysiology, etc
- Provide reference/standard for tumor molecular profiling
stage-specific, effect of standard tx regimens, relapse, etc
- Diagnostics development
prospectively and retrospectively in conjunction with specimens banked from clinical trials

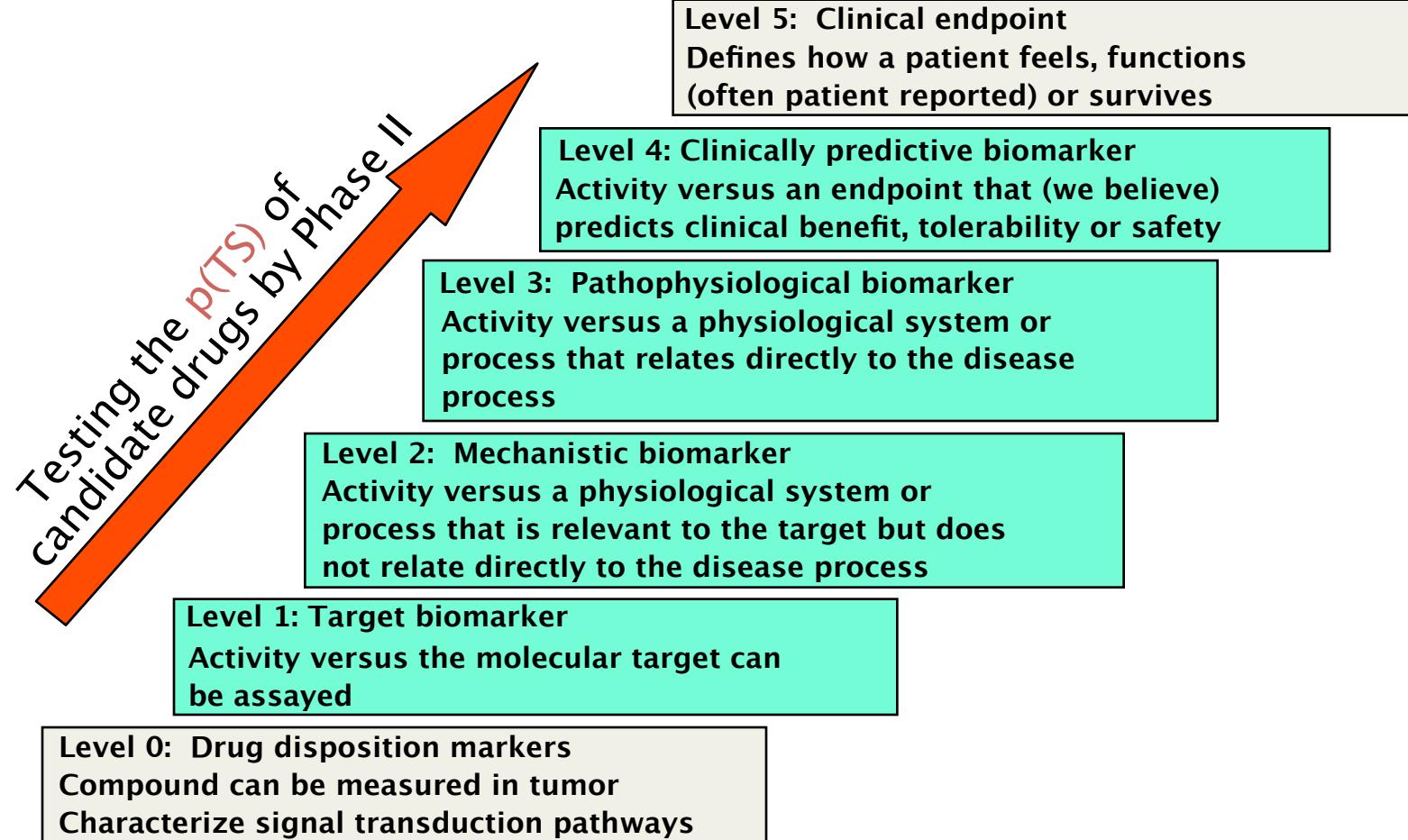
Requires access to specialized biorepositories through pharma service providers or strategic partnerships/collaborations

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Impact of Biomarkers on Productivity



BIOMARKER STRATEGIES ARE FOUNDATIONAL TO DIAGNOSTICS DEVELOPMENT

Finding Biomarkers that Enable Cancer Drug Development and Provide Candidate Diagnostics

