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Personal Genome Diagnostics

Implementation of an IVD Compliant Quality System in a Laboratory QMS Background

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Summary

- Background - IVD (Medical Device) QMS vs. Lab QMS
- Strategies for implementation of an IVD QMS for a clinical lab
- PGDx's approach
- Tips and recommendations

About Me

- 15 years experience in IVD, RUO industry – R&D and process development
- 8 years at FDA – reviewer and postmarket team lead in CDRH/OIR
  - Division of Immunology and Hematology
  - Division of Molecular Genetics and Pathology
- Recently moved to PGDx as Associate Director, Manufacturing Quality

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Background

Lab QMS vs. IVD QMS

- Lab QMS – governs the operation of the clinical laboratory –> patient safety
  - CLIA regulations
  - CAP checklist
  - CLSI QMS-01
  - ISO 15189

- IVD (Medical Device) QMS – governs product design, verification/validation, and manufacturing -> patient safety
  - 21 CFR 820
  - ISO 13485
  - MDSAP

Why develop an IVD QMS in a lab QMS background?

- ~~FDA regulation of LDTs~~
- CDx requirements *(driven by CDER, not CDRH)*
- Global business strategy

FDA clearances/approvals of mol Dx laboratory tests

Type of sub-mission	Sponsor	Product	Intended Use	Technology	Associated Drug
510(k)	Agendia	Mammaprint	Breast cancer prognosis	Microarray gene expression	N/A
510(k)	CareDx	AlloMap	Risk of heart transplant rejection	RT-PCR	N/A
HDE	ARUP	PDGFRβ FISH Assay	Aid in selection for MPD/MPS patients	FISH	Gleevec
HDE	ARUP	KIT D816V Assay	Eligibility in aggressive systemic mastocytosis	PCR	Gleevec
PMA	Myriad	BRACAnalysis CDx	Eligibility in ovarian cancer	Sanger sequencing	Olaparib
PMA	Foundation Medicine	FoundationFocus CDx BRCA	Eligibility in ovarian cancer	NGS	Rucaparib
PMA	Invivoscribe	LeukoStrat CDx FLT3 Mutation Assay	Selection of AML patients	PCR	Midostaurin

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Strategies for Implementation

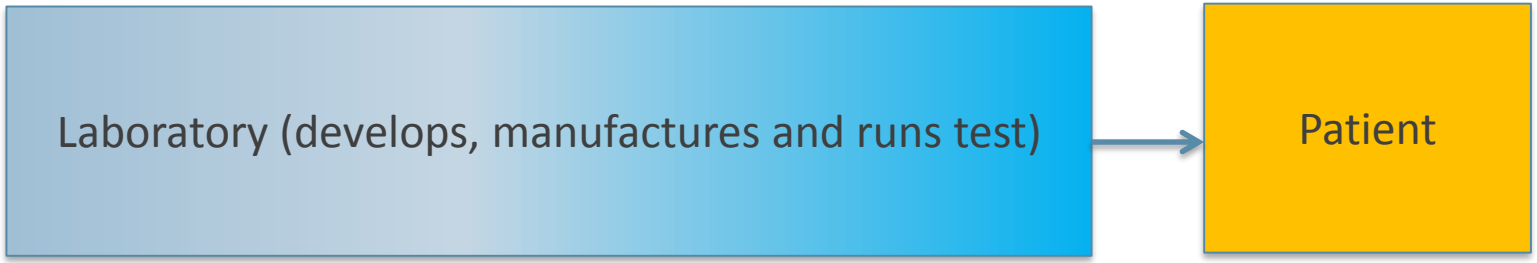
The “LDT PMA” model – FDA approved lab test

- Advantages
  - No distribution
  - Adapt existing processes
- Disadvantages
  - May be overly burdensome for lab processes
  - FDA inspectors may pick on “CLIA” items
  - Separate IVD space vs. using the same space for routine patient testing
  - Messy parts of the IVD QMS

Traditional IVD vs. LDT

Traditional IVD workflow:

LDT workflow:



Device description for a hypothetical NGS clinical laboratory test

Sequencing

Sample Collection

Sample DNA prep

Reagents
Instruments
Software

DNA quantification

Reaction plate prep

PCR library prep

Some “messy” parts of the QMS for an LDT PMA

- Device Description
- Final acceptance
- Nonconformity handling
- Complaint handling
- MDRs

Reference: Levin, J.D., Riddick, K.N., and Lee, E.Y., DIA Global Forum, February 2016. FDA Quality System implementation for companion diagnostic laboratory developed tests: A case study.

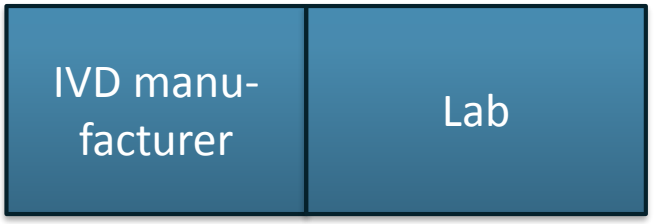
Example of the “instrument serialization” challenge

Instrument	Approved Serial Number(s)
ABI 3730xl	1408-038; 16112-019; 18127-015; 25193-005; 24189-002; 24180-009; 25193-003; 1412-027

Source: Summary of Safety and Effectiveness, P140020, BRACAnalysis CDx™, Myriad Genetic Laboratories, Inc.

