

Bringing Personalized Medicine to the Clinic



# Overcoming the Challenges of Complex Cancers in Companion Diagnostics

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PrimeraDx

# Challenges in Cancer Companion Diagnostic Development

## Current CDx Development is Complicated

*--Traditional pharmaceutical companies have limited expertise in the development of companion diagnostics*

- **Logistical challenges:**
  - Fragmented outsourcing
- **Strategic business challenges:**
  - Conflicting motivations and business interests between diagnostic companies and their pharmaceutical partners
- **Regulatory challenges:**
  - Different regulations for in vitro diagnostics and drug development
- **Financial challenges:**
  - CDx in drug clinical trials: adding the complexity, burden, risks and cost for the drug-development process
  - Uncertain reimbursement for high-value tests
- **Technical challenges:**
  - High performance required
  - One solution: hardware, software and reagents required
  - Complexity of the test, sample size, sample source, TAT, throughput, cost, ease of use, quality concerns

# PrimeradX – Simplifying Molecular Diagnostics with a Proprietary Platform

## Only technology available to enable Multi-Modal Multiplex testing

- Ability to detect and quantify DNA, RNA, mRNA and miRNA all in a single-well reaction
- Proprietary technology with large IP estate
- Automated platform that dramatically improves lab workflow, reduces costs, and enables new markets

## Technology advantages provide opportunity for differentiated content; several assays in development

- cMET/EGFR and other oncology assays in partnership with Pharma
- KRAS/NRAS/BRAF, EGFR and several ID products currently in development

## Technology is validated and in the market now

- Eli Lilly companion diagnostics relationship, with multiple other opportunities in progress
- Initial open platform placements ramping up

## Technology has unique and large commercial opportunity

- “Open platform” approach
- Cleared IVD kit sales
- Companion diagnostic partnerships

## Regulatory path is clear and in process



# Unique Technology Addresses Current Problems While Enabling New Markets and Applications

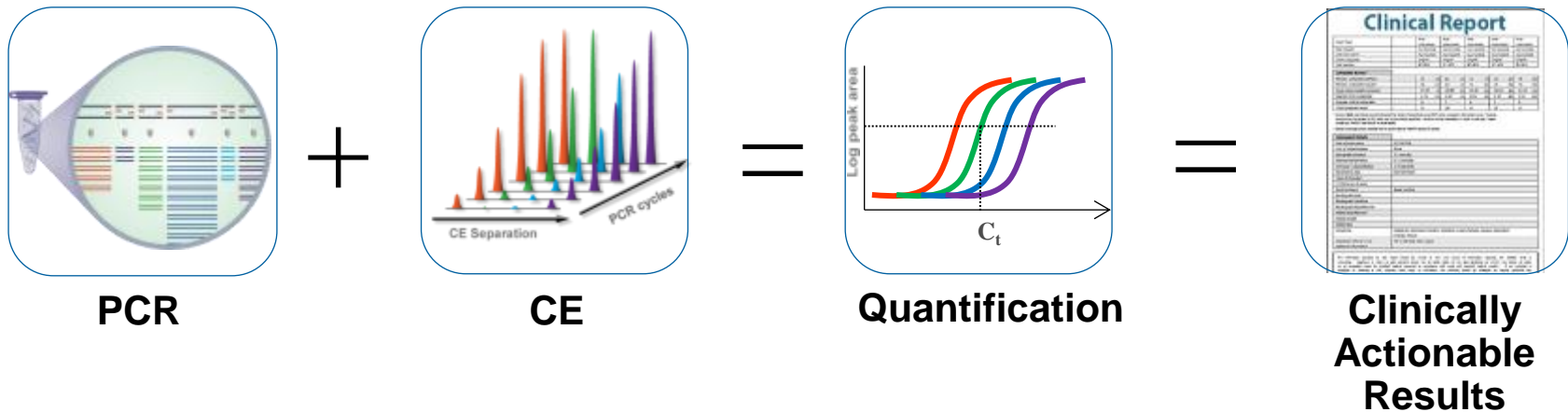
## The Marriage of PCR and Capillary Electrophoresis

Integrated PCR, CE, fluidics, detection and analysis software

Real-time detection of PCR products separates targets by size

Sampling as the reaction progresses allows quantitation

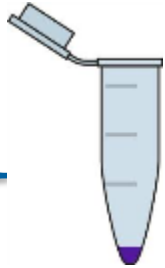
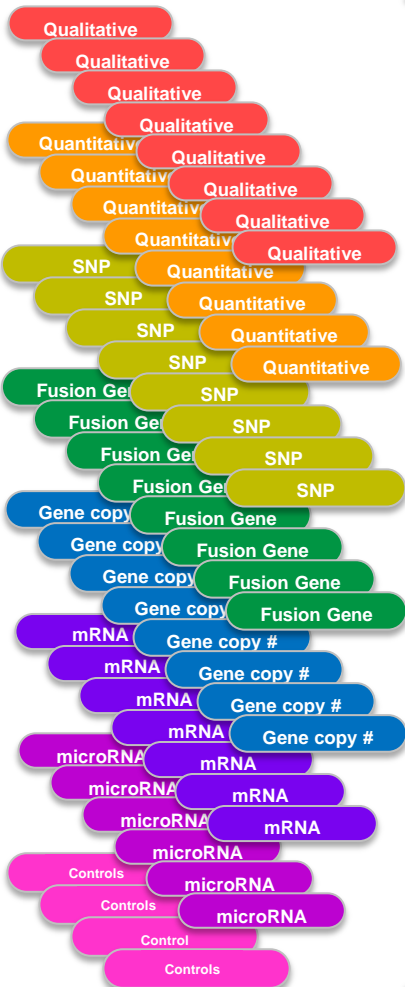
Multiplex, multimodal, quantitative results provide unique, clinically actionable data



# Multi-Modal Testing is the Future of MDx – Breakthrough for Labs and Clinicians

Diagnostics Now Require Next Generation “All in one Well” Capabilities

- End-point Qualitative Detection
- Real-time Quantification
- SNP
- Fusion Gene
- Gene copy #
- mRNA
- microRNA
- Controls



A real-time, multiplex, multi-modal “All in one well” MDx solution

Only PrimeraDx Can Do This

# Unique, Critical Capability in the Molecular Dx Space

## Many Tests, One Reaction/One Platform

Current practice: many platforms, many techs



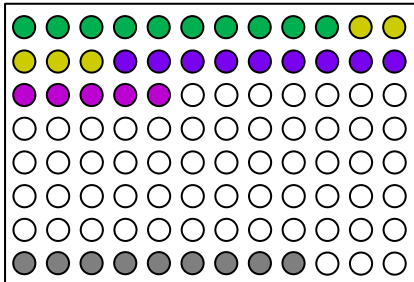
PrimeradX



ICEPlex

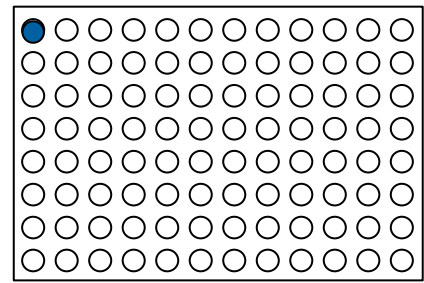
**Oncology Multi-Modal Panel:**  
 Fusion gene variants  
 +  
 SNPs  
 +  
 Gene Expression Signature  
 +  
 MicroRNAs  
 +  
 Standards and controls

