Evaluation of NGS for Companion Diagnostic Use

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IOM, Washington DC,
November 10, 2014

What is Precision Medicine?

"Identify the right patient for the right drug"

Precision Medicine Leverages

- Tumor Biology
- Biomarkers (PD, predictive, Imaging)
- Translational Medicine

To Deliver

- Better Patient Selection
- Better Patient Outcomes (Efficacy/Saf)

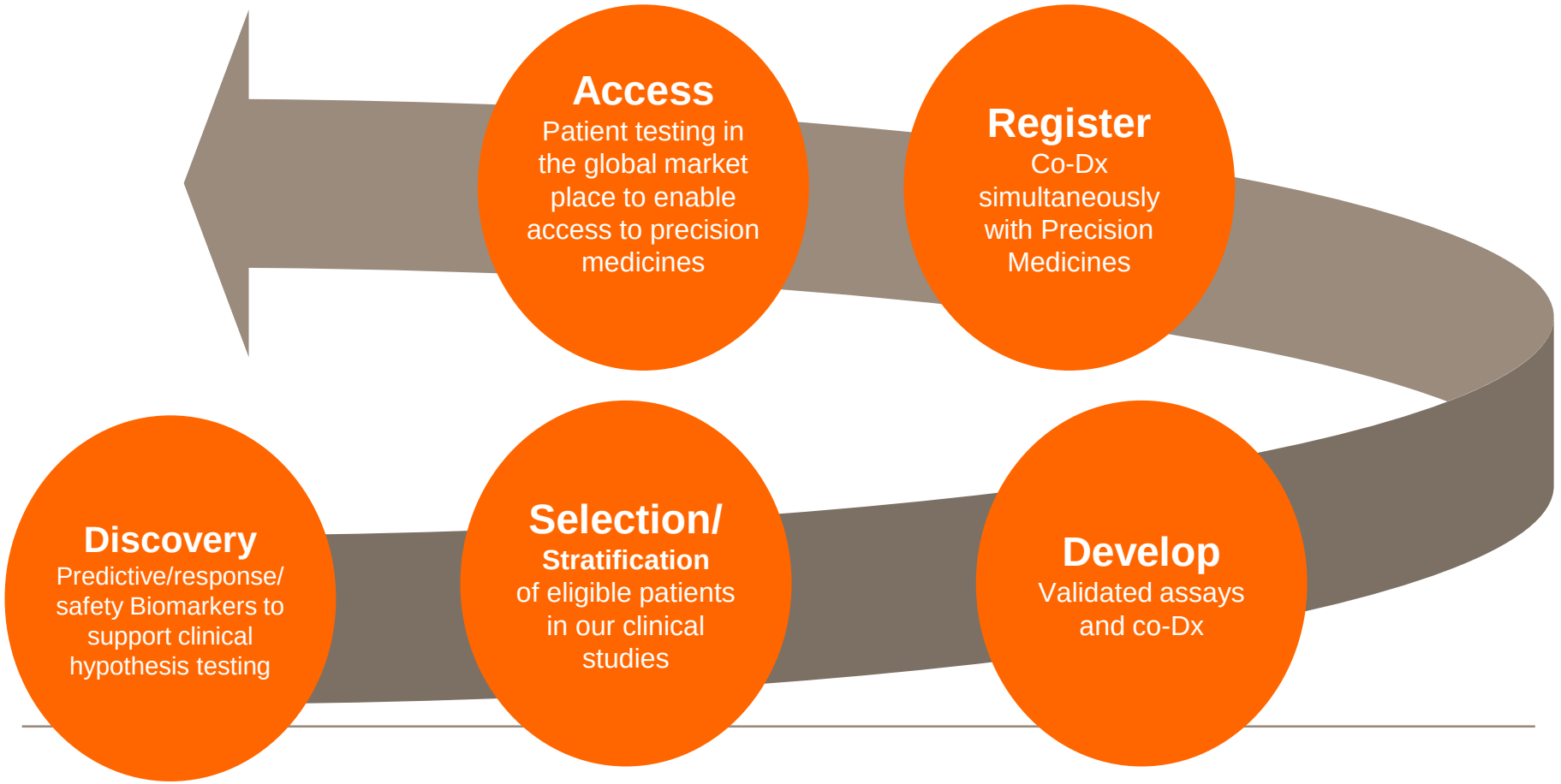
Resulting in

- **More efficient clinical dev**
- **Improved Benefit/Risk**
- **Stronger Value Proposition (for PM stakeholders)**

