

Bringing Personalized Medicine to the Clinic



PrimeraDx Technology Overview

November 2011

PrimeraDx

CONFIDENTIAL

PrimeruDx

Bringing Personalized Medicine to the Clinic

Breakthrough capabilities in molecular diagnostics – detecting and quantitating all molecular target types in one well.

- Cost-effective, high impact molecular tests for clinical labs.
- Blockbuster, next generation companion diagnostic tests.



Two Pronged Strategy Mirrors Market Opportunity

Build Base and Volume in CLIA Labs, Pipeline with Pharma Partners

Sell into clinical (CLIA) labs

Enabling development of LDTs

Market/commercial and clinical validation

“Proof source” revenue

Builds sufficient installed base to attract
Pharma content partnerships

Develop CDx pipeline with Pharma

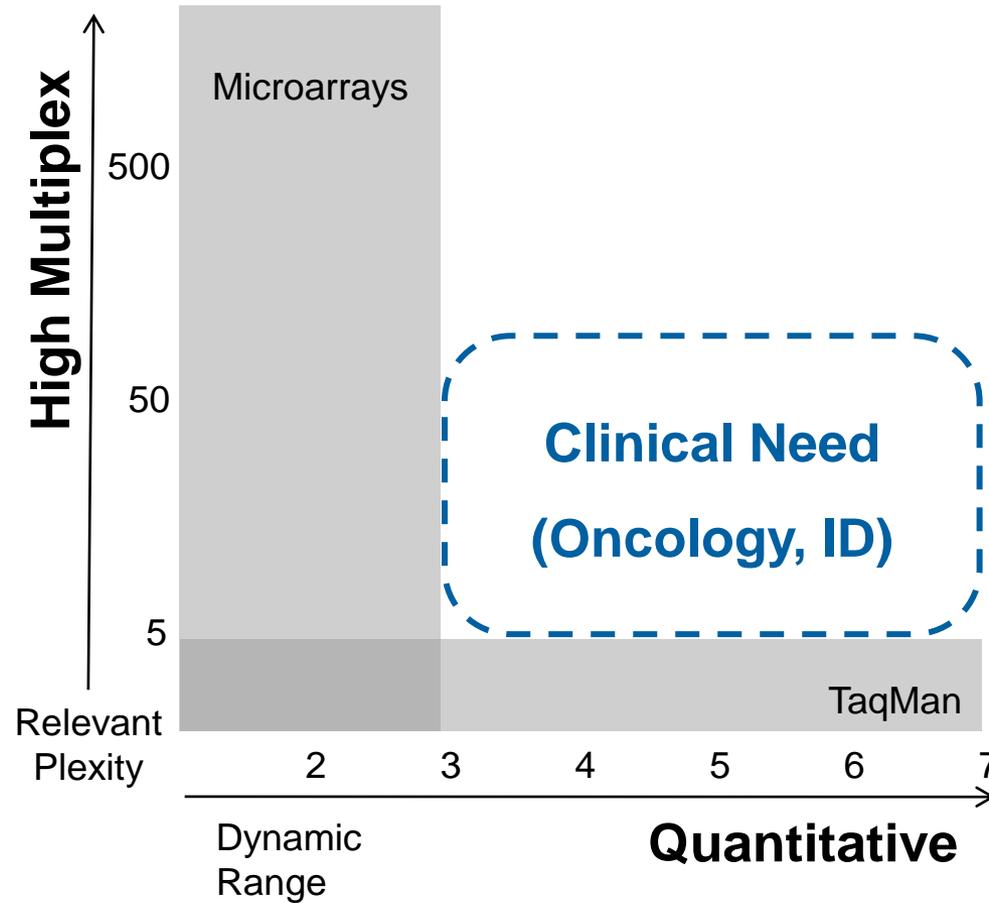
Leverage enabling technology to access
Pharma content

Creates high value, high margin products
in large markets

Non-dilutive funding during development

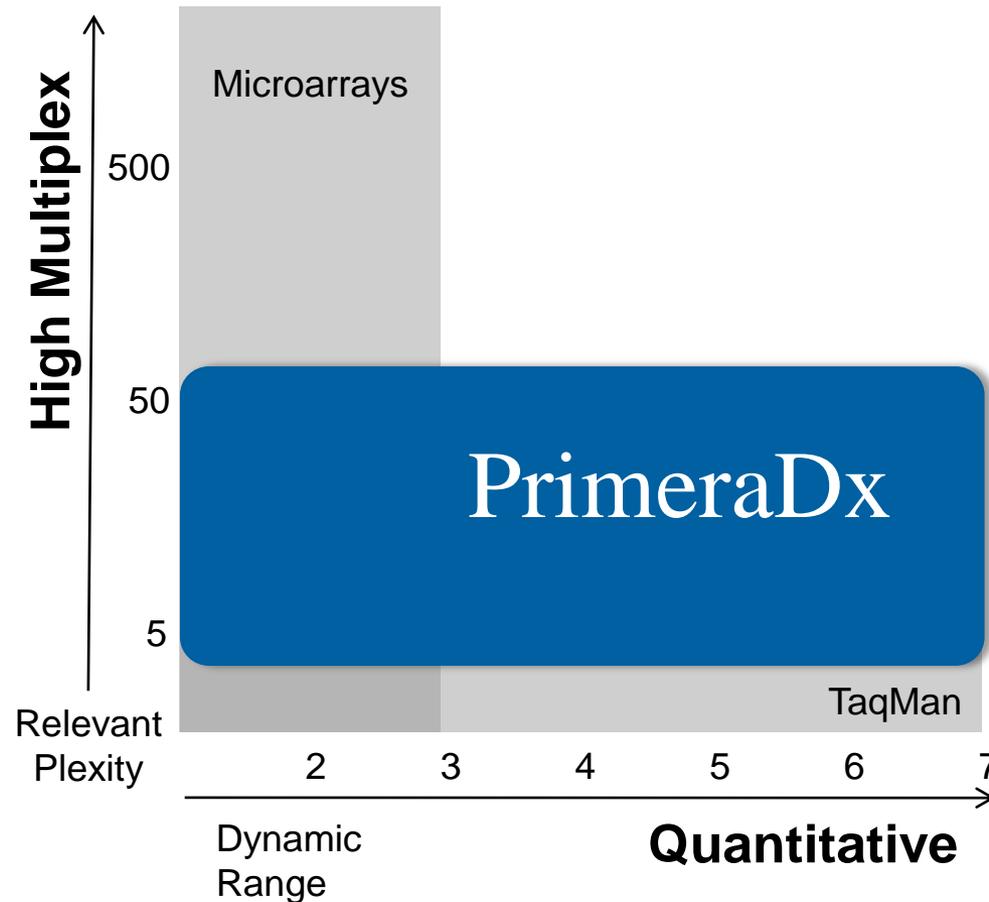
Unmet Need In Clinical Labs – Quantitative Multiplexing

Clinical Market Requires High Multiplex AND Dynamic Range



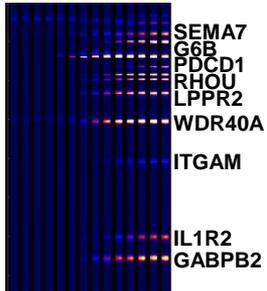
Only PrimeraDx Can Solve These Market Needs