CHALLENGES

- Access to tissue
- Limitations of current surrogates and models
- Reliance on solid tissue markers
- Dynamic nature of tumor genotype, phenotype and signaling pathways
- Identifying phenotype of responsive patient
(absent markers for mechanistic-based hypothesis)
- Pace of scientific and technological advances relative to development cycle time and regulatory science
- Integrating molecular markers into CTs and clinical practice



Tissue Acquisition Challenges

Tissue for target identification/evaluation/characterization

- Limited availability of high quality, fully annotated tissue appropriately quality controlled for sources of collection, storage and fixation artifacts
- Consent due diligence and documentation issues (especially with “low cost” international vendors)
- Minimal quality control regarding representative samples
TCGA/OBBR experience: >98% dropout rate; of those that qualified, >29% failed to meet molecular testing quality standards
- Limitations of FFPE specimens
- Cost
Exorbitant expense: eg \$ 25,000/ 25 specimens of multiple myeloma or mesothelioma

NCI identified access to quality tissue as the largest impediment to translational oncology research



Tissue Acquisition Challenges (cont.)

Specimen collection in clinical trials

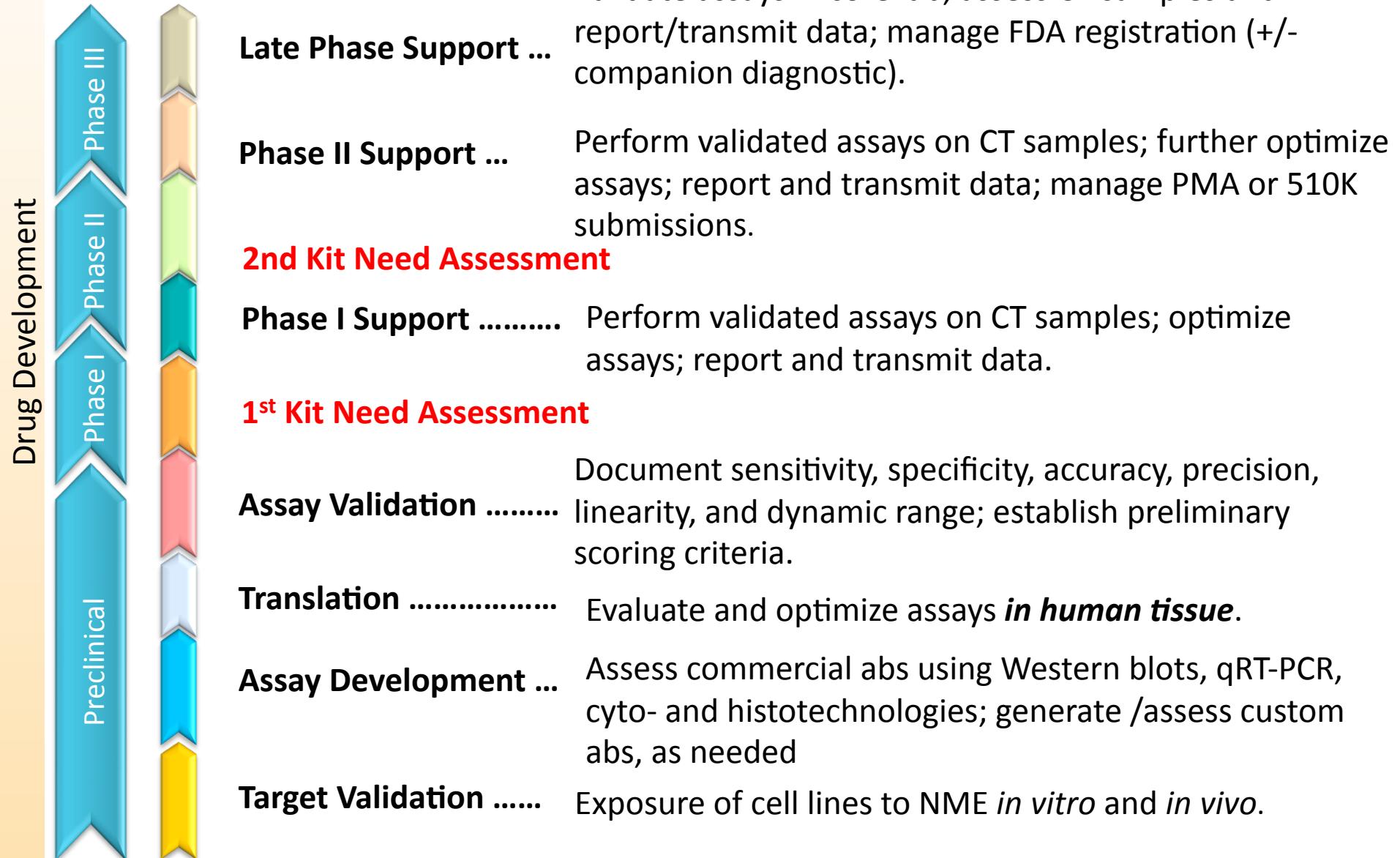
- Having care giver and subject agree to pre- and post-tx biopsies
- Difficulty accessing archived (pre-tx) diagnostic specimens
 - reliance on “good will” of site pathologist (cost of retrieval, quality assessment and histotech support rarely compensated)
 - patchy documentation and annotation
 - result = as low as 30 % success in retrieving pre-tx diagnostic tissue that is appropriately annotated, quality controlled and consented
- Reluctance to have site take measures that ensure quality of biopsies (i.e. engaging interventional radiologists to ensure appropriate tissue is biopsied)
- Competency