Precision Medicine and Diagnostics

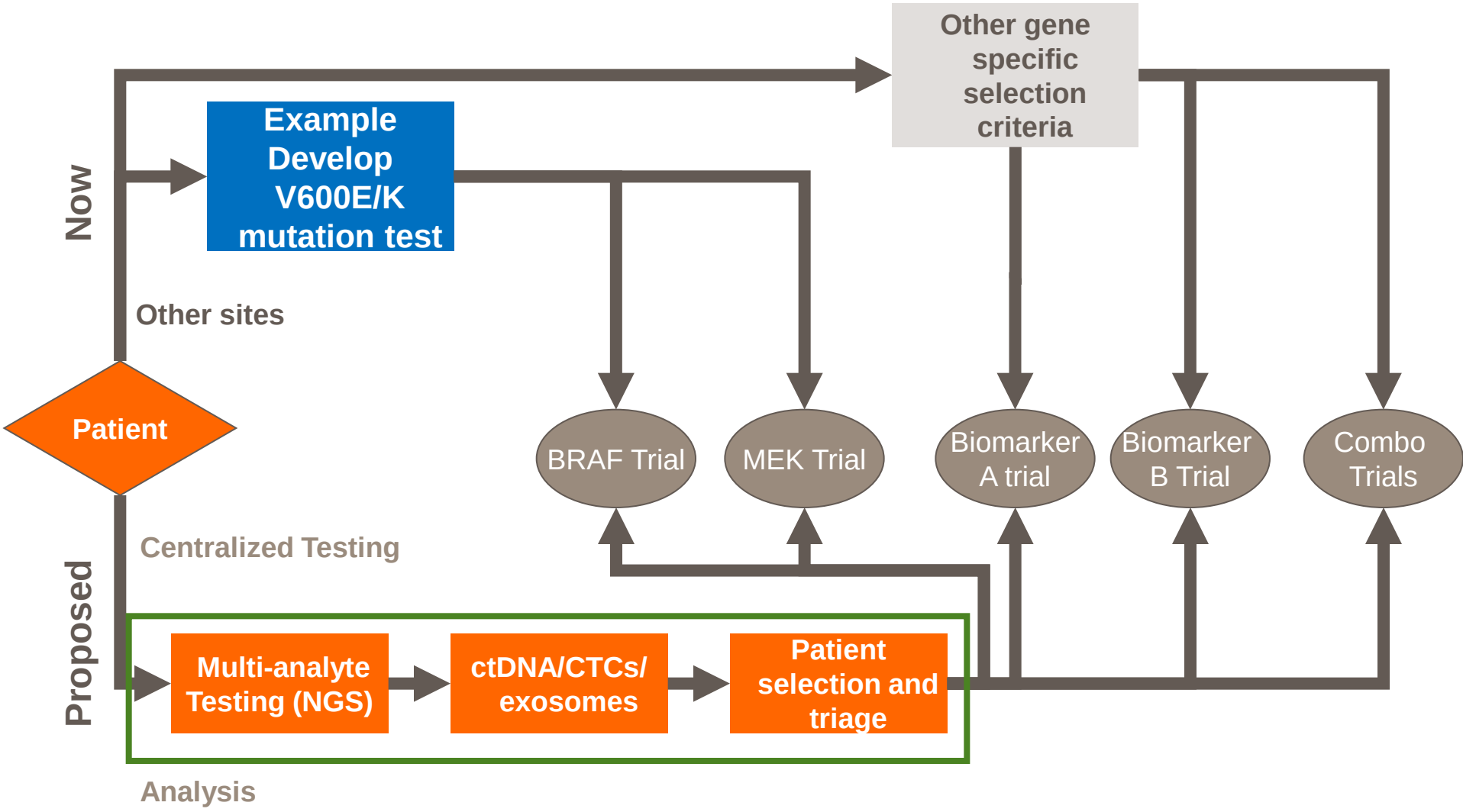
Integrated Delivery of Precision Medicine across the value chain

Requires excellence in biomarker discovery, patient sample collection, clinical translation and companion diagnostic development to select the right patient for the right medicine



Path to Precision Medicine

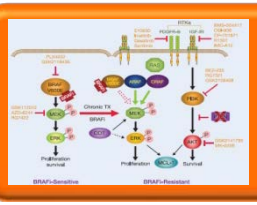
"One biomarker, one test, one drug" to multiple markers, multiple drugs



Bio-Informatics

Developing Targeted Agents in Cancer

Key considerations



Robustness of Science

Tumor Heterogeneity

- Complex molecular signaling cascades
- Multiple mechanisms of resistance

Patient Population & Unmet Medical Need

Clinical Trial Feasibility

- Incidence/prevalence of disease
- Frequency/presence of biomarker
- Patient consent; Access to tumor tissue (e.g. biopsy)

Cutting Edge Technology

Diagnostic Development Capabilities

- Assay validation (e.g. sensitivity/specificity)
- Sample processing and biomarker platforms
- Multiple biomarkers