ICE Plex Enables Multi-modal, Multiplex, Quantitative Tests

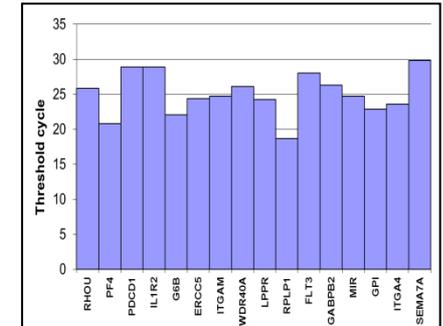
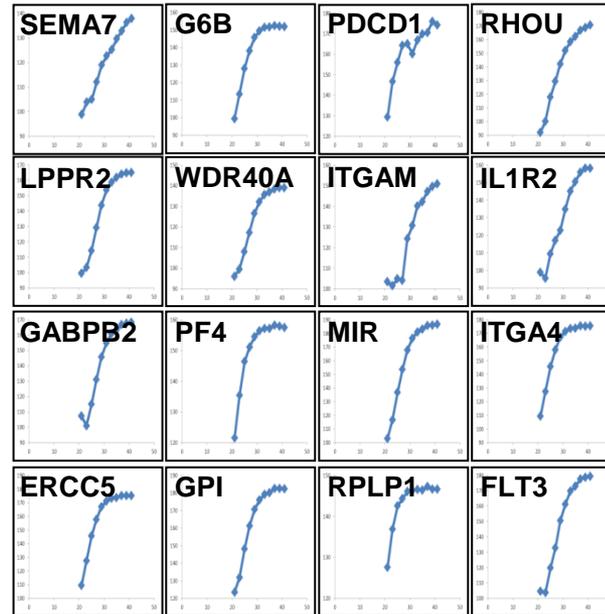
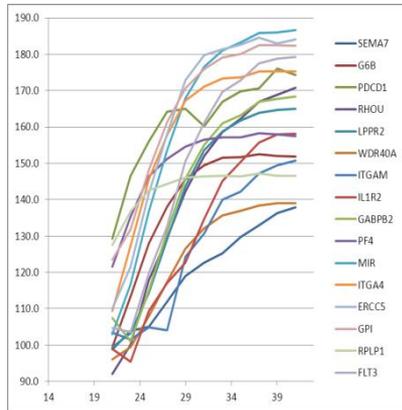
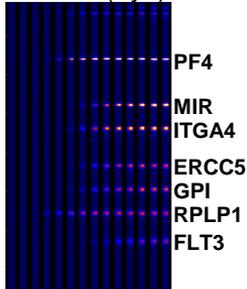


16-plex Gene Expression Panel in 2 colors – High Quality / Low Operating Cost / Simple Workflow

488nm (FAM)



635nm (Tye)

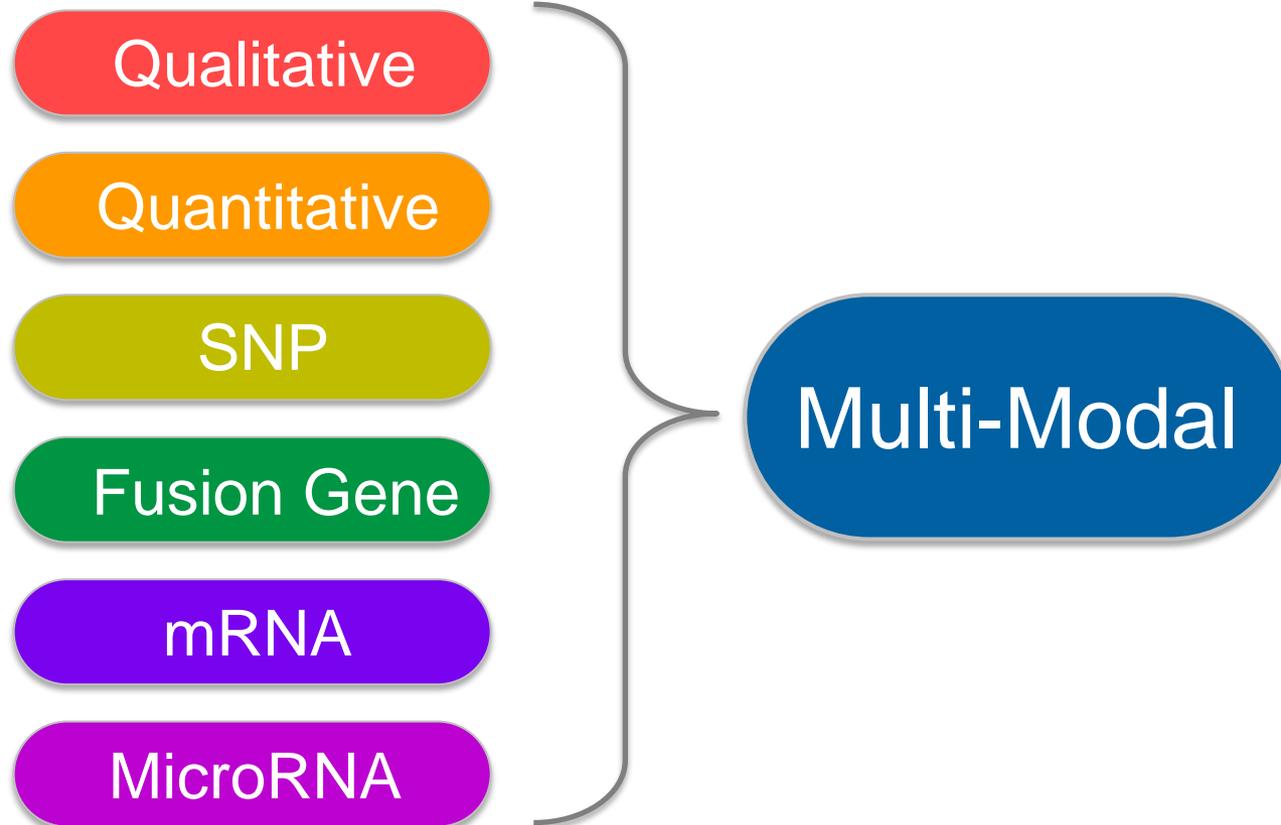


All in one well

Example Assay. For Research Use Only

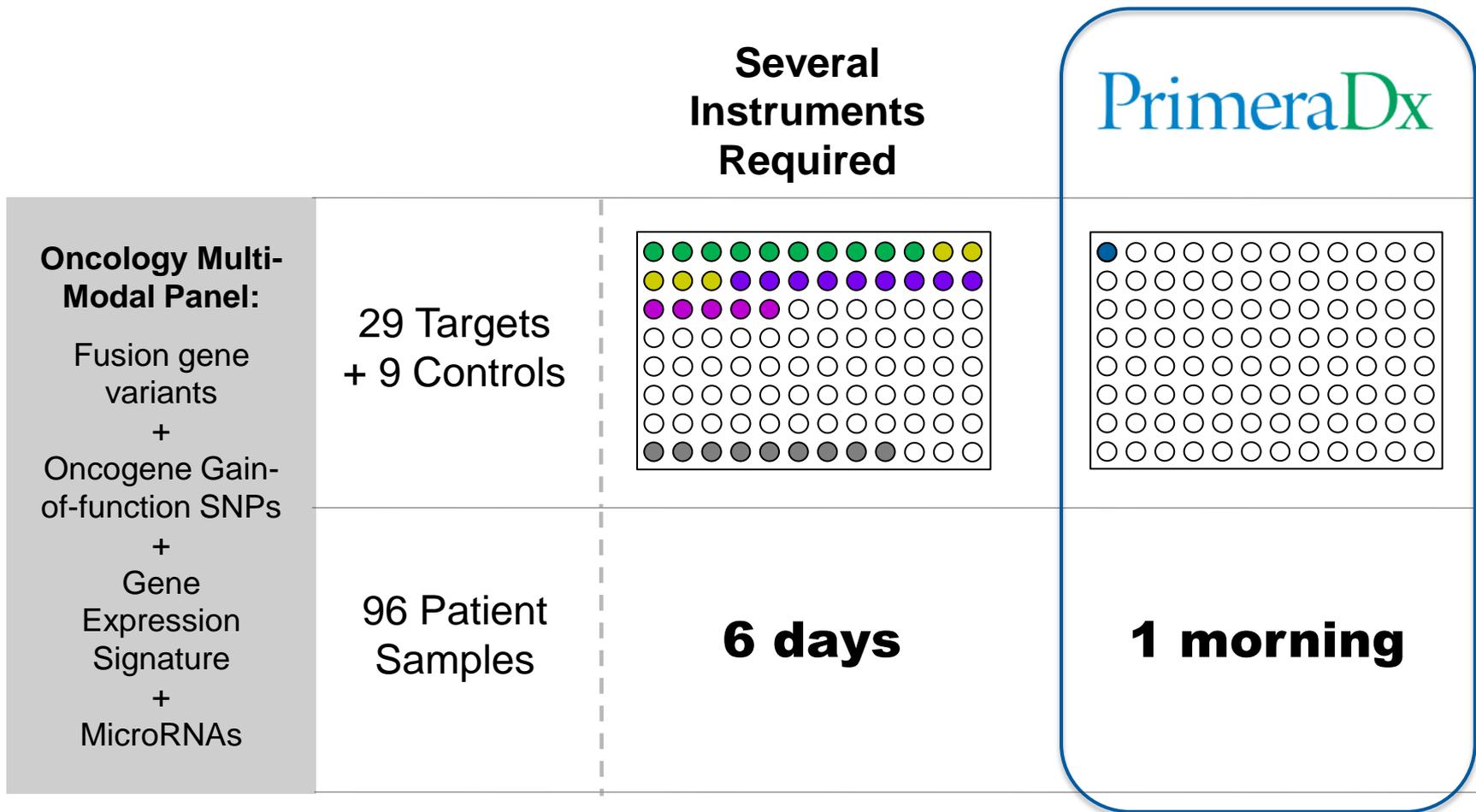
The Progression Towards Multi-Modal Testing