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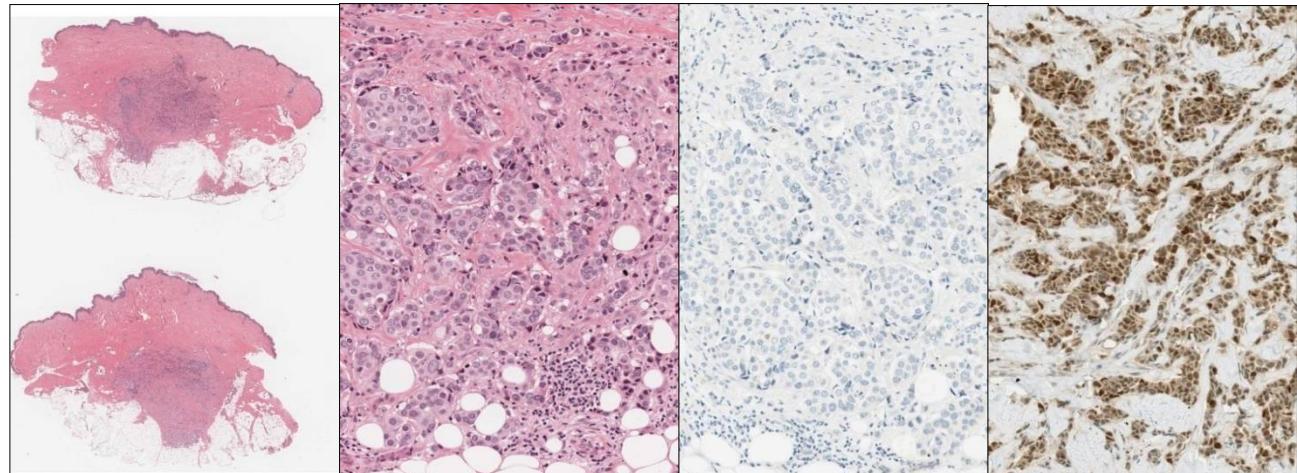
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IHC Assay Development and Application