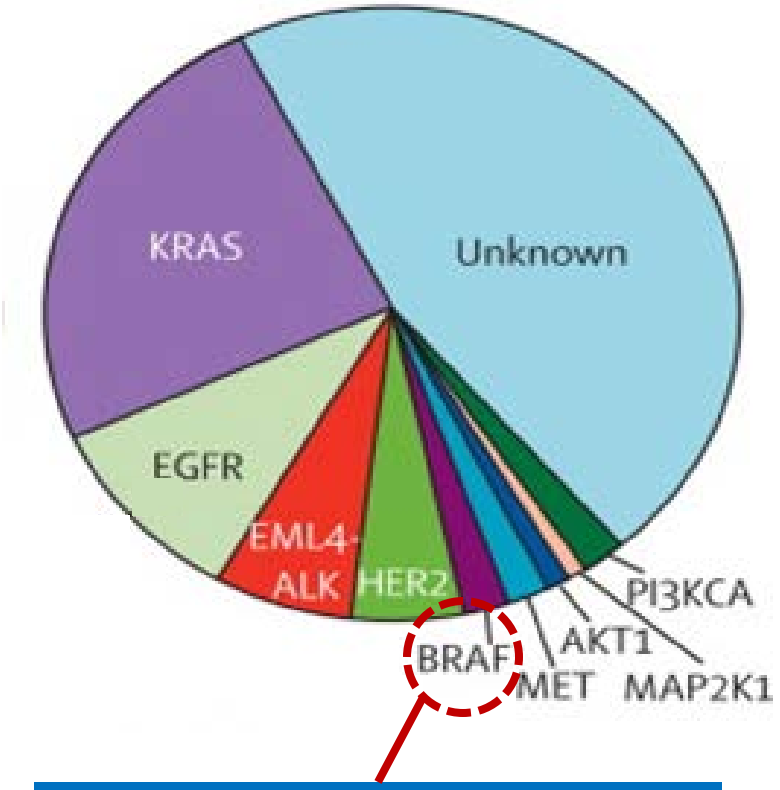
Evolving Regulatory Environment

Integrating Drug and Diagnostic Development

- Requirements for companion diagnostic
- Third party collaborations/partnerships
- Lack of global standards

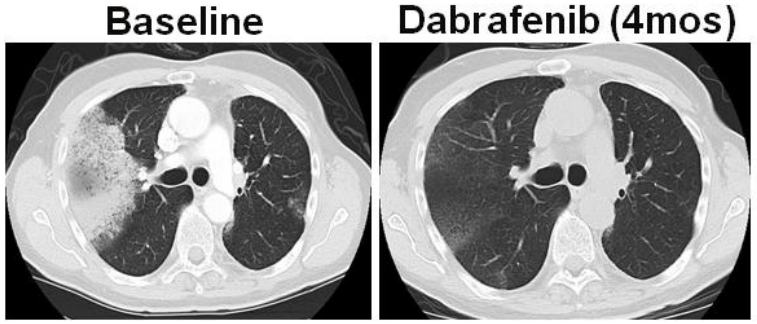
Challenges of Drug Development in Rare NSCLC Populations

BRAF V600E



1-2 % of NSCLC harbor BRAF V600E-mutations

- **Ongoing Phase 2 study (BRF113928) in advanced BRAF V600E+ NSCLC**
  - **> 11,000 subjects screened to enroll 23 patients (at interim)**
- **Complexity of conducting randomized Phase 3 trial in BRAF V600E+ NSCLC:**
  - **> 20,000 subjects to identify 300 eligible patients**
  - **~14yrs projected to complete study**