Companion Diagnostics Now Require “All in one Well” Capabilities



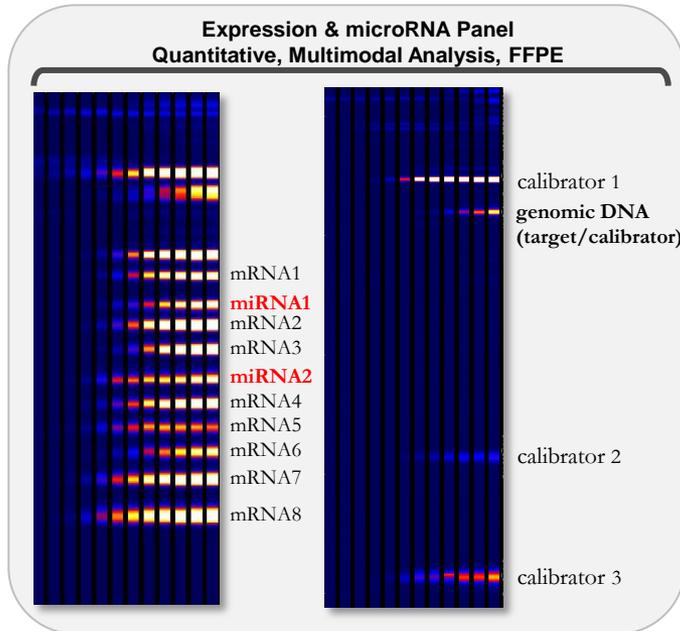
Companion Diagnostics Require Single-Well Reactions

Technology that Redefines the Market, Enables Our Partners



Multi-modal Testing Enables New Ways to Care for Patients

Oncology – “Single sample, Single slice, Single prep, Single well...
Answers to Complex Questions”



- ✓ Companion Dx require multi-modality
- ✓ Simultaneous detection of multiple target types
- ✓ Consolidates multiple FDA submissions

“No one else can do this – it fundamentally changes the kinds of questions we can ask”

*Senior Director of Diagnostics.
Large pharmaceutical company*

Example Assay. For Research Use Only

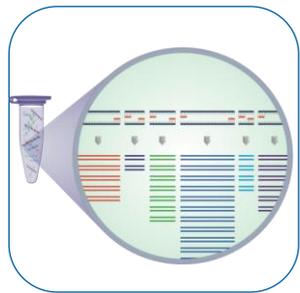
ICEplex Technology: Providing Answers That Matter

The Marriage of PCR and Capillary Electrophoresis

Real-time detection of PCR products separates targets by size.

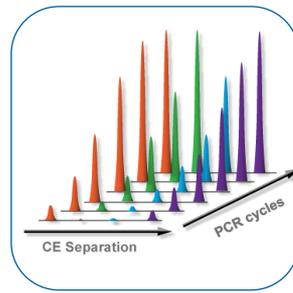
Sampling as the reaction progresses allows quantitation.

Multiplex quantitative results provide clinically actionable data.



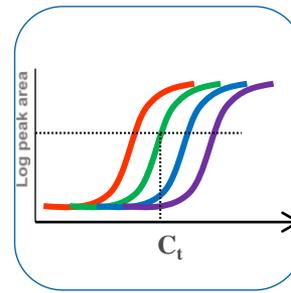
PCR

+



CE

=



Quantification

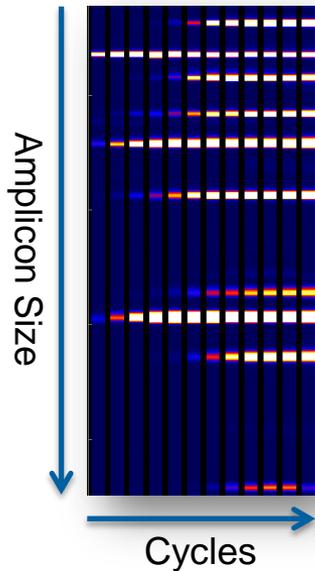
=

Clinical Report											
Test Name	Unit	Ref	Unit								
PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR
CE	CE	CE	CE	CE	CE	CE	CE	CE	CE	CE	CE

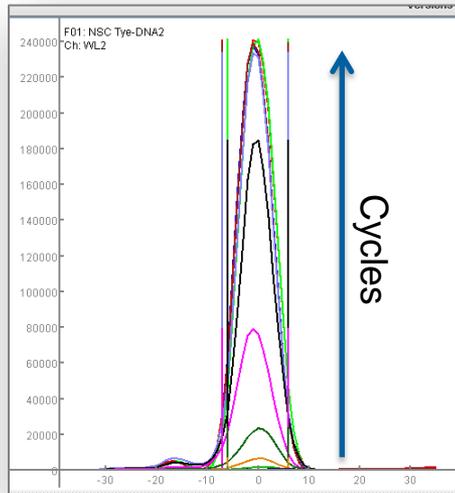
Clinically Actionable Results

Multiple Data Analysis Options for Open Mode Users

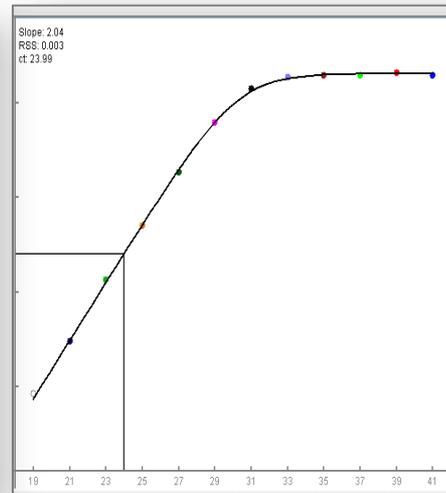
Gel View
(all Amplicons
all Cycles)



Peak Identification and
tracking (One Amplicon)



Amplification Curve
(One Amplicon)



Comprehensive
Report

Event Type	Peak	Peak	Peak	Peak	Peak
	Amplification	Amplification	Amplification	Amplification	Amplification
Gene Control	0.000000	0.000000	0.000000	0.000000	0.000000
Gene Control	0.000000	0.000000	0.000000	0.000000	0.000000
Gene Control	0.000000	0.000000	0.000000	0.000000	0.000000
Gene Control	0.000000	0.000000	0.000000	0.000000	0.000000
Gene Control	0.000000	0.000000	0.000000	0.000000	0.000000

Parameter	Value	Unit
Amplification Efficiency	0.98	%

Parameter	Value	Unit
Amplification Efficiency	0.98	%

Only ICEPlex Does It All

Capital Efficient For Labs. Workflow Efficient for Employees.