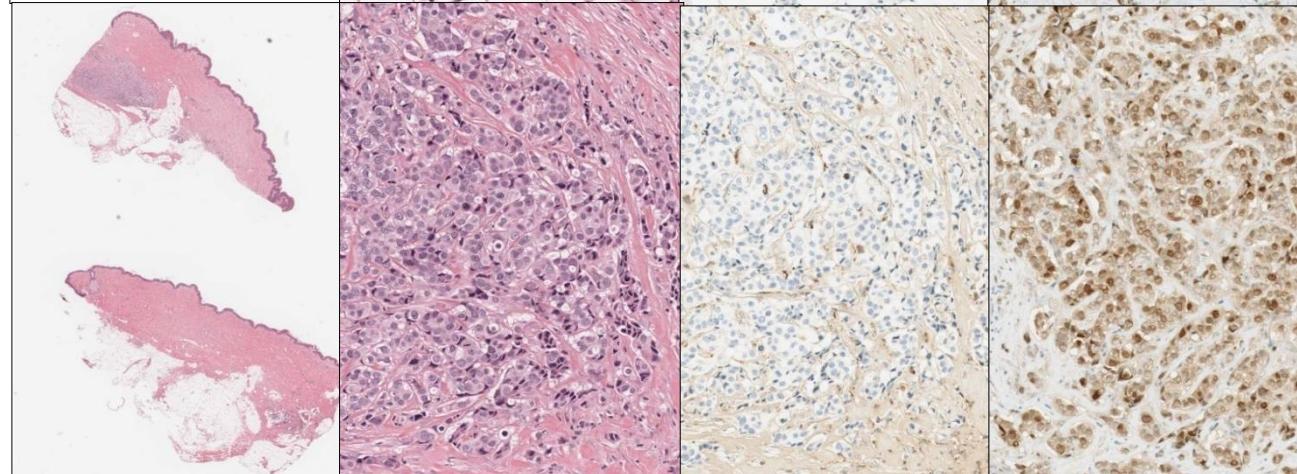


Invasive Ductal Carcinoma of Breast

Pre-Treatment



Post-Treatment



1X H&E

20X H&E

20X ASO

20X Survivin

Talbot et al, Abstr # 3507
ASCO Annual '09 Mtg

Biomarker strategy for a Small Molecule Signal Transduction Inhibitor of an Overexpressed Growth Factor Receptor (con't)

Pharmacodynamic Biomarker Strategy

Preclinical

- Phosphorylated receptor measured in *acquired tumor tissues*
- ELISA assay for phosphoprotein validated for use in PBMC and Xenografts to measure target modulation; corroborated with IHC to compare dynamic range

Clinical

- Phosphoprotein to be measured in biopsy samples using ELISA and IHC
- Ki67 in latter measured to establish proliferative index
- Validated ECD ELISA to be used to monitor response
- Explore use of target expression on CTC to stratify patients
- Explore use of FDG PET imaging to demonstrate mechanistic link between phosphoprotein and perfusion-related glucose uptake

Biomarker strategy for a Small Molecule Signal Transduction Inhibitor of an Overexpressed Growth Factor Receptor: *Importance of Access to Well-annotated Specimens*

Patient stratification strategy

- **Markers for target receptor overexpression:**
IHC assay- developed and validated in house; assay/reagent transferred to vendor.
Using multiple tumor microarrays, identified histologic tumor subtypes that have significant overexpression (***requires access to well-annotated specimens***)
Genomic amplification demonstrated with FISH assay; validated for use on clinical samples.
Previously reported extracellular domain (ECD) confirmed using ELISA- blood based assay. Correlation with upregulation of receptor in tumor under investigation
- **Receptor mutation investigated using hotspot mutation detection assay**
- **Ligand measured using commercially available ELISA; elevated levels detected in patients with the above histologic subtypes of tumors.**

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Plenary Session on Cancer Genomes

- Bert Vogelstein: “*After sequencing 21,000 exomes in 100 tumors, where are we?*” (a real sleeper of a title!)Reviewed mutations in genes identified in 353 cancer subtypes
130,072 mutations in 3142 genes: (**only approx 320 “driver genes”**
(286 tumor suppressor and 33 oncogenes)
Almost all fall in 12 “core” signaling pathways
Profound implications for dx and tx! (problem= tumor heterogeneity)
requires molecular profiling of each patient’s tumor
Use of (quantitative) IHC and cell-based systems
- BATTLE (Bmkr-integrated Approaches of Targeted Tx for Lung Ca Elimination)
First completed biopsy-mandated study in 255 pre-treated NSCLC pts
Markers from 4 NSCLC molecular pathways: EGFR, KRAS, BRAF/M (PCR);
EGFR, Cyclin D1 (FISH); VEGF, VEGFR, 3 RXR receptors + Cyclin D (IHC)
Patients adaptively randomized based on eligibility criteria and bmkr analysis
Predictable and variable improvement in 8 wk disease control
Confirmed value and feasibility of routine biopsy and profiling for all NSCLC pts

Requirements for Integrating Molecular Markers Into Clinical Trials and Clinical Practice

- Protocol/testing standardization
- Marker validation
- Commitment to and feasibility of tissue collection
- Access to high quality, practical technical platforms and services
- Role of sponsor, CRO, analytical service provider

Access to well-annotated reference specimens is critical!