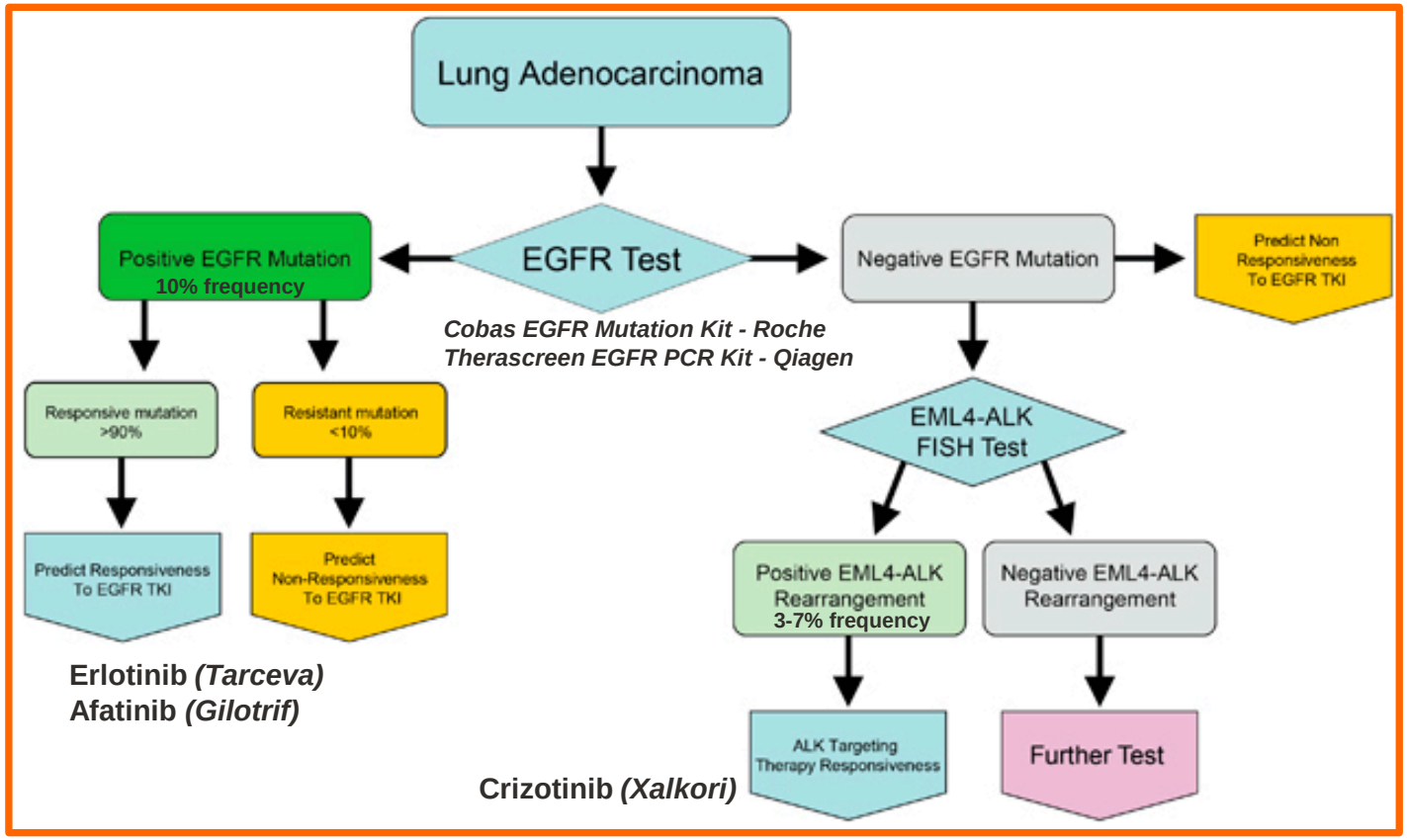


A. Marchetti et al., J. Clin. Oncol. 29, 1, 2011, P. Paik et al., J. Clin. Oncol. 29, 2046, 2011

G. Riely (MSKCC), Personal Communication

Molecular Testing Algorithm in Lung Cancer

The conundrum of insufficient tissue



- Small size & volume of lung biopsies
- Tissue is scarce following hierarchal biomarker screening
- Physician reluctance to obtain repeat biopsies- risk of invasive procedure
- High cost associated with multiple tests

Cheng, et al. 2012. Modern Pathology 25:347-369

Screening for Clinical Trials: BRAF, ROS1, RET, HER2, MET, KRAS…

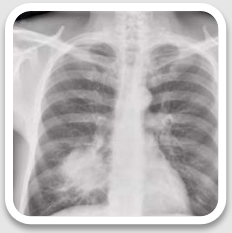
Patient Selection and cDx Development is Challenging

Path to developing targeted agents in Lung Cancer

Path to developing targeted agents in Lung Cancer

Molecular characterization of tumors

A large proportion of lung cancers have potentially actionable mutations



Segmentation of Lung Cancer

Develop therapeutics that target specific altered genes or pathways.