29 Targets plus 9 Standards and Controls



96 Patient Samples

**6 days**



**1 morning**

# Regulatory Plan and Quality Systems Enable PDx in the Market

## Market Needs Drive Approach

### Achieving Regulatory Clearances

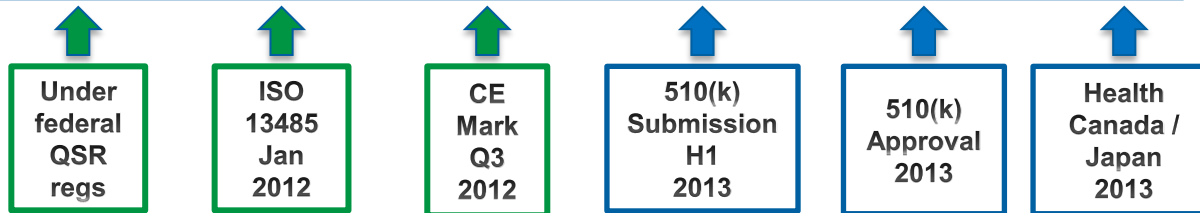
- IVD kit sales are a major portion of market
- CDx Partners need a Cleared Platform
  - Will be a major differentiator for PrimeraDx



## Regulatory Milestones

- Operate under QSRs ✓
- ISO 13485 ✓
- CE marks ✓
- FDA *de novo* 510(k) 2013

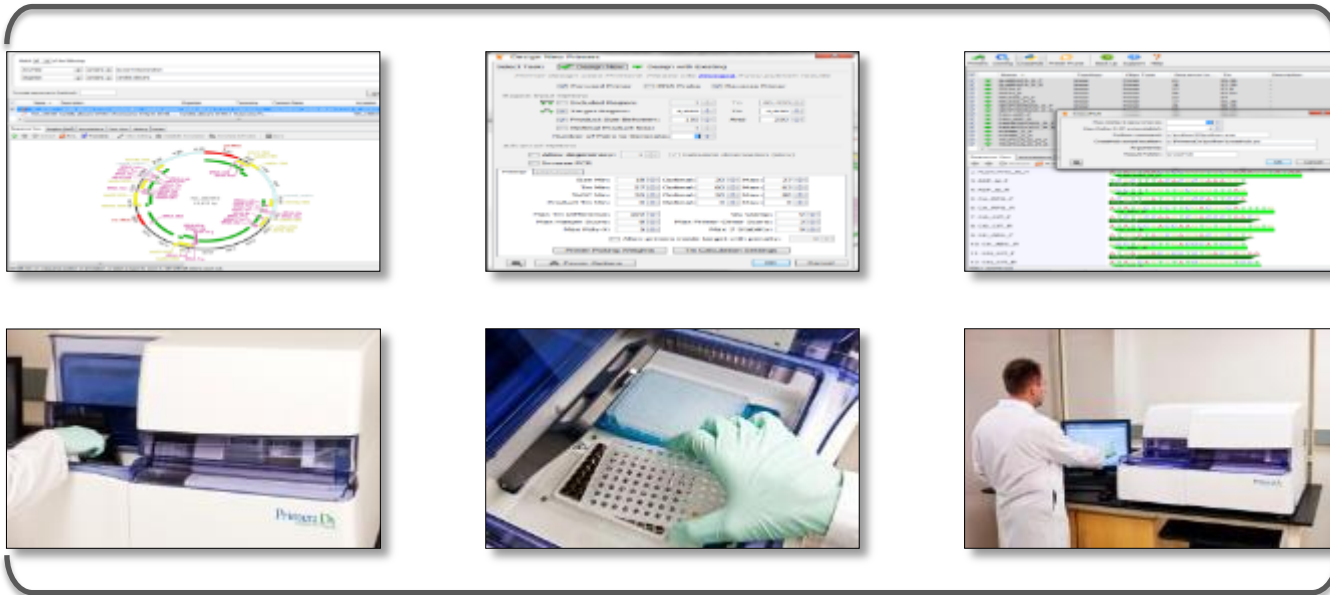
### PrimeraDx Progress on Quality Systems and Regulatory Approvals



# PrimerDx's Open Platform Product: Next Generation qPCR

Users Design Complex Multiplex Assays with Ease....

In Silico Multiplex Assay Design SW Tools Enable Customers



Automated Workflow Simplifies Testing Procedures

.....and PrimerDx Provides the Tools Needed to Diagnose Disease



# PrimeraDx Technology Has Very Broad Clinical IVD Utility

Proven Capabilities in All Major Diagnostic Areas....

## Oncology

- Expression panels
- Copy number variation
- SNP panels
- Polysomy
- Insertions
- Deletions
- Fusion products (replaces FISH)
- Methylation
- Combinations of **any and all** of the above

More in Development



## Others

- Food Safety Testing
- Pharma QC
- Drug Metab
- Genetic Dis

More in Development

## ID

- Quantitative, multi-pathogen detection
- Mixed pathogen panels
- Viral load
- Resistance detection
- Hospital acquired infections
- Multiple sample/swab types
- Panels that represent physician ordering patterns

More in Development

Panels for demonstration purposes only. Not for clinical diagnostic use.

# PrimeraDx Products Have Very Broad Clinical IVD Utility

Proven Capabilities in All Major Diagnostic Areas....

## Oncology

- KRAS/NRAS/BRAF
- EGFR
- cMET/EGFR CNV with cMET Expression
- cMET Mutation Panel
- EML4-ALK
- Lymphoma
- BCR-ABL
- Methylation
- microRNA/mRNA/gDNA Panel

More in Development



## Others

- Food Safety Testing
- Pharma QC
- Drug Metab
- Genetic Dis

More in Development

## ID

- Fungal Panel  
(direct blood detection)
- Transplant Panel  
(multiple viral loads)
- C. difficile*
- STI Panel  
(yeast, virus, bacteria, parasites)
- Ultra-Sensitive JCV/BKV  
(differentiation, viral loads)
- Respiratory Panel  
(pathogens including drug-resistant strains)

More in Development

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## Bringing Personalized Medicine to the Clinic