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Effect of Tumor Progression and Treatment on Molecular Profile

- Additional mutations
- Emerging clones
- Transient nature of effects of tx on key signaling pathways e.g. phosphoprotein modulation with kinase inhibitor how to best capture and interpret
- *Underscores importance of access to and full characterization of pre- and post-tx specimen from subject and reference tissue from matched controls*

FDA requires assessment of $\geq 90\%$ subjects to support claims based on such changes



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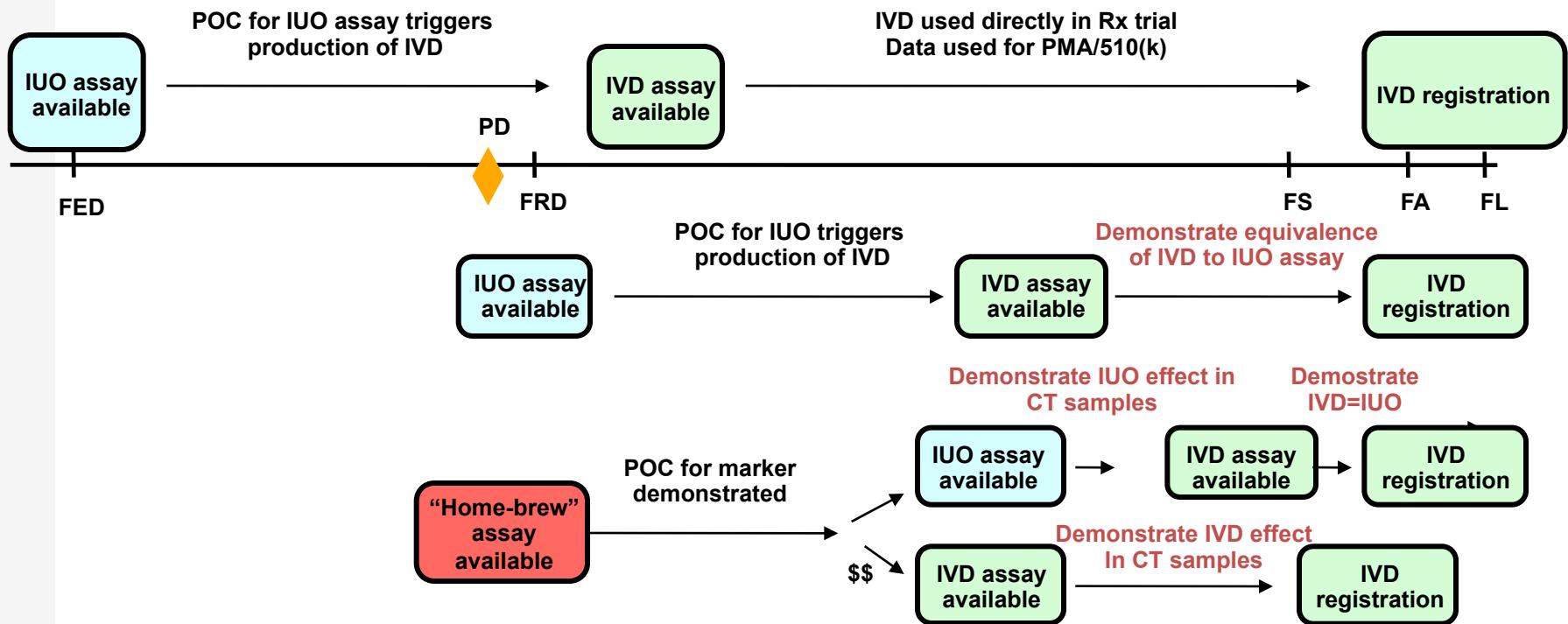
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Developing Diagnostics in an R&D Setting: *Guiding Principles*

1. Overarching priority: use diagnostics to optimize the value of sponsor's drugs in the marketplace
 - Critical to corporate strategies (eg Lilly): *improve outcomes for individual patients*
 - “Stand-alone” business value of diagnostics is limited, compared with new drugs
2. Range of assay-driven technologies and commercialization needs requires multiple, and often novel, partnerships
3. Indication/opportunity for a value-added diagnostic can occur at any point of the drug development/commercialization chain
4. The diagnostic registration process is regulatory-driven and well-defined
5. Factors critical to successful diagnostic development include:
 - Freedom to operate through enabling IP and regulatory strategies
 - Effective strategic partnership development and management
 - **Access to human specimens**
 - Organizational effectiveness with functional expertise/alignment

Alternate DX Development Scenarios

Because DX needs may arise at any point in the drug development process, the idealized timeline will not always be possible.