Revolutionize Drug Development

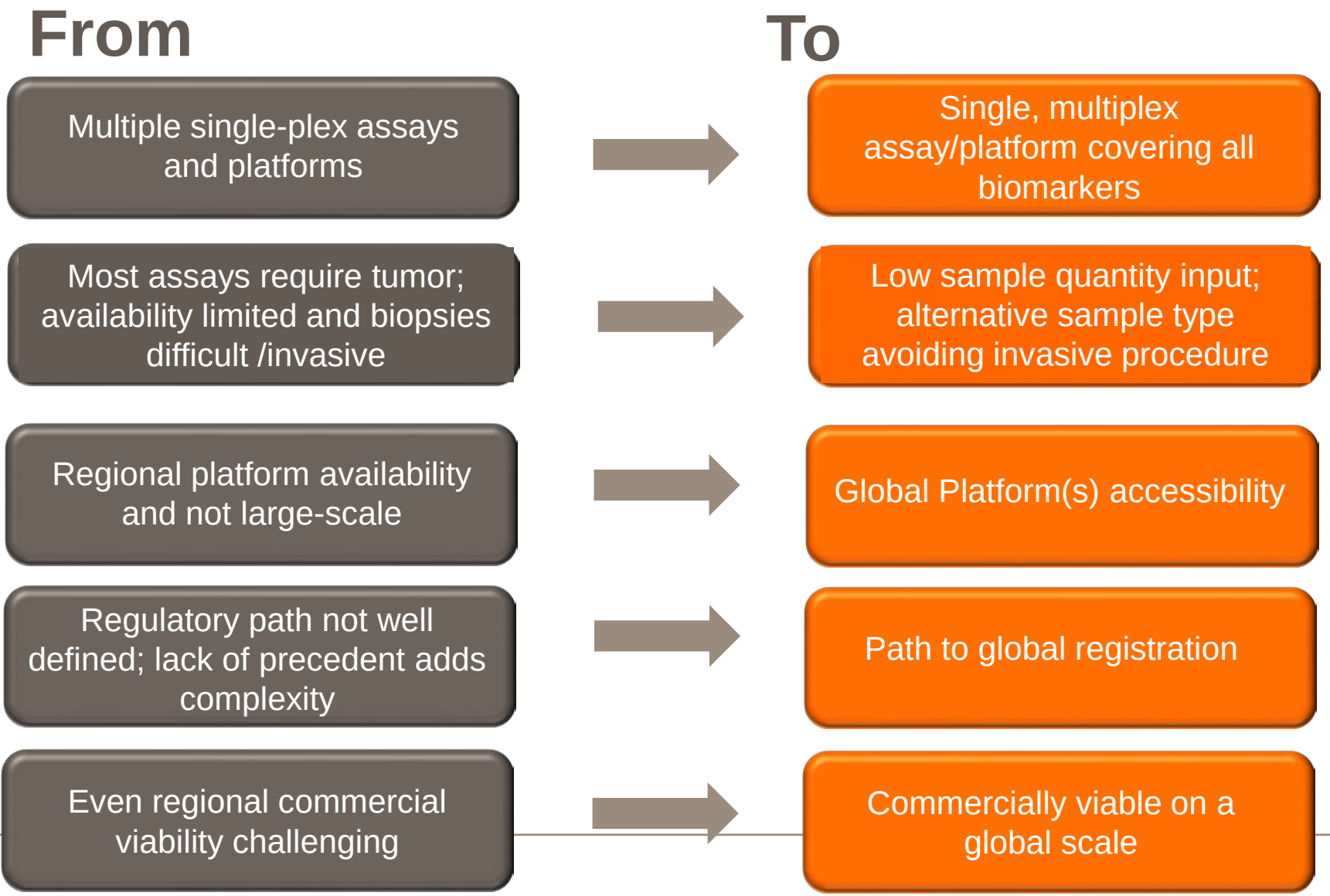
This requires patient screening/selection, novel trial designs with appropriate incorporation of diagnostic.

Deliver Products of Value

Products with greater clinical benefit in a smaller population of patients selected for a biomarker; value to PM stakeholders

Innovation in cDx Development

Cross pipeline – global footprint



Collaborative Multi-Pharma/partner Network to Advance Multi-biomarker Diagnostics

- Engage multiple PM stakeholders
  - NCI, Academia, Advocacy, Regulatory, Payer
  - Pharma/Diagnostic
- Enable standardized, shared screening between pharma companies to make clinical development for rare mutations cost effective
- Advance the regulatory paradigm for companion diagnostics
  - Create a path for multi-biomarker panels
  - Enable the use of new sequencing technologies, including NGS
- Disseminate NGS screening to help create a market for drugs targeting rare mutations