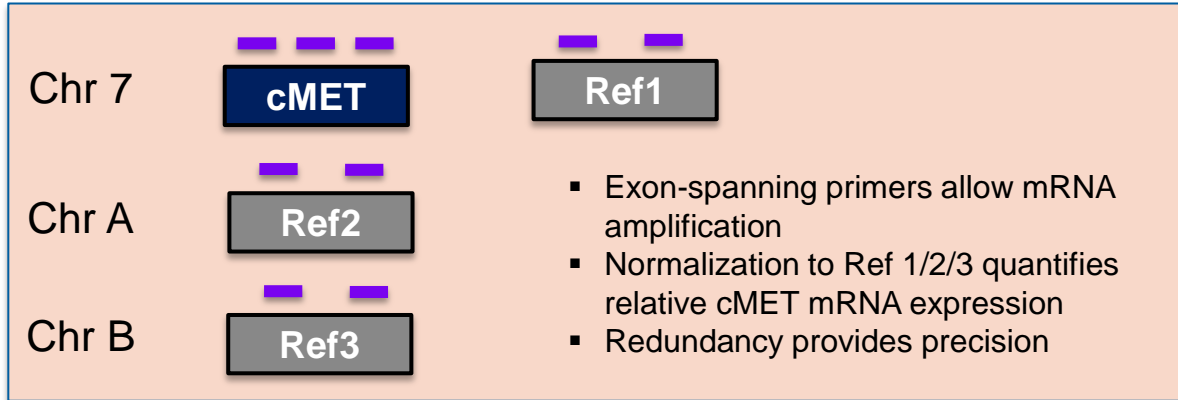
## PrimeradX Oncology Panels

PrimeradX

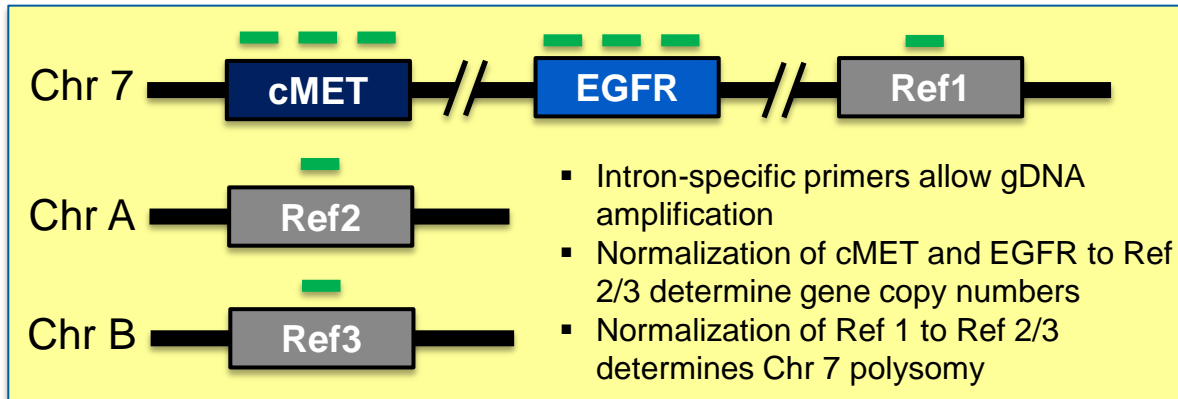
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# A Single-tube “Killer App” For a High Unmet Need -- cMET/EGFR Copy Number and cMET Gene Expression Panel

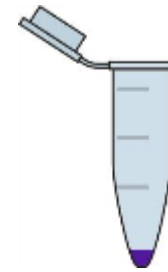
## cMET Gene Expression Assessment



## cMET / EGFR Gene Copy Number Assessment



Single-tube  
Quantitative  
21-plex reaction

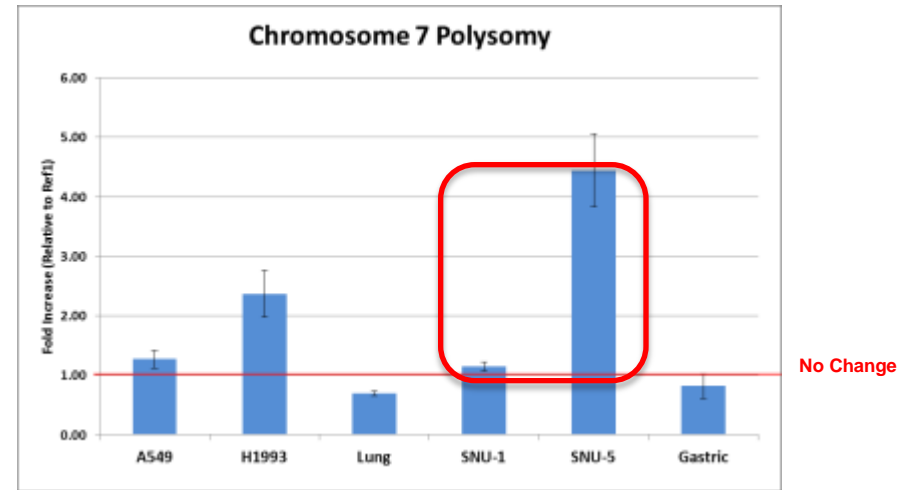
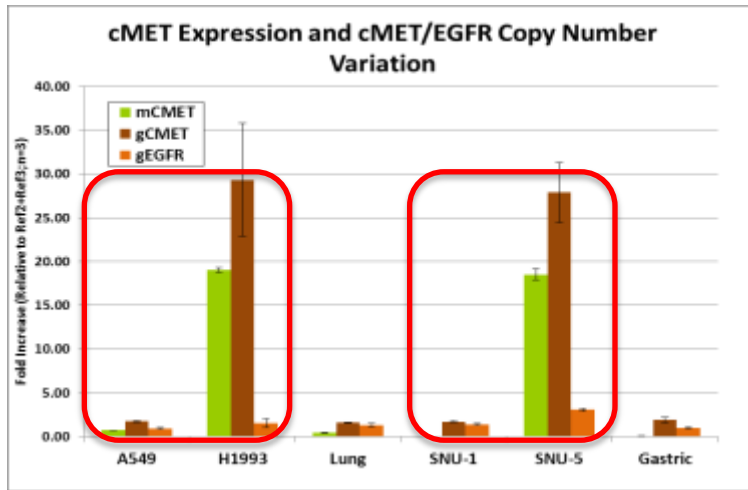


- 9 mRNA targets
- 9 gDNA targets
- Quantitation standards
- External process controls for all steps to assure quality of the assay

Replaces IHC, FISH  
and qPCR  
with a single reaction

Panels are designed for demonstration purposes only. Not for clinical diagnostic use.