Company Brand	Technology	Singleplex	Multiplex	Qualitative	Quantitative	Multi Modal	Size Based
Luminex HTG	Bead	•	•	•			
Affymetrix Curetis	Array		•	•			
Life Tech Cepheid	Probe	•		•	•		
Ion Torrent 454, etc.	Sequencing		•	•	•		
Fluidigm OpenArray	Massively Parallel		•	•	•		
RainDance QuantaLife	Emulsion PCR		•		•		
T2 Biosystems	MRI	•	•	•			
NanoString	Molecular Barcodes		•	•		•	
PrimeruDx	ICEPlex	✓	✓	✓	✓	✓	✓

Proven Solutions for Very Large, High-Need Markets

A Selection of Assays that have been Run on the ICE Plex System

Infectious Disease

Transplant & Transfusion Med. (Multiplex Viral Load Panel)

Women's Health-STD (Mixed Microbial Detection)

Hospital Acquired Infections (Toxigenic *C. difficile* Detection)

US Army Wound Project (Fungal Detection Panel)

Oncology

mRNA Profiling in one reaction (Allomap in a tube)

Multi-modal (mRNA + microRNA + DNA + Calibrators and Controls)

Malignant Melanoma (DNA Methylation Assay)

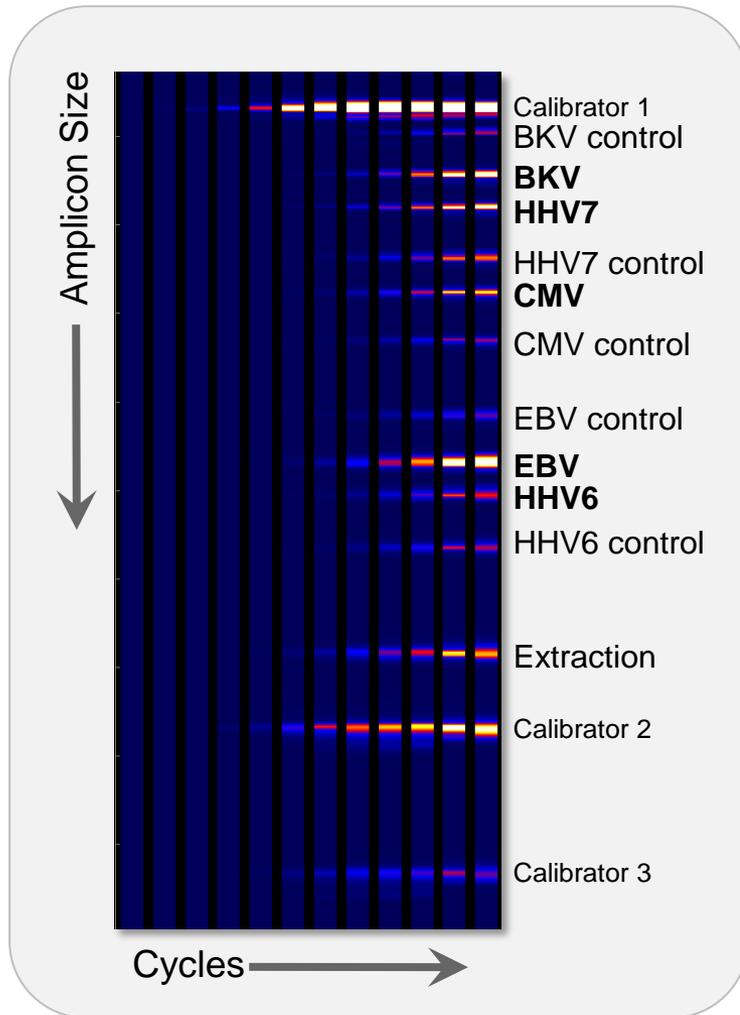
Colorectal Cancer (KRAS/BRAF mutations)

Non-Small Cell Lung Cancer (Fusion Gene Variants)

Pan-Myeloproliferative Disease (BCR-ABL /JAK2/T315I Gleevec resistance)

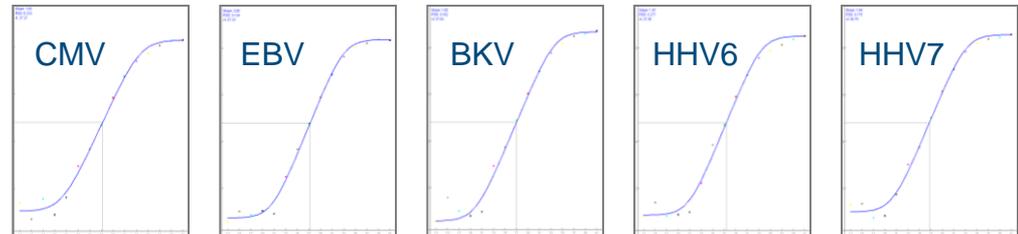
For Research Use Only

Infectious Disease – Automated Multiplex Results



Result Report

Viral load	CMV	EBV	BKV	HHV6	HHV7
Log ₁₀ cps/ml	4.5	4.6	4.5	4.5	4.7

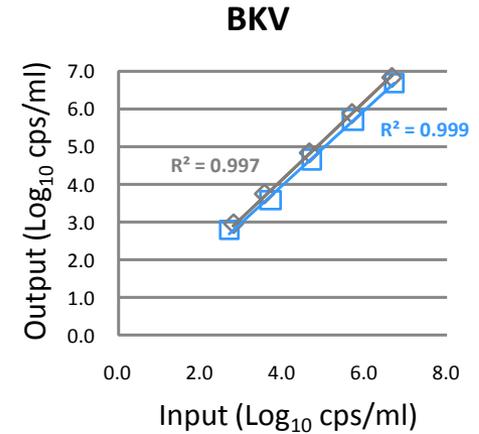
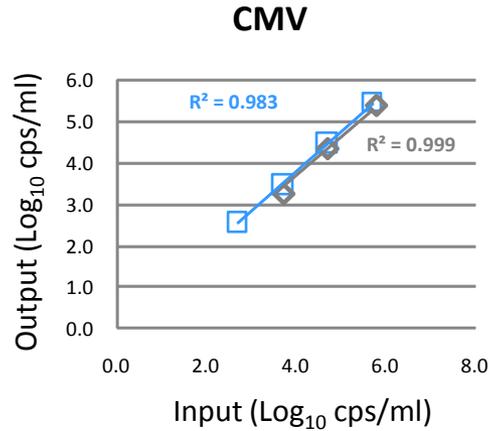
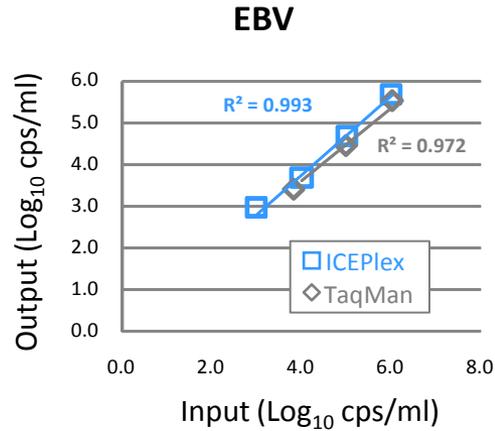


Background

Simultaneously detection and quantification of CMV, EBV, BKV, HHV-6 and HHV-7 in whole blood. The high level of multiplexing available on the ICEPlex instrument enables the incorporation of important quantification standards as well as quality controls for extraction efficiency into one test. These important features can decrease the occurrence of false negatives and increase confidence in results.

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Viral Load – Multiplex with Singleplex Performance



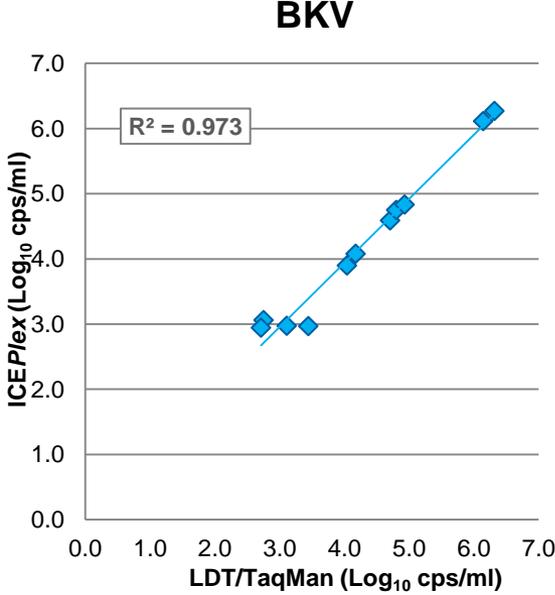
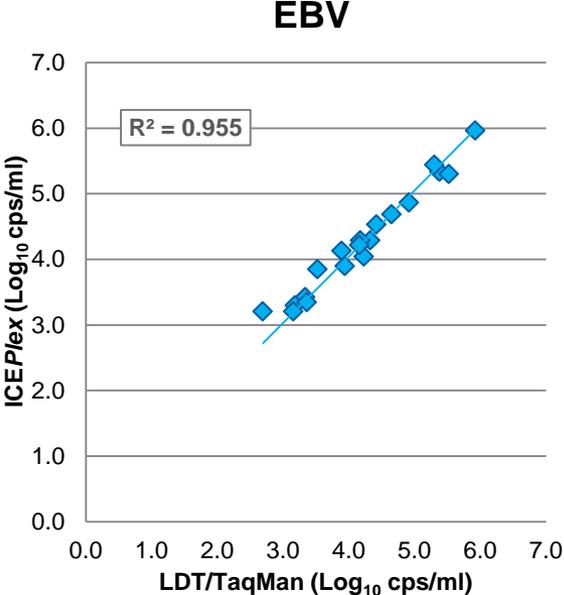
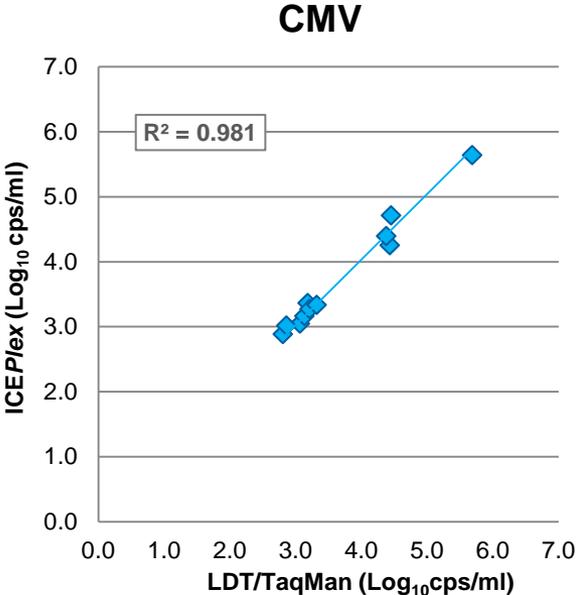
Results