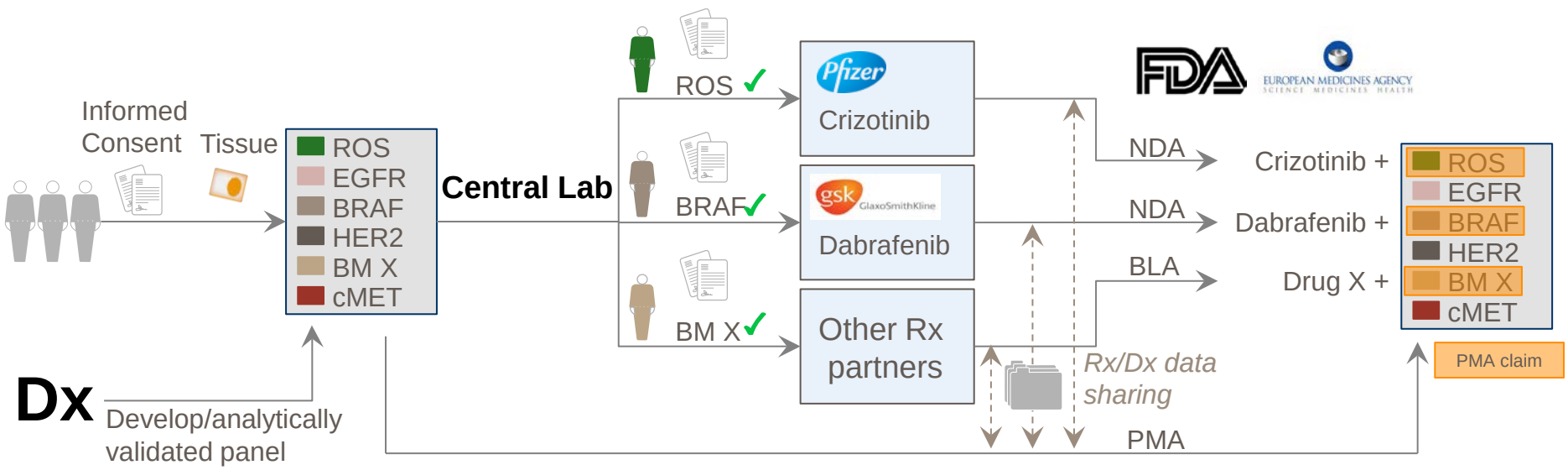
The Approach

ILLUSTRATIVE

Master screening network for all interested pharma

Treatment trial

Regulatory Rx/Dx co-approval



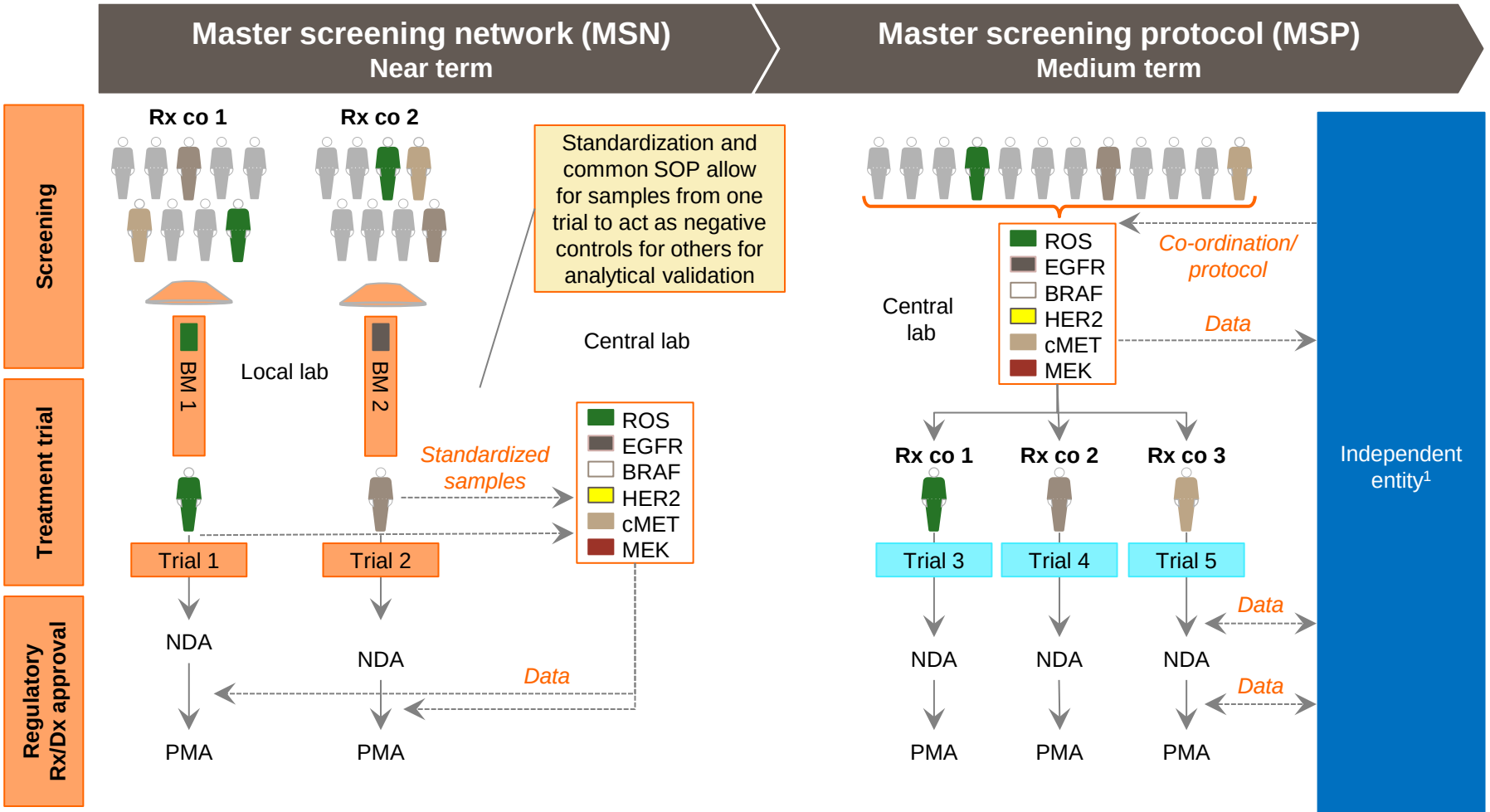
- Panel contains genes relevant to current and future assets across cancer types and pipeline
- Initial screening effort focuses on NSCLC