# cMET/EGFR: Copy Number, Expression and Polysomy in ONE TUBE



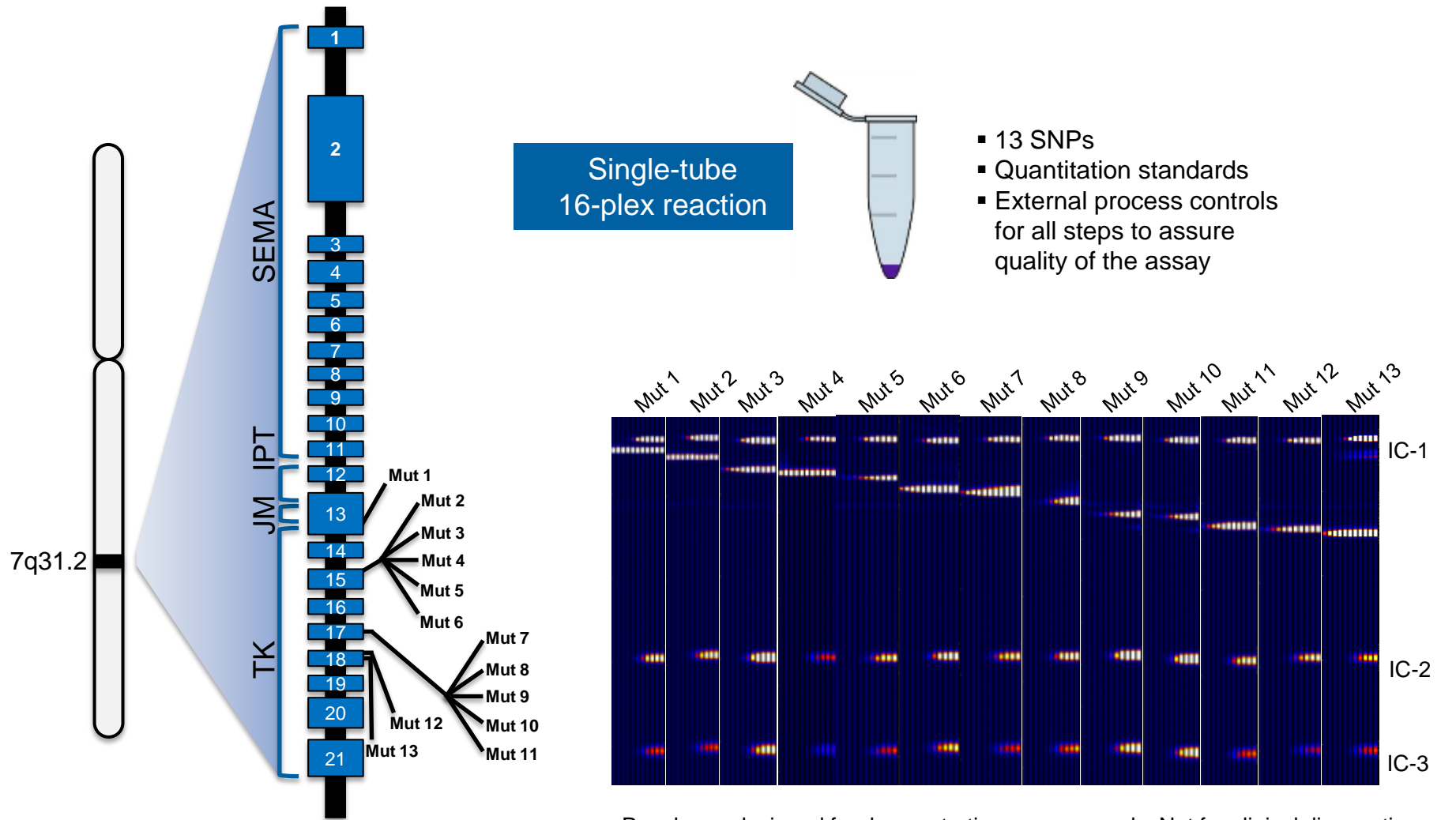
Sample	Source	Tissue Origin	Matrix	MET Copy Number	MET Expression	Chromosome 7 Polysomy	Reference*	Confirmation of Published Data
A549	Cell Line	Lung	Fresh Frozen	2	Low	Unknown	3	✓
H1993	Cell Line	Lung	Fresh Frozen	>10	High	Unknown	3	✓
SNU-1	Cell Line	Gastric	Fresh Frozen	2	No	No	1, 2	✓
SNU-5	Cell Line	Gastric	Fresh Frozen	>10	High	Yes	1, 2	✓

\*(1) Catenacci D, Cancer BioTher, 2011, 12(1): 9-46  
 (2) Smolen G, PNAS, 2006 103(7): 2316-2321  
 (3) Lutterbach B, Cancer Res, 2007, 67: 2081

Assay under development – preliminary data only

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# cMET Mutation Panel Completes cMET Franchise

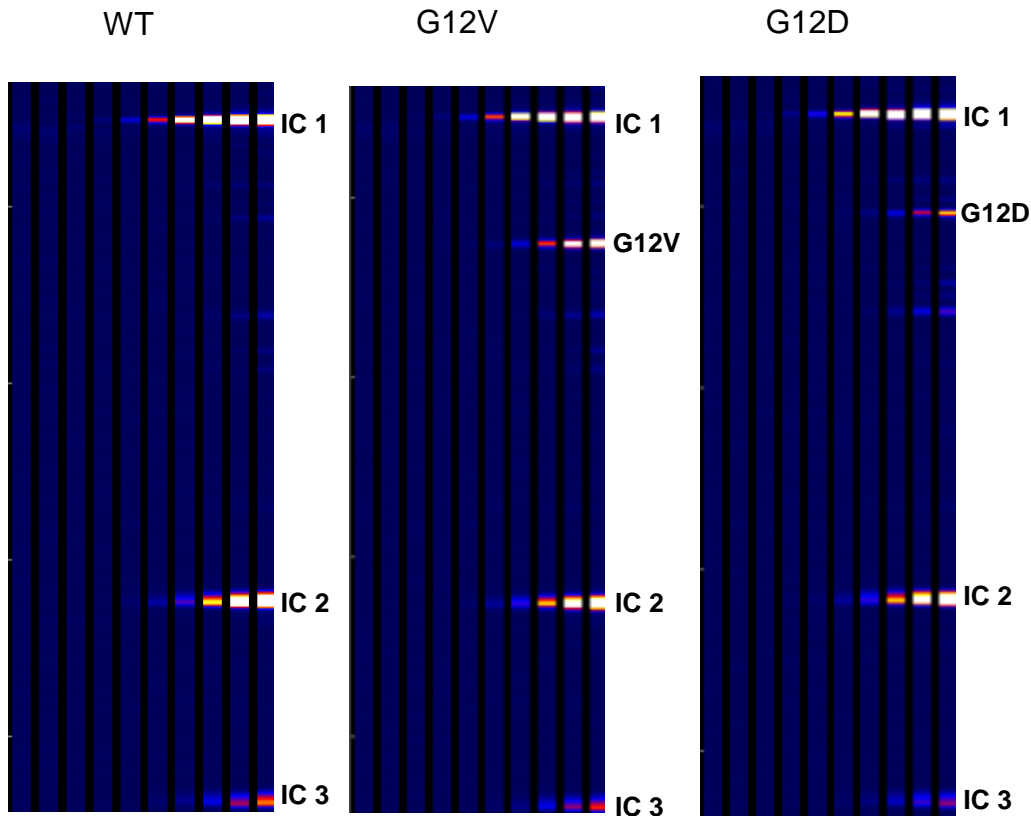


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# PDx Makes “Liquid Biopsy” Possible – Massive Potential Market in Cancer Screening