A clinical partner compared results from the multiplex viral panel developed by PrimeraDx and their own, TaqMan based LDTs for BKV, EBV or CMV. The Input-Output graphs show very strong correlations between viral starting material and the quantification by TaqMan and ICEPlex. Also, the two techniques show nearly identical results, even though the TaqMan assays were run in singleplex, while the assays run on the ICEPlex were run in multiplex in one single reaction.

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Multiplex vs Singleplex Performance with Clinical Specimens

Strong Correlation to Singleplex TaqMan Assay

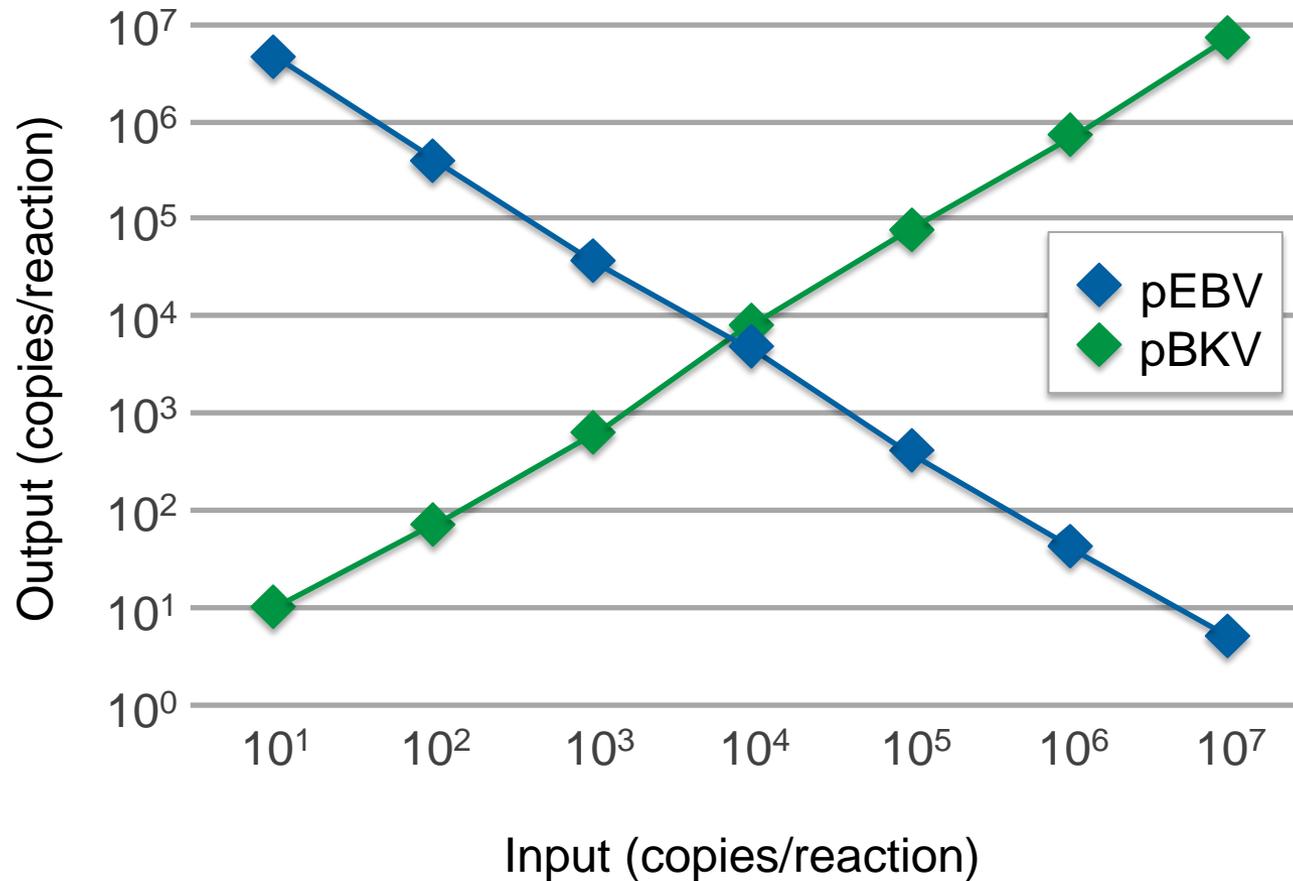


A clinical partner compared testing results from the multiplex viral panel developed by PrimeraDx and their own, TaqMan based LDTs for BKV, EBV or CMV, on clinical specimens (whole blood). Serum and urine data not shown.

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ICEPlex - Sensitive and Specific

High-Low Dual Target Ranges: pBKV + pEBV



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Viral Load – Clinical Benefits of Detecting Co-infection

SampleID	BKV		EBV		CMV	
	CCF	PDX	CCF	PDX	CCF	PDX
11	3.4	3.0	ND	<LOD	ND	<LOD
28	4.0	3.9	ND	<LOD	ND	<LOD
40	4.2	4.1	ND	<LOD	ND	<LOD
87	ND	<LOD	5.5	5.3	ND	5.7
116	ND	<LOD	4.7	4.7	ND	<LOD
44	ND	<LOD	ND	4.1	3.2	3.4
55	ND	<LOD	ND	3.3	2.8	2.9
57	ND	<LOD	ND	5.1	<LOD	2.9
58	ND	<LOD	ND	5.2	4.4	4.2
65	ND	<LOD	ND	4.3	5.7	5.6
70	ND	<LOD	ND	4.7	4.4	4.4
78	ND	<LOD	ND	4.7	3.3	3.3

Results

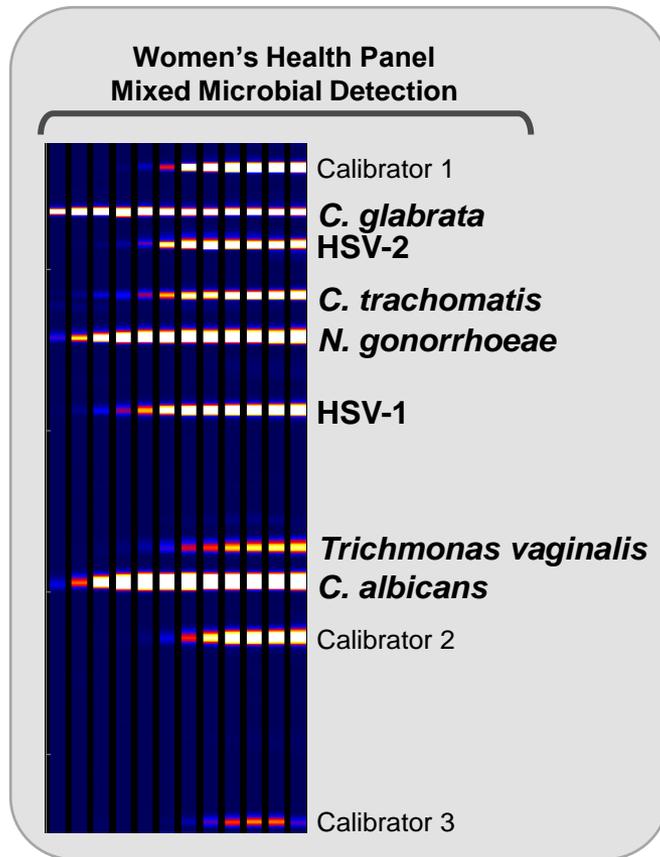
The Cleveland Clinic, tested whole blood samples in singleplex using their TaqMan based LDTs for BKV, EBV or CMV. Samples that were positive for one of the three viruses (**green boxes**) were tested on the ICEPlex instrument, using the viral panel developed at PrimeraDx. The results show that the multiplexing method on the ICEPlex instrument has a high degree of concordance with the results from the TaqMan singleplex, but the multiplex method detected eight additional co-infections (**blue boxes**). The same study was conducted with another clinical partner using plasma and urine samples with very similar results.