PMA claims to support drug approvals

Panel would be used commercially to support adoption of the Rx associated with the panel

MSN (Network) addresses near term needs and sets stage for MSP (Protocol)

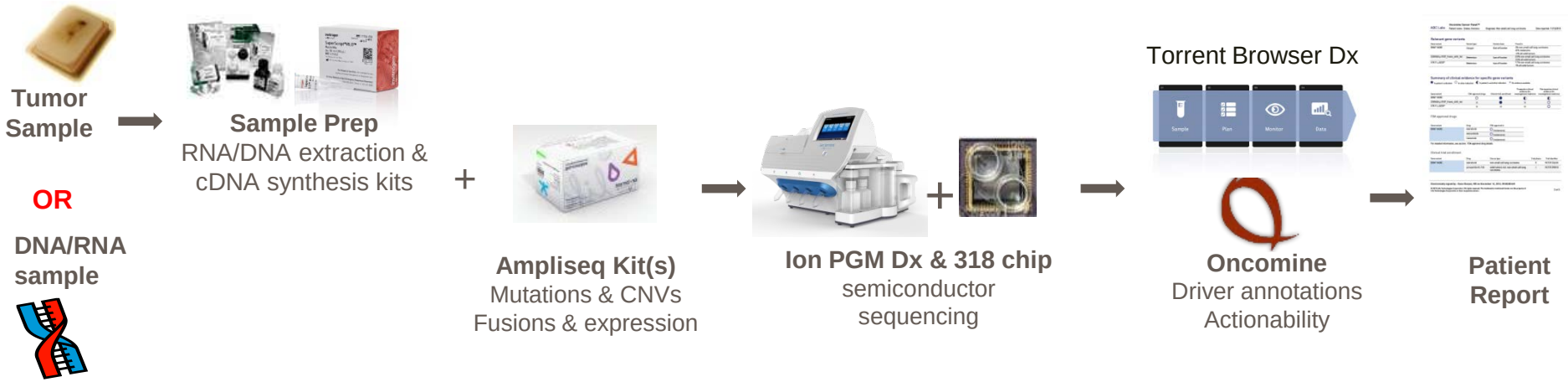
ILLUSTRATIVE



1. Central lab could act as the independent entity

Assay overview: Oncomine Cancer Panel

To detect relevant somatic alterations in solid tumors with evidence linking alterations to targeted therapies



- The Oncomine Cancer Panel (OCP) has two versions
  - OCP 150 – validate for clinical trial use
  - OCP 50 – Validate for registration and commercialization
- Enables detection of somatic alterations with high accuracy and precision
- Both DNA and RNA isolated from FFPE tumor specimens
- Detection of these variants will be performed using the Ion Torrent™ PGM™ Dx system

Desired criteria to be satisfied by the NGS platform/assay

Workflow	Criteria for evaluation	Desired Metrics
Sample Acquisition	• Sample input	•Low quantity input
Sample Prep	•Easy to perform/minimal steps •FFPE •Approved via multiple kits	•High quality DNA/RNA at good yields •Can utilize other FDA-approved kits
Library Prep	•QA/QC, quantity assessment •TaT •Multiple or single processing •GC rich coverage	•Minimal need for multiple QA steps •Rapid TaT •Multiple processing
Sequencing/detection	•Coverage •Sensitivity •Throughput	•Minimal 500X coverage •At least 5% •Multiple samples?
Analysis/BioInformatics	•Speed to variant call •Mut/Indel/CNV/rearrangement •FASTQ data •Standard workflow	•TaT w/all possible variants in software studio
Reporting	•Statistics •User interface	•Report confidence measurement •Link to original data (e.g. BAM files)
Others	•Sample handling •Data storage and management	•Cost effective for single clinical sample •Easy and secure access, scalable