KRAS/BRAF Panel: Detects DNA in Serum/Plasma, and Also Works on FFPE

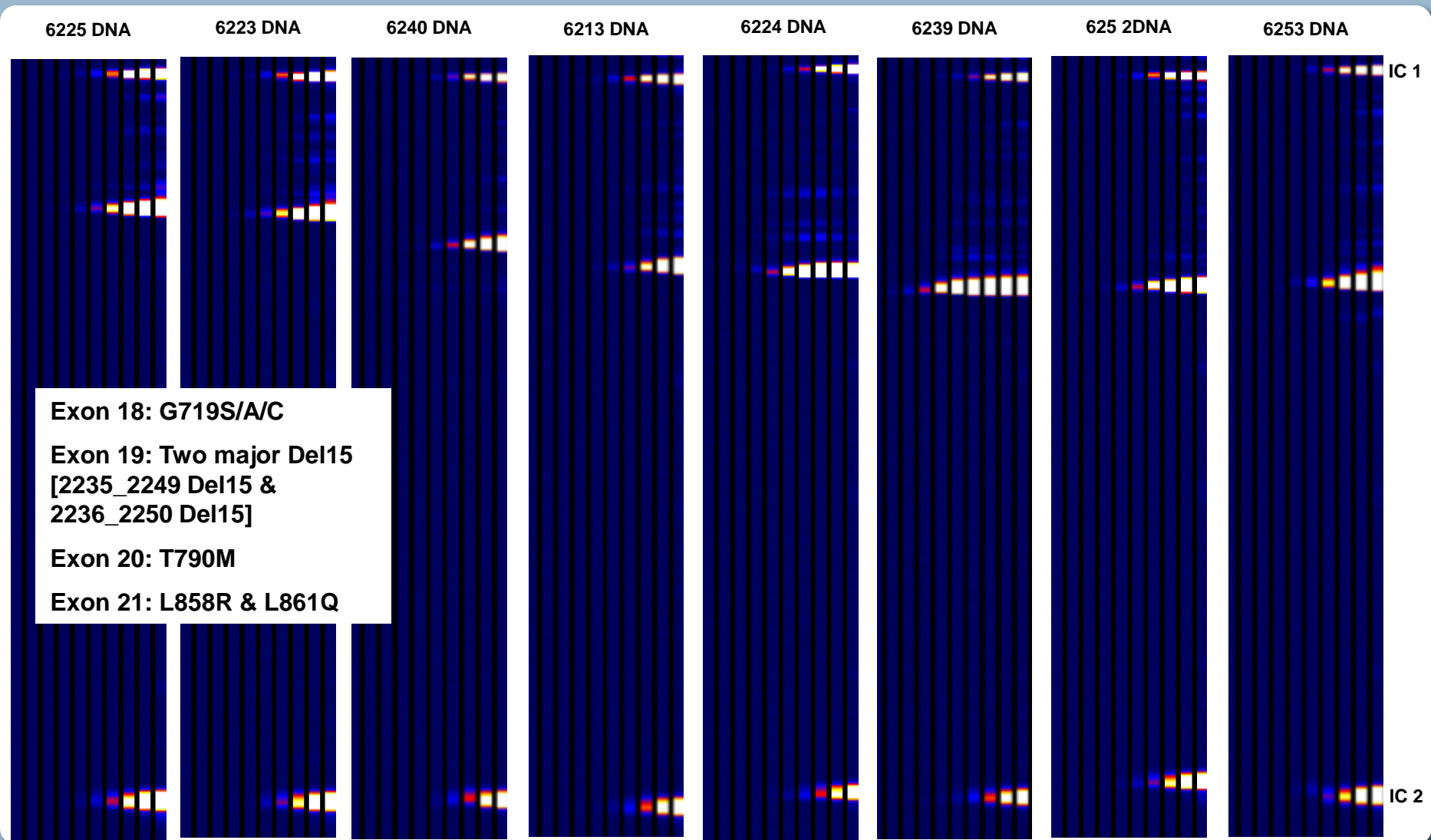
One-tube KRAS / BRAF Panel
G12D
G12V
G12R
G12C
G12A
G12S
G13D
G13C
Q61H
Q61R
Q61L
A146T
V600E
V600K
V600D



Screening and  
disease  
recurrence  
monitoring  
require repeated  
testing

Panels are designed for demonstration purposes only. Not for clinical diagnostic use.

# Multiplex Detection of EGFR Mutations in One Single Reaction

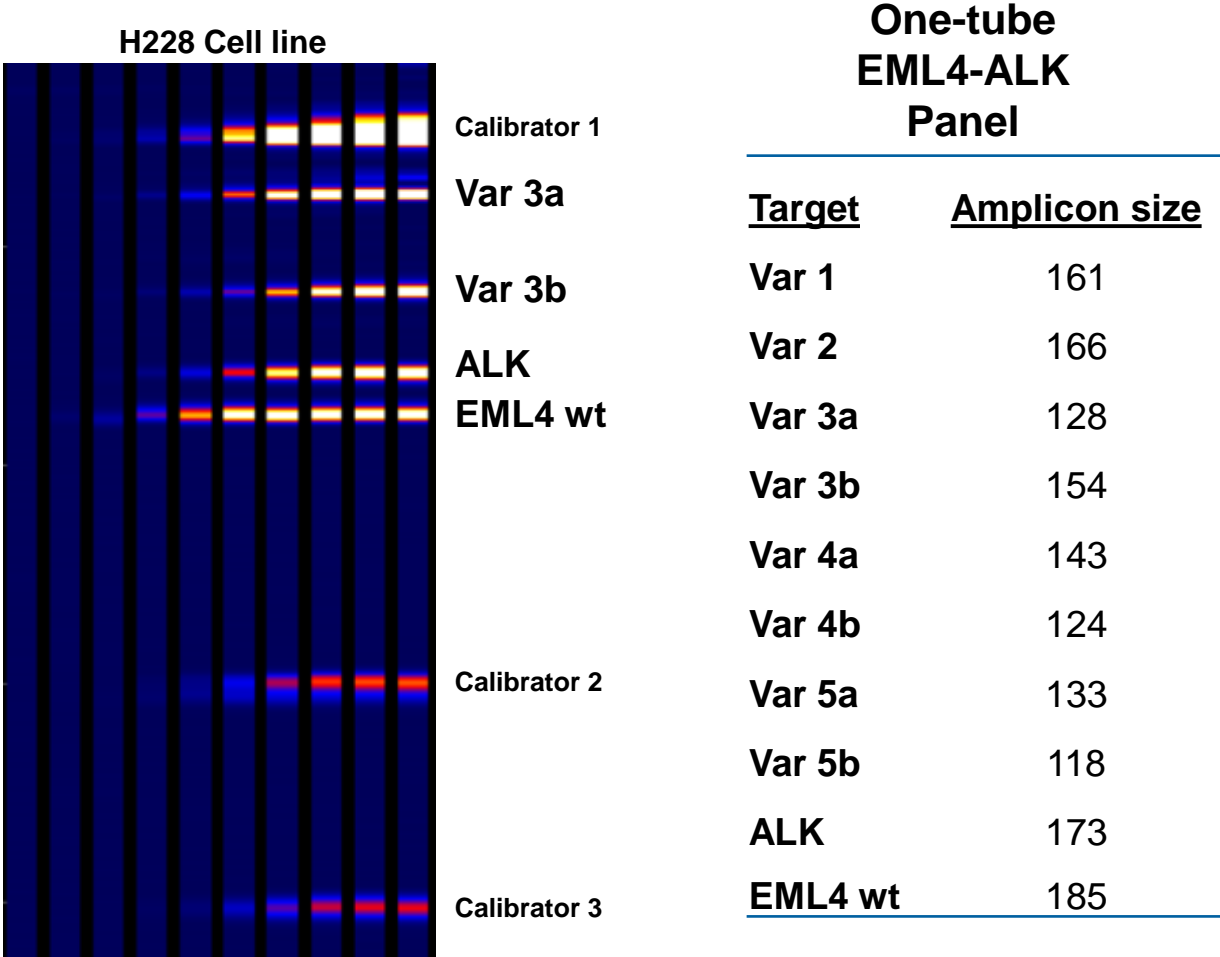


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# EML4-ALK: Fusion Gene Assay Detects Eight Fusion Variants