Without multiplex, co-infection can be missed

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With One Panel, PrimeraDx Spans An Entire Market

Women's Health + ICEPlex = Lower cost, improved workflow and patient care



ICEPlex:

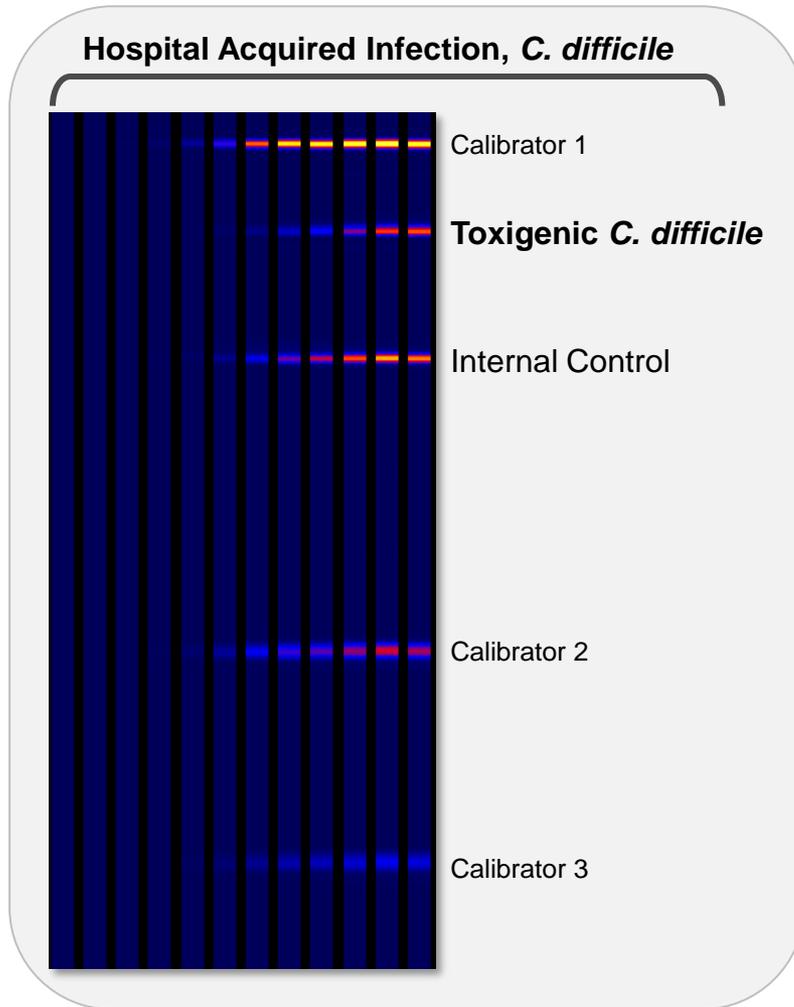
Simultaneous detection of disparate targets (yeast, bacteria, viruses)

Reduced turnaround time & cost

True value add to clinical labs

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Hospital Acquired Infections – Rapidly Growing Market



Background

Toxigenic *C. difficile* is a major cause (for approximately 20%) of antibiotic associated diarrhea. *C. difficile* is a gram-positive, spore-forming, anaerobic bacillus. Toxigenicity of the *C. difficile* is linked to expression of two toxins, A and B, encoded by genes *tcdA* and *tcdB* respectively. The toxin encoding gene, *tcdB*, is most commonly targeted by clinical tests for *C. difficile*.

Results

The gel image to the left shows results from one stool sample positive for *C. difficile*.

***C. difficile* assay will be submitted to the
FDA for 510(k) clearance in 2012**

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Performance is Comparable to FDA Cleared Devices

Hospital Acquired Infections – *C. difficile* Detection

Category	Agreement	
Negative	271/272	99.6%
Low Positive	267/267	100%
High Positive	204/204	100%
Overall	742/743	99.9%

Results

DNA was extracted from stool samples with high CFU, low CFU or negative CFU for *C. difficile*. PrimeraDx tested the accuracy of the *C. difficile* multiplex assay on the ICEPlex instrument. Overall, the assay exhibited 99.9% concordance with the CFUs.

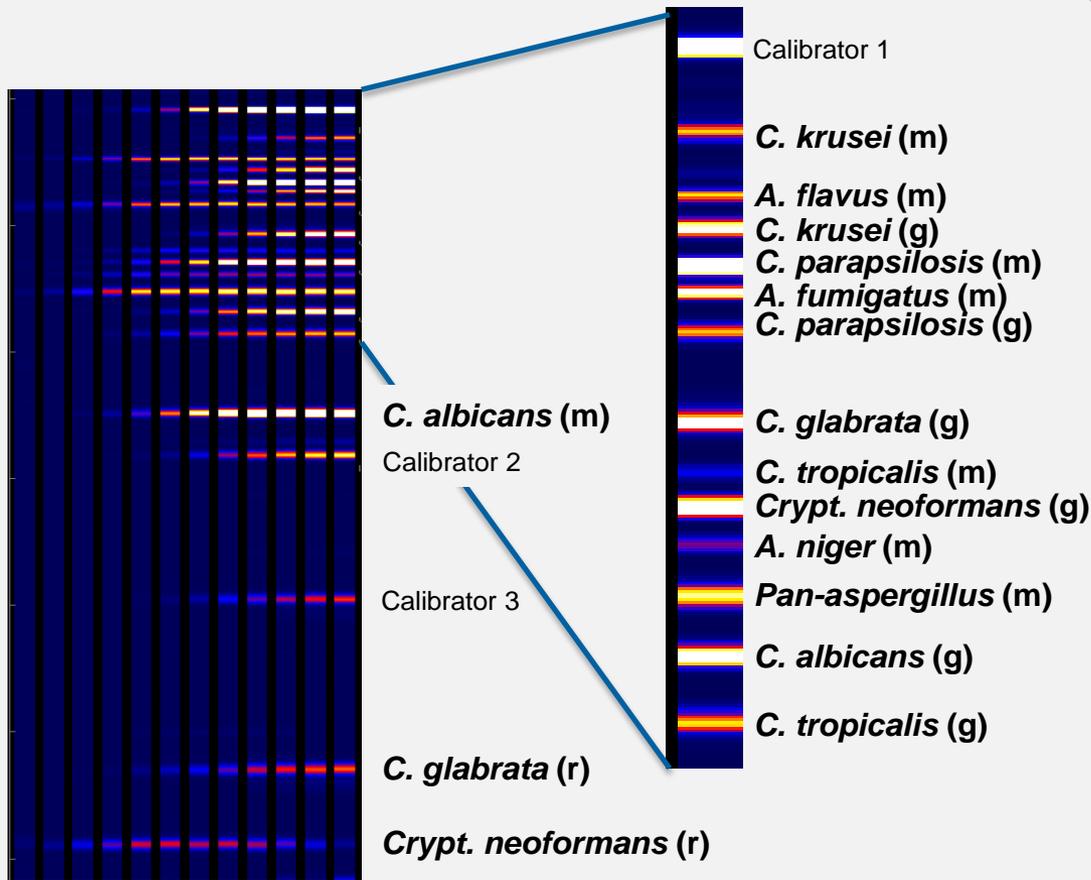
The Limit of Detection (LOD) of the ICEPlex *C. difficile* assay was determined on two *C. difficile* strains:

- ATCC 43255 (Toxinotype 0): 7.2 cfu/rxn
- ATCC BAA-1805 (Toxinotype III): 3.0 cfu/rxn

ICEPlex *C. difficile* assay is comparable to other 510(k) cleared devices.