Testing Paradigm: Support Patient Screening in clinical trials and cDx assay validation/development

Patient Sample

Minimal Lung Marker Panel
EGFR
ALK
BRAF
ROS1
RET
KRAS
~140 additional genes*

Screen using Oncomine Cancer Panel

Testing to be performed in central reference lab(s)

BRAF	Pos	Neg	Neg	Neg	Neg
ROS1	Neg	Pos	Neg	Neg	Neg
BRAF	Neg	Neg	Pos	Neg	Neg
EGFR	Neg	Neg	Neg	Pos	Pos
KRAS	Neg	Neg	Neg	Pos	Neg
RET	Neg	Neg	Neg	Neg	Neg
ALK	Pos	Neg	Neg	Neg	Neg

Remaining tumor sample reserved for
1. Biomarker result confirmation with validated test
2. To serve as negative control for other biomarker validated assays

* NGS OCP 150 has ~150 cancer genes, OCP50 has 50 cancer genes

Dx Labeling Framework

- Scalable labeling framework is key to industry's decision to pursue development and registration of multiplex/NGS platforms

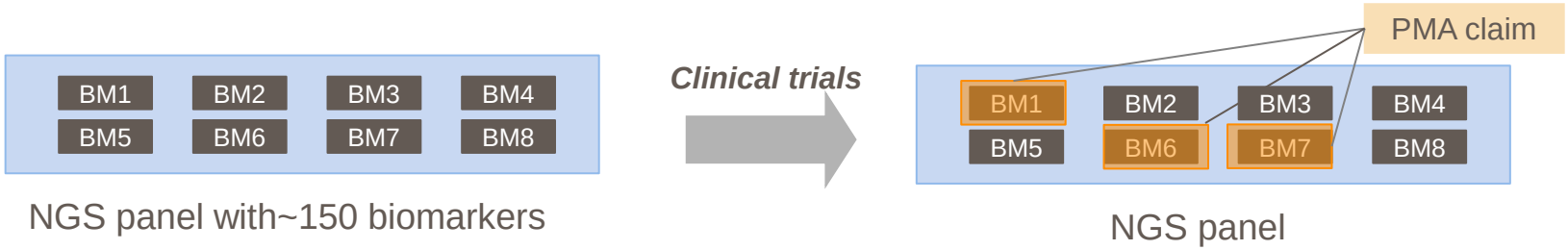
	Biomarker A	Biomarker Z (Analyte of Unknown Significance)
Type of Claim	Predictive	Analytical
Intended To Be Used for Treatment Selection	Yes	No (not outside clinical trials)
Subject to FDA Review	PMA (Quality, Analytical, Clinical)	Yes (Quality, Analytical)
Clinical Utility Data	Yes	Not at present

- Biomarker Z (AoUS) could be *"upgraded"* to an FDA-approved Predictive Claim after submission of additional clinical utility data and PMA review/approval

To Enable Master Screening, we are Working with US Regulators to Establish a Novel Regulatory Framework

Start by analytically validating the full panel

Then over time upgrade specific markers to predictive PMA claims using clinical trial data



NGS panel with~150 biomarkers

NGS panel

Aim to establish a novel approach to NGS CDx, which will require:

- Move from 'one-test, one-drug' to 'one-test, multiple drugs'
- Pushing forward despite lack of precedent in multiple areas
- Navigating novel and cutting edge approaches / technologies
- Working across CDRH and CDER to develop guidelines in a changing regulatory environment
  - Will engage other HAs
- Engaging NCI, academic KOLs and patient advocacy groups

Summary

- Medicine is evolving
  - Advances in technology leads to greater data access
  - Comprehensive data in smaller samples
  - Information revolution brought to the patient at molecular level
- Enables Drug development
  - Screen multiple targets, triage patients to multiple targeted agents (e.g. Umbrella studies, NCI MATCH, LUNG MSP
- Better identification of patients eligible for treatment
  - Improved benefit/risk
  - Better clinical outcomes / better value
  - More efficient drug development
- Evolving regulatory environment

Acknowledgements

- **GSK**
- Rafael Amado
- Lini Pandite
- Jonathan Pan
- Jennifer Dudinak
- Noemi Rosa
- Yuchen Bai
- Cindy Kurtis
- Jeff Legos

- **Pfizer**
- Barbara Dalton
- Chris Boshoff
- Omar Perez
- Erling Donnelly
- Laurie Strawn

- **ThermoFisher/Life**
- Dan Rhodes
- Amber Swindell
- Thomas McElroy
- Lynne McBride
- Jody Schulz

- **NCI**
- Barbara Conley
- Mickey Williams

- **MGH**
- Keith Flaherty