Fusion Detection Will Displace FISH in the Marketplace – Huge Potential



**Fusion Gene Variant Detection on the ICEPlex is simple, and provides definitive answers in just a few hours.**

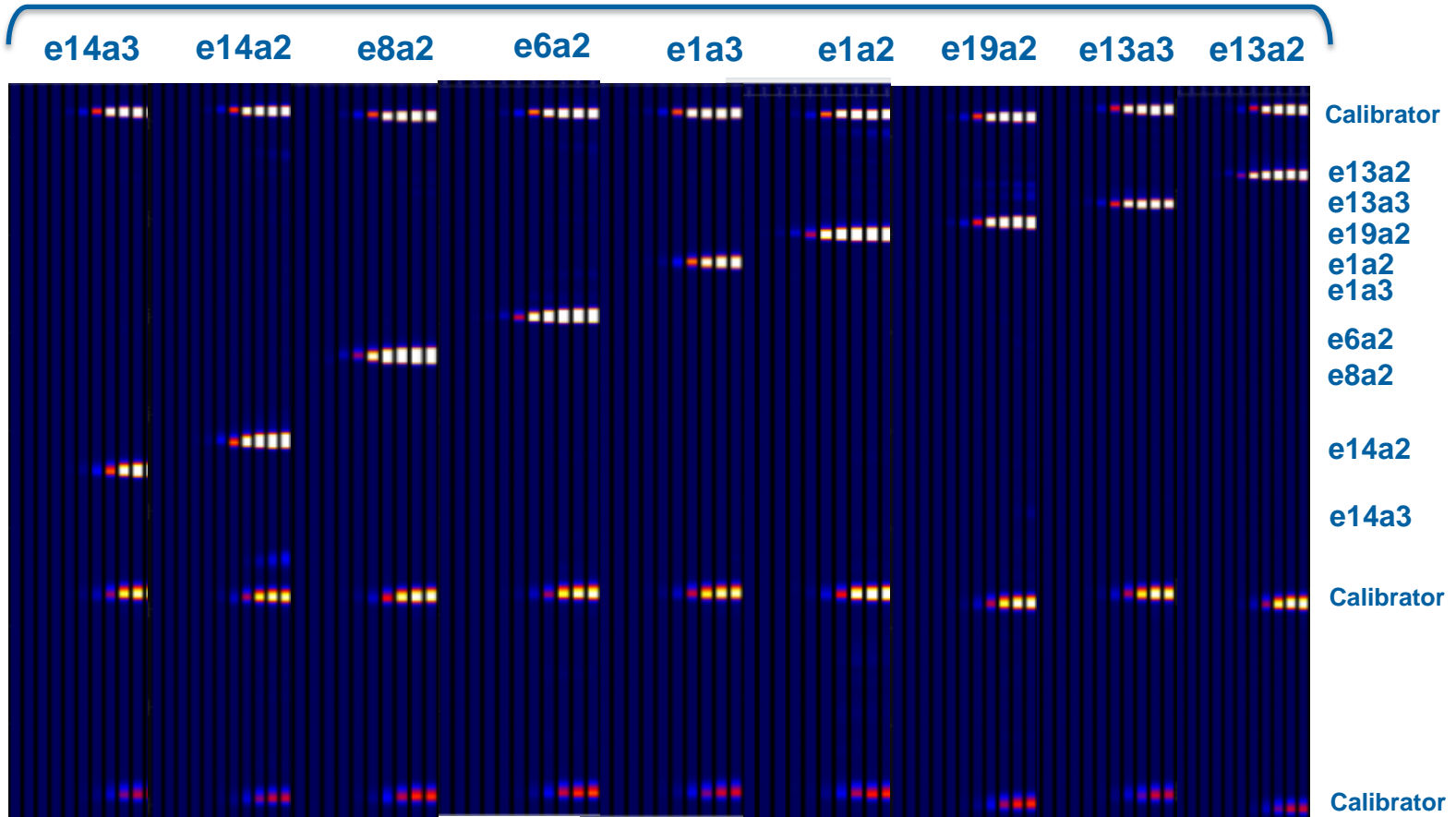
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# BCR-ABL Fusion Gene Assay Detects Nine Fusion Variants

PrimeradX Panel Represents the Best Test Available

One-tube  
BCR-ABL  
Panel

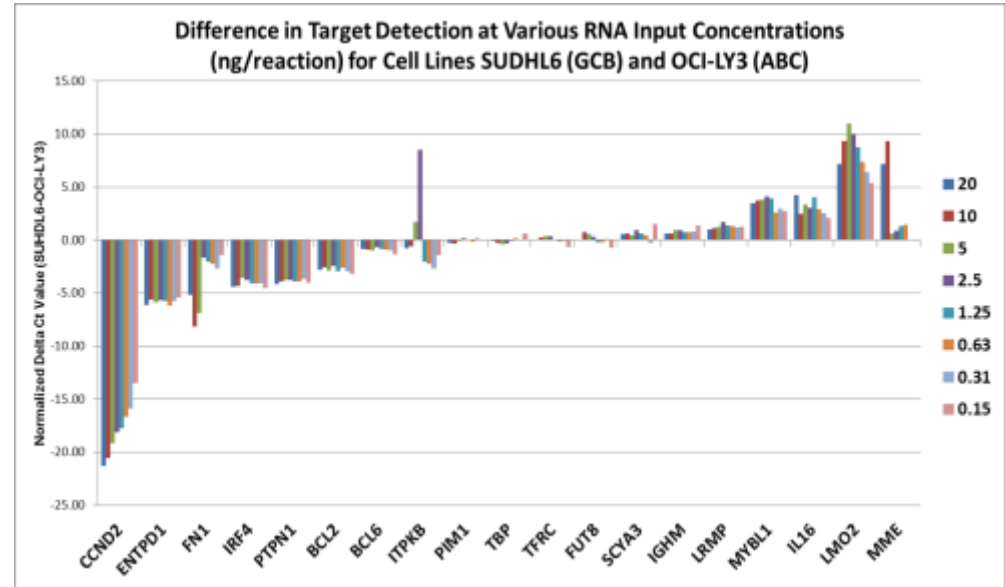
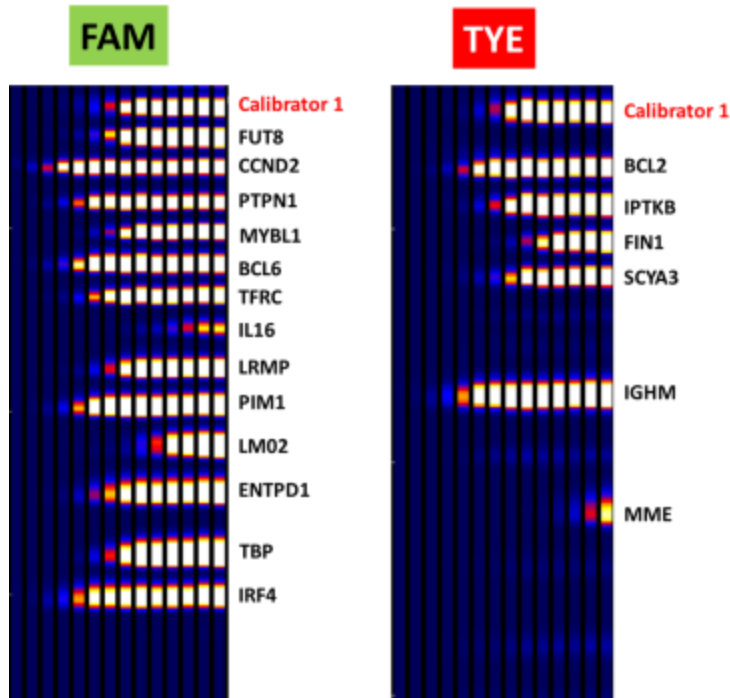
Target	Amplicon Size (bp)
e13a2	128
e13a3	137
e19a2	139
e1a2	144
e1a3	153
e6a2	168
e8a2	179
e14a2	204
e14a3	212
ABL wt	223