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US Army Wound Care Project – Quantitative Fungal Panel



Background

A multiplex panel designed for detecting, discriminating and quantifying the following targets in whole blood:

Candida albicans
Candida glabrata
Candida krusei
Candida parapsilosis
Candida tropicalis
Cryptococcus neoformans
Aspergillus fumigatus
Aspergillus flavus
Aspergillus niger
Pan-fungal species
Pan-aspergillus species

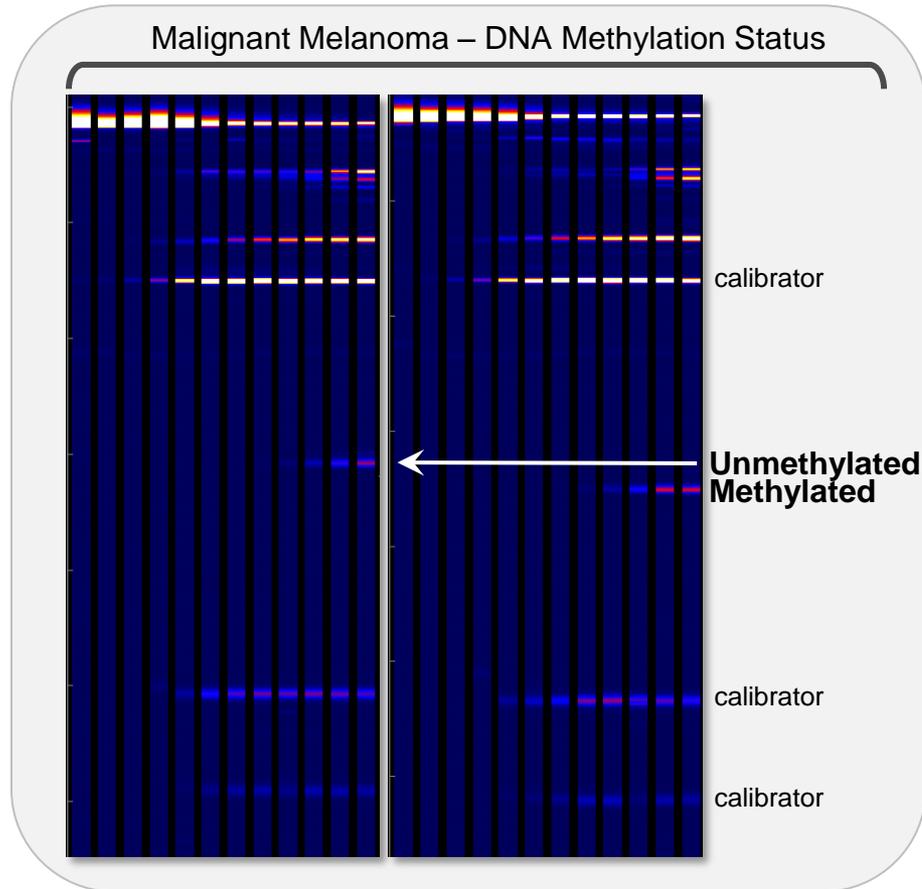
Sample preparation method has been developed.

Schizosaccharomyces pombe serves as extraction control.

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Malignant Melanoma

Detect Methylation in Multiplex



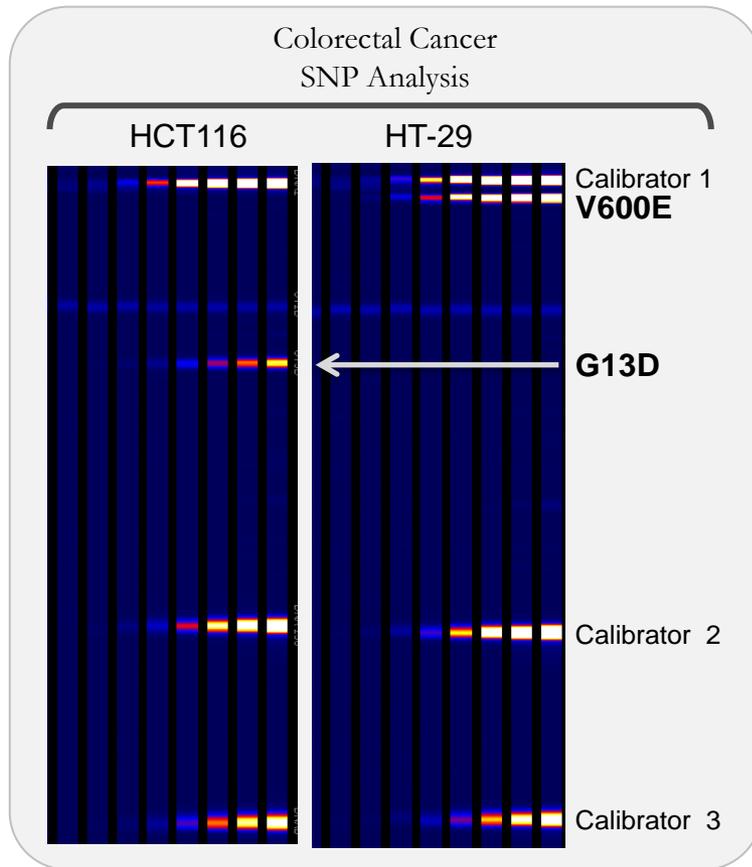
The Methylation state of some genes has been used as a biomarker for tumorigenesis. Here we tested for methylation status of a gene in malignant melanoma tissue.

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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KRAS/BRAF Mutation Detection in Colorectal Cancer Tissue

Detect SNPs in Multiplex



This multiplex KRAS/BRAF mutations assay is used for the rapid detection of mutations in genomic DNA extracted from human cell lines or fresh, frozen or fixed tissues:

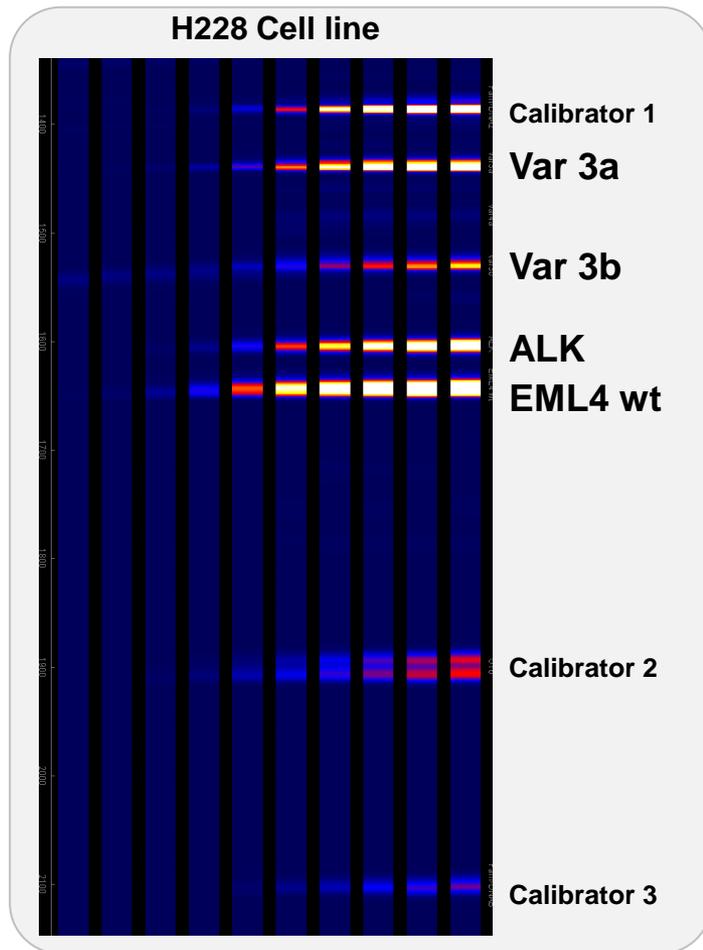
KRAS codon 12	codon 13
G12S	G13S
G12R	G13R
G12C	G13C
G12D	G13D
G12A	G13A
G12V	G13V

BRAF V600E

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Non-Small Cell Lung Cancer Fusion Gene Panel