Having ready access to clinical trial samples is the key resource to allow accelerated registration of the diagnostic.

Examples of Late-phase Diagnostic Needs/Opportunities Requiring Banked Specimens

Platelet aggregation

- Dx for clopidogrel and prasugrel-induced platelet inhibition (ADP receptor blockade).
- partnered with Accumetrics
- late phase development opportunity driven by emerging PD profile of prasugrel vs. clopidogrel
- Lilly provided clinical context **and specimens** to assess performance, refine assay and validate

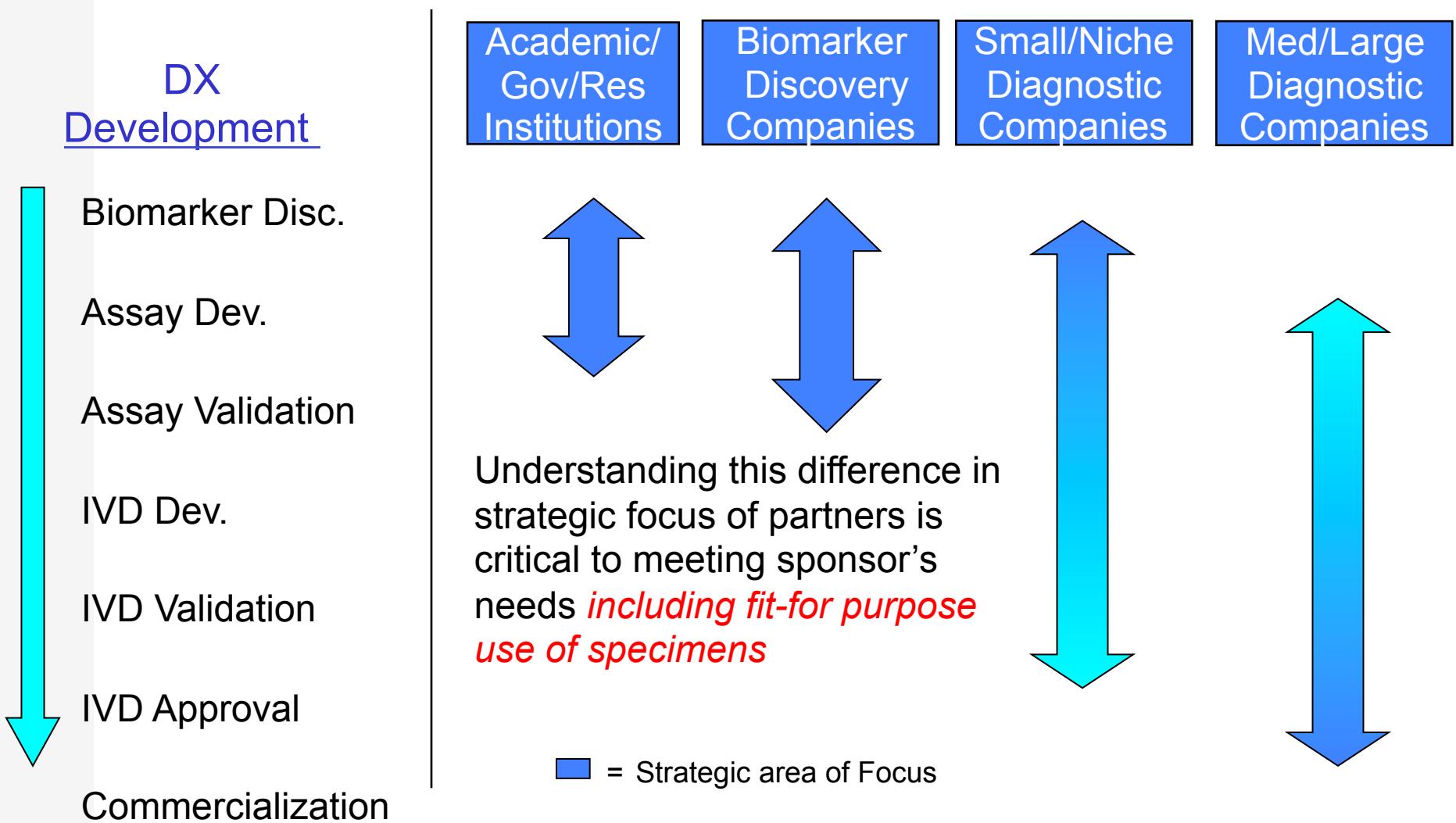
Protein C Assay for Sepsis

- marker to predict severity of disease and monitor response to Xigris
- partnered with Biosite to develop and validate **using CT specimens**

P1NP

- amino-terminal propeptide of type 1 procollagen
- marker of osteoblastic (anabolic) activity in patients with osteoporosis
- potential diagnostic for compliance in patients treated with teriparatide
- collaborated with two partners to develop, register and commercialize **using CT banked specimens** to ensure access and optimize value of drug

Spectrum of Dx Development Partnerships



Examples of Academic/Government Biobanking Partnerships

- NCI/OBBR national human cancer biobank
- Dept of Veterans Affairs genetic database
- UK Biobank (Univ of Manchester)
- Karolinska Institute Biobank
- European Research Infrastructure for Biobanking and Biomolecular Research (BBMRI)
- Qatar Biobank
- Most major academic cancer research centers
- Many academic-based specialized biobanks (cancer subtypes, schizophrenia, autism, diabetes, psoriasis, etc)
- Private partnerships such as Kaiser Permenente, Oakland, CA

Biobanking Equipment, Service and Specimen Provider Companies

Aperio	Expression Pathology	Qiagen
Agencourt Biosciences	GenVault	Rigaku
Agilent Technologies	Hamilton Robotics	RTS Life Science
Asterand	HistoRx	Thermo Fisher Scientific
Asuragen	Illumina	StarLIMS
Bacus Laboratories	Imgenex	US Biomax
Beecher Instruments	Indivumed	Zyagen
Biochain	ILSbio LLC	
BioFortis	ISU ABXIS	
Biomatrica	Kreatech Biotechnology	
Biostorage Technologies	htLabVantage Solutions	
Clontech	LabWare LIMS Solutions	
Cybrdi	Life Technologies	
Cytomyx	M2Gen	