Individual plasmid target templates were detected by the single tube BCR-ABL Assay

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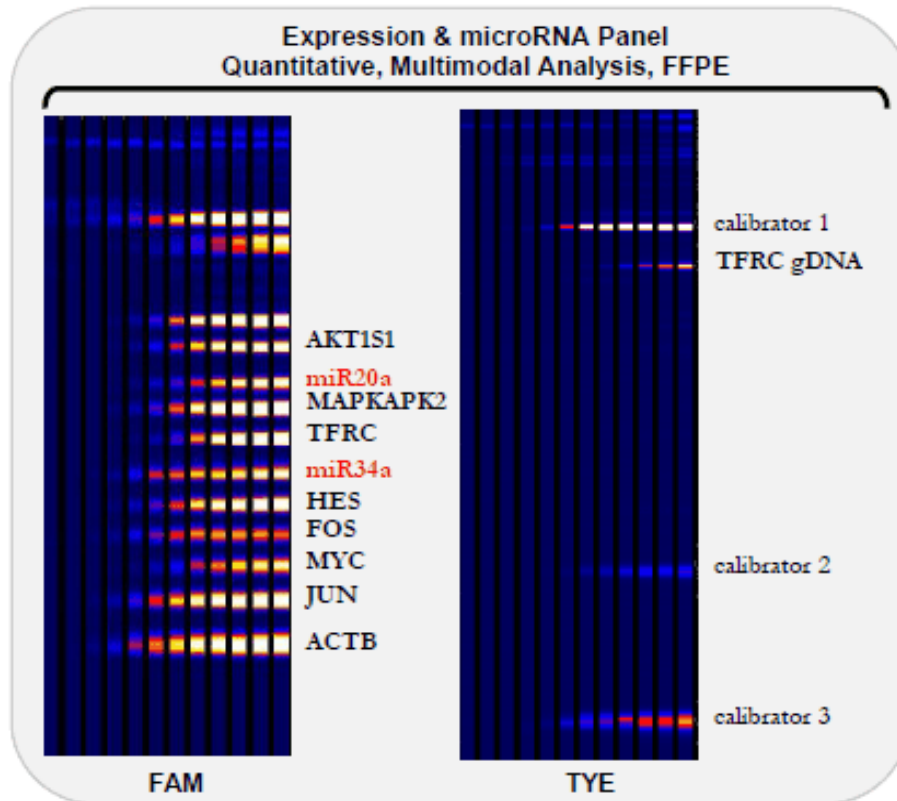
# Lymphoma Gene Expression Panel Differentiates GCB from ABC



- A novel quantitative 19-plex mRNA expression profiling assay designed to allow DLBCL tumor classification on FFPE specimens in a single tube PCR reaction was developed on the ICEPlex system.
- The ICEPlex DLBCL assay allowed discrimination of ABC and GCB cell lines based on specific target expression patterns generated from < 1ng of RNA from FFPE-isolated material.

Panels are designed for demonstration purposes only. Not for clinical diagnostic use.

# Simultaneous Quantification of mRNA and miRNA expression



Currently being investigated for complex molecular assays (multimodal multiplex qPCR) supporting drug development with expectation that taking a single assay through regulatory approval will be more feasible

Platform selection is important:

Robust assay performance

Ease of development

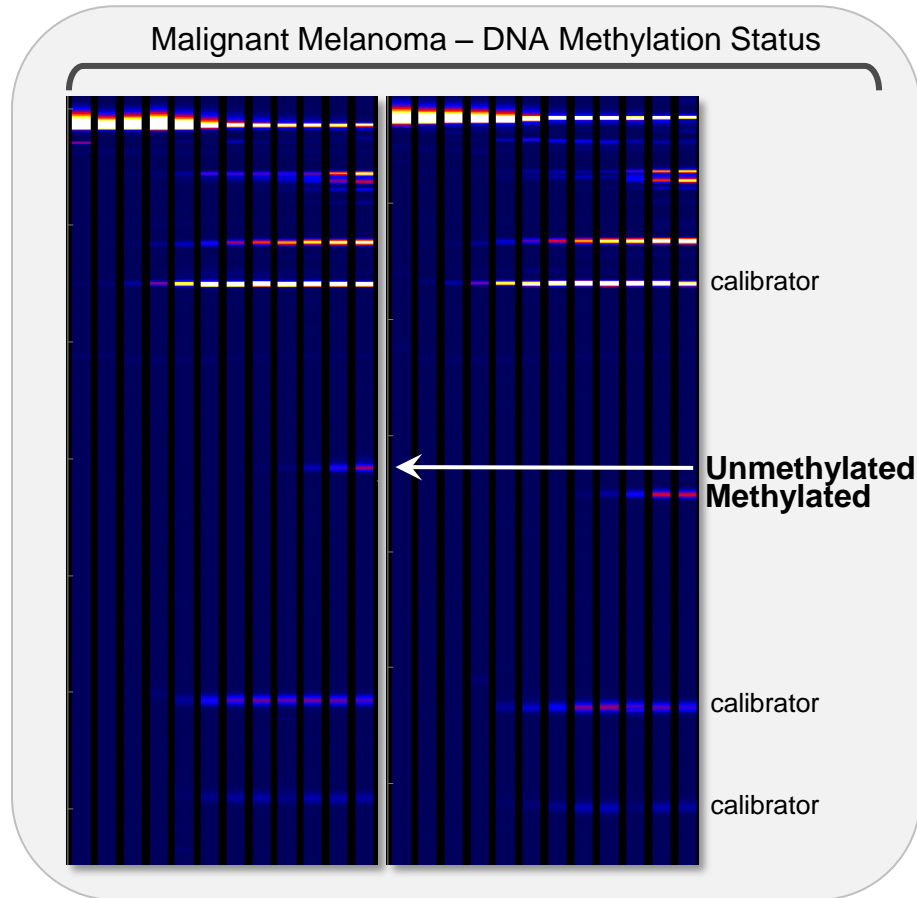
Regulatory path

Clinical laboratory accessibility

Meeting the need of the CDx effort

# Malignant Melanoma

## Methylation Detection in Multiplex



The Methylation state of some genes has been used as a biomarker for tumorigenesis. Here we tested for methylation status of a gene in malignant melanoma tissue.

The *ICEplex* platform can very easily distinguish between unmethylated and methylated genes. The ability to do this in multiplex will provide a needed tool to clinical labs that are currently finding it difficult to run similar assays.