10-plex Assay Targeting 8 EML4-ALK variants, EML4 wt & ALK



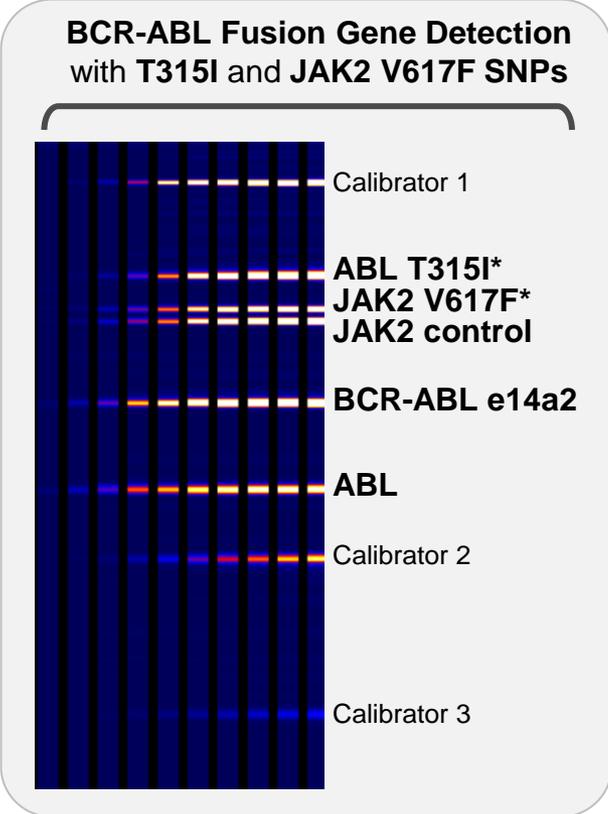
Amplicon sizes

<u>Target</u>	<u>Template</u>	<u>Actual</u>
Var 1	95	161
Var 2	100	166
Var 3a	98	128
Var 3b	100	154
Var 4a	99	143
Var 4b	89	124
Var 5a	102	133
Var 5b	70	118
ALK	86	173
EML4 wt	103	185

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Enabling FDA Clearance of Complex Companion Diagnostics

Liquid Tumor: Diagnose, Monitor and Determine Treatment – Huge Patient Benefit



- ✓ Simultaneous detection of all common variants and meaningful SNPs
- ✓ Reduced turnaround time & cost
- ✓ Improved patient care

“No one else can do this – it would change the way I manage patients”

*Hematopathologist.
Large academic medical center*

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The ICEPlex System – Fully Automated Multiplex qPCR

Offers on-board proprietary software for automated answer reporting

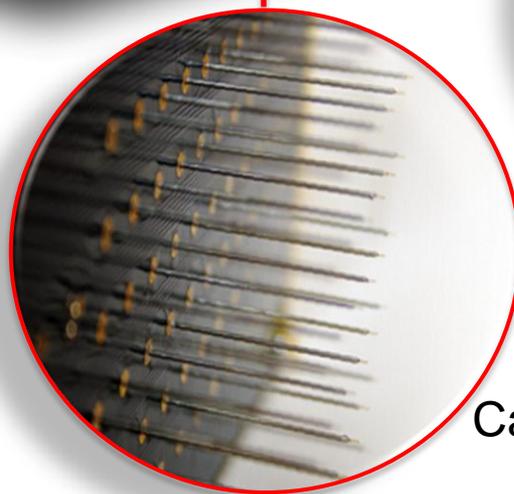
Thermal cycler



On-board Reagents



Capillary Cartridge



PrimeraDx Product Lines

Instrument

ICE*Plex* enables CLIA labs to run laboratory developed tests *and* PrimeraDx IVDs



Consumables



Three cartridge sizes

24 well

48 well

96 well (coming soon)

Universal Assay Kit

Capillary Electrophoresis plates

All on-board consumables
(buffers, gel, etc.)

Products

Open Platform Product

Instrument, software and consumables needed for CLIA labs to run LDTs

IVD Kits

C. diff. (early 2012)

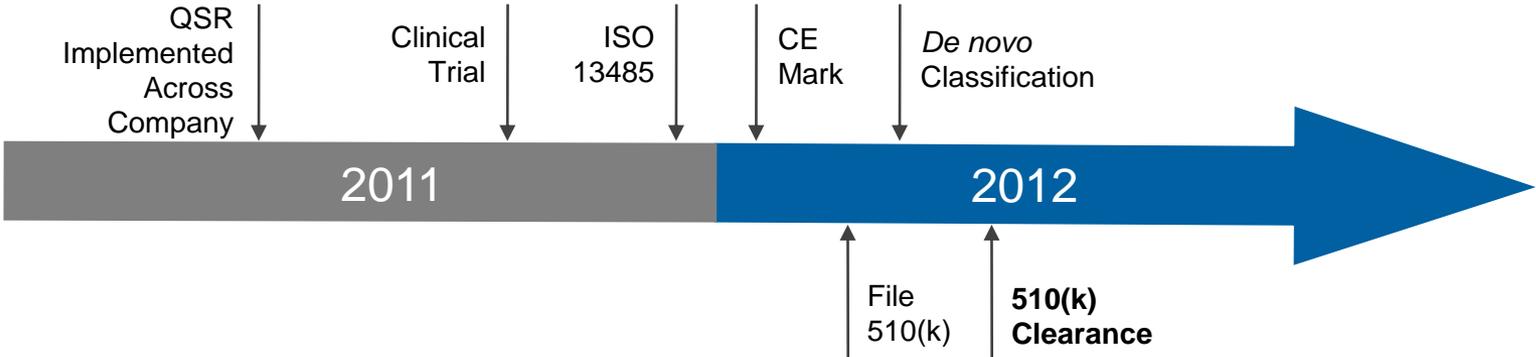
Companion Diagnostic (2015)

Companion Diagnostic (2016)



1st Product – Target FDA Clearance With Most Straightforward Path

Streamlined Regulatory Strategy – *C. diff.* is well understood



- Technology is **well understood**/accepted by regulators
- PrimeraDx plan **matches recent FDA guidance**
- **510(k) submission**: planned for 2012

Seasoned Management Team

	Background	Expertise
Matthew McManus, MD, PhD President and CEO	Cleveland Clinic Foundation, Novartis, McKinsey & Company, Procter & Gamble	Business leaders who know how to introduce new technology in the diagnostics market and how to build and grow a commercial operation.
Ted Myles CFO & VP of Operations	Pressure Biosciences, Merck KGaA, Cowen & Co., PWC	
Lilly Kong, DVM Chief Scientific Officer	Quest Diagnostics, Focus Diagnostics	Experienced science and technology leaders who have successfully developed ICEPlex and who understand how to scale up and meet customer needs.
David Heffelfinger VP of Eng./Systems Development	Beckman Coulter, Becton Dickinson, Bio-Rad	
Fayyaz Memon VP of Quality Systems & Regulatory	Thermo Fisher , Innovative Neurotronics, Digene, J&J, SmithKline Beecham	
Robert Millman* J.D. Chief IP Counsel	MPM Capital, Alnylam Pharma, Infinity Pharma, Celera Genomics	Experts in the regulatory and IP aspects of new technologies that are key to successful rollout and value creation.

* Consultant

Scientific Advisory Board

	Affiliation
Leroy Hood, MD, PhD	President and co-founder, Institute for Systems Biology
Jay Fishman, MD	Associate Professor of Medicine at Harvard Medical School
David Hillyard, MD	Associate Professor of Pathology, University of Utah School of Medicine
Gregory Tsongalis, PhD	Director of Molecular Pathology, Dartmouth-Hitchcock MC
Gregory Storch, MD	Director, Clinical Microbiology Laboratories, St. Louis Children's Hospital
Belinda Yen-Lieberman, PhD	Director of Clinical Virology, Serology, and Cellular Immunology in the Department of Clinical Pathology at Cleveland Clinic

Last words...

New Paradigm For Multi-modal Multiplex Diagnostics

- Quantitative
- Save Time and Money
- Broad Dynamic Range (what is needed)
- Mid/High Multiplex (the sweet spot)

Breadth of Applications

- Infectious Disease
 - Pathogen Detection
 - Viral Load
- Oncology
 - Cancer Classification
 - Fusion Gene Variant Detection
 - Methylation, SNP, CNV
- Non-Clinical Fields of Use
 - Microbial Detection-Food, Pharma QC

Future Directions

- Expect 510(k) Clearance in 2012

PrimeraDx

The Multiplex PCR Company