deCODE Genetics	NuGen	
Epicentre	Pathology Devices	

Value Proposition for Banking During Clinical Development

Critical resource for follow-up candidate discovery, optimization and development

Essential for candidate- and CT subject-specific biomarker development

- Predict PK/PD, efficacy and safety
- selection and stratification of CT subjects
- address regulatory concerns
- prospective and retrospective diagnostic development

Post-registration challenges and opportunities

- characterize/predict response on broader exposure
- apply new technologies, biomarkers and diagnostics
- address claims such as genetic associations
(*critical insurance policy*)

Key ROI debate: specific research objective/hypothesis-driven vs resource for addressing unanticipated future needs

Late Stage Opportunities Lost or Delayed due to Availability of CT Banked Specimens

- **Zyprexa** – Weight gain studies – significant finding with PKHD1 gene on hold until additional samples collected
- **Strattera** – Relationship of response to NET1 polymorphism delayed because <200 samples of patients on Strattera collected = inability to differentiate Strattera from methylphenidate
- **PTH** – DNA banked, but not plasma/serum. No protein samples to perform P1NP studies
- **Duloxetine** – External data, of low quality, implying effect of serotonin transporter polymorphism with response and SAEs. No samples in bank to performed adequately powered study to respond.
- **Cialis** – Differentiate cialis from competitors by defining which patients on nitrates could take PDE5 inhibitors.
- **Xigris** – Predicting response markers – no samples banked during registration. Lengthy delay in obtaining ethics approval to use the samples on FTA cards (limited value due to low amount of DNA on cards).

OBBR Opportunities and Challenges

- Uses of CT subject vs patient/hospital-derived specimens
- FDA/OBBR mutual interests and support CTs as a source for caHUB?
 - Facilitate/encourage specimen collection in CTs
 - Align stakeholders re value proposition, expectations, fit-for-purpose practices, logistics, etc
 - FDA COE initiative
- Expand definition/utility of caHUB specimens
 - CTC
 - Optimized for circ DNA, exosomes, miRNA, etc