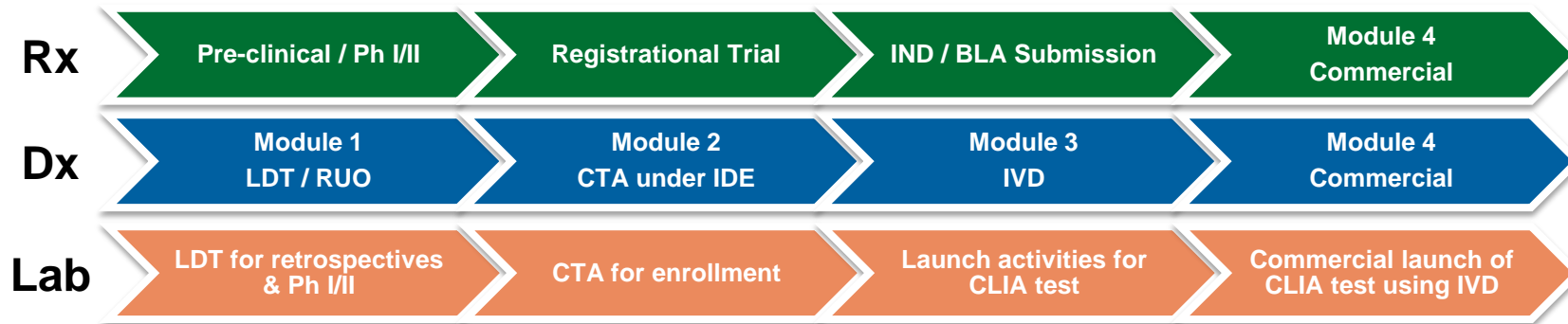
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# Modular CDx Program Structure



<b>Features</b>	<ul style="list-style-type: none"> <li>• Assay design</li> <li>• Assay development</li> <li>• Under Design Control</li> <li>• Tissue-specific</li> </ul>	<ul style="list-style-type: none"> <li>• Final robustness testing</li> <li>• Transfer to manufacturing</li> <li>• cGMP production lots</li> <li>• IDE negotiation, approval</li> <li>• CE Mark</li> </ul>	<ul style="list-style-type: none"> <li>• Trial support to CROs</li> <li>• V&amp;V studies</li> <li>• Concordance analyses</li> <li>• PMA preparation and submission</li> <li>• XUS registrations</li> </ul>	<ul style="list-style-type: none"> <li>• Pre-launch conversion from CROs to commercial lab</li> <li>• Facilitate lab partner reimbursement</li> <li>• Support post-approval surveillance trial</li> </ul>
<b>Deliverables</b>	IVD-track assay for use in CLIA or R&D setting	IVD-track IUO for use in registrational trial	<ul style="list-style-type: none"> <li>• PMA submission</li> <li>• Global registrations</li> </ul>	Global distribution
<b>Benefits</b>	<ul style="list-style-type: none"> <li>• Identical formulation</li> <li>• Design History File established</li> <li>• Risk of discordance very low</li> <li>• Remains flexible to iterations</li> <li>• Smooth tech transfer</li> </ul>	<ul style="list-style-type: none"> <li>• cGMP lots identical to IVD</li> <li>• Risk of discordance extremely low</li> <li>• Can be deployed at CRO labs in parallel to V&amp;V studies</li> <li>• IDE in place for patient selection</li> </ul>	<ul style="list-style-type: none"> <li>• Eliminates risk of off-protocol use of IUO</li> <li>• Risk of discordance extremely low</li> <li>• Discordance tie-breaker not required</li> <li>• PMA submission ahead of NDA</li> </ul>	<ul style="list-style-type: none"> <li>• Use of CROs that also have large lab network commercial capabilities allows smooth conversion at launch</li> <li>• Reimbursement in major territories more streamlined</li> </ul>

# Rx-Dx-Lab Solution to CDx Development & Commercialization



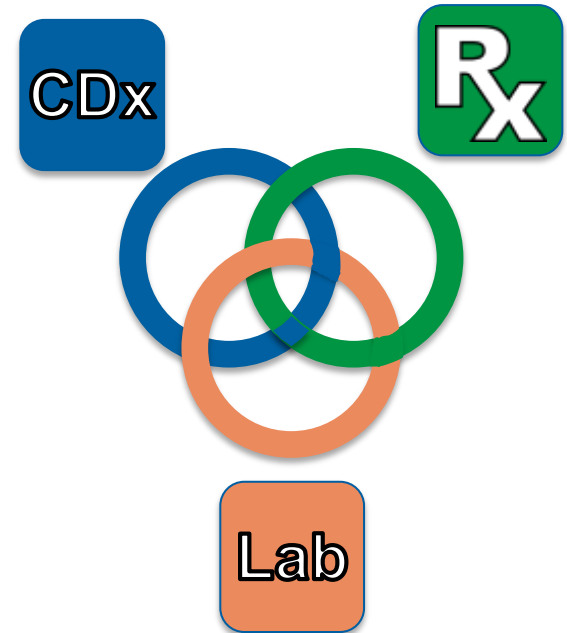
<b>Features</b>	<ul style="list-style-type: none"> <li>LDT / RUO on platform and on protocol for using in early work</li> </ul>	<ul style="list-style-type: none"> <li>CTA under IDE at designated lab</li> </ul>	<ul style="list-style-type: none"> <li>Lab prepares for IVD and drug launch during FDA review period</li> </ul>	<ul style="list-style-type: none"> <li>Lab launches full commercial activities simultaneous with Rx/CDx</li> </ul>
<b>Benefits</b>	<ul style="list-style-type: none"> <li>LDT / RUO approximates the proper test so low risk of discordance</li> <li>Relationship between PDx and Lab independent of Pharma</li> </ul>	<ul style="list-style-type: none"> <li>Conversion from LDT to CTA is seamless and low risk</li> </ul>	<ul style="list-style-type: none"> <li>Lab has transparency with Rx/CDx timelines and commercial strategies</li> <li>Allows reimbursement to be in place at CDx launch</li> </ul>	<ul style="list-style-type: none"> <li>Launch of Rx/CDx has missing partner to seamlessly migrate from CTA to CLIA</li> <li>Option to share commercial data and incorporate into strategy</li> </ul>

## Broad benefits to pharma clients:

- Reduces deal time and tech transfer risk to Lab
- Reduces platform adoption risk for CTA deployment
- Provides ready CDx access solution at commercial launch

# PrimeraDx 3-Way Partnership Structure

- ✓ Aligned with Rx development
- ✓ Aligned with Rx budgetary constraints
- ✓ Aligned with Rx commercialization
- ✓ Addresses commercial path
- ✓ Mitigates Rx AND Dx risk





# Overcoming the Challenges of Complex Cancers in CDx

## Solution: Simplify, Integrate and Find the Right Fit

- Streamline business partners for co-development
- Find the right partner, business model, and technology

- **Logistical challenges:**
  - ✓ Fragmented outsourcing
- **Strategic business challenges:**
  - ✓ Conflicting motivations and business interests between diagnostic companies and their pharmaceutical partners
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PrimeraDx

*The Multiplex PCR Company*