IVD Manufacturer with One Customer Model – "ship it across the hall"

- Advantages
  - Protects the clinical lab from FDA oversight…somewhat
  - No need to kit and distribute product
  - Independently trained workforces
- Disadvantages
  - Need separate spaces
  - Limits IVD distribution



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PGDx Approach – Full IVD QMS Implementation

PGDx Company Milestones

2010

Founded with technology developed at Johns Hopkins University

2011

First exome sequencing CLIA lab for Research & Clinical applications

2012

First 100 tests completed

2013

First 1,000 tests completed

Licensed DK and PARE IP for tissue and liquid biopsy analysis from JHU

2014

First discovery of actionable genetic alterations in cancer reported by PGDx and Blueprint

2015

First 5,000 tests completed

Landmark studies in cancer genomics and immunotherapy (Le et al., NEJM, 2015)

First liquid biopsy detection of pancreatic cancer recurrence (Sausen et al., Nature Comm.)

2016

Partnership with Illumina in IVD development

Licensed MSI mutation burden from JHU

Collaboration with Takeda for liquid biopsy genomic testing in SCLC

Initiated 1st IVD development program

2017

Partnership with contract manufacturer

Expanded facility to 42,000 square feet

Initiated 2nd IVD development program

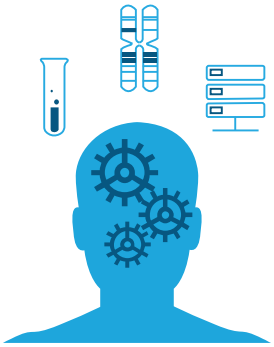
Initiated 3rd IVD development program

Initiated 1st, 2nd, and 3rd CDx Co-development programs

PGDx Lab Services and Product Portfolio

ANALYSIS METRICS	CancerXOME/ ImmunoSELECT™	RNAcomplete™	METdetect™	CancerSELECT™	PlasmaSELECT™
Sample Types	Frozen tumor, FFPE, cell lines, blood, saliva, and xenograft	FFPE tissue blocks	Plasma or frozen tumor, FFPE and cell lines	Frozen or FFPE tumor	Plasma
Regions Analyzed	Coding regions of >20,000 genes	>34,000 genes; >88,000 isoforms	MET region	125 genes	64 genes
Assay Sensitivity & Limit of Detection	≥95%	Na	Sensitivity: 100% LOD: 0.25% ctDNA	Sequence Mutations: 99% Rearrangements: 90% Amplifications: 95%	Sequence Mutations: 99.4% Rearrangements: 94.4% Amplifications: 97.2%
Application	RUO	RUO	RUO	RUO/CLIA	RUO/CLIA

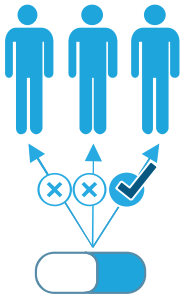
Solutions From Discovery Through Commercialization



BIOMARKER DISCOVERY

Identify & Refine Biomarker Hypotheses with Custom & Off-the-Shelf Service Assays

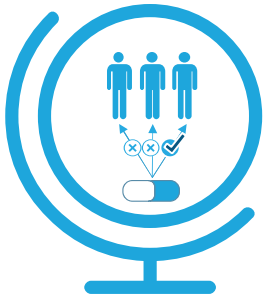
23 Pharma / Biotech Clients
>56 Customized RPAs
(>40 in Plasma)



EARLY CLINICAL TRIAL TESTING

Stratify Patients Using Assays in PGDx CLIA Lab

CancerSELECT™ 125
CancerXOME™
CancerCOMPLETE™
METDETECT™
PlasmaSELECT™ 64



PIVOTAL TRIAL ENROLLMENT ASSAY

Global IUO System Placement & Support

GLOBAL ACCESS

IVD Development, Commercialization & Support

MSI IVD
TMB IVD
Plasma IVD

Decentralized IVD Systems for NGS: Enabling Global Reach

PGDx
Reagent Kits

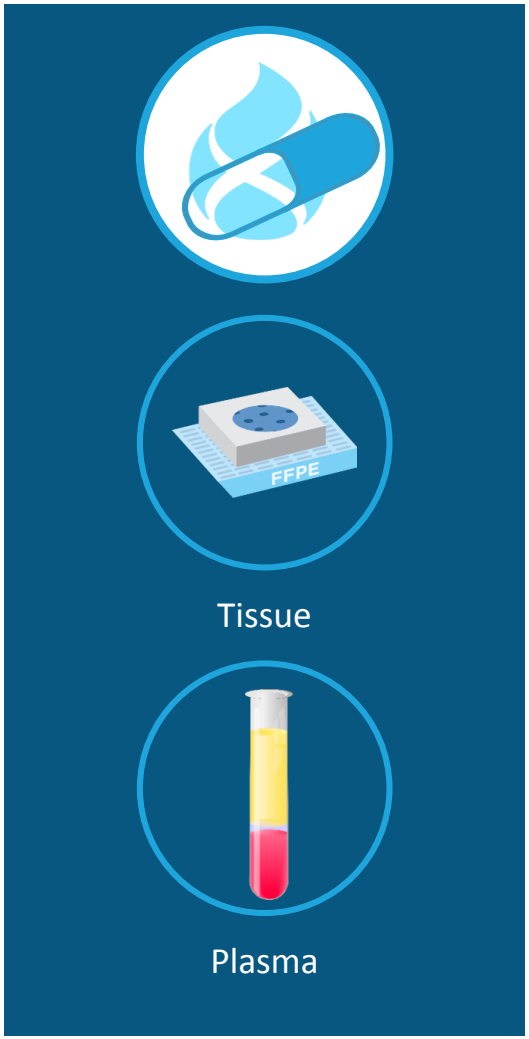
PGDx
Software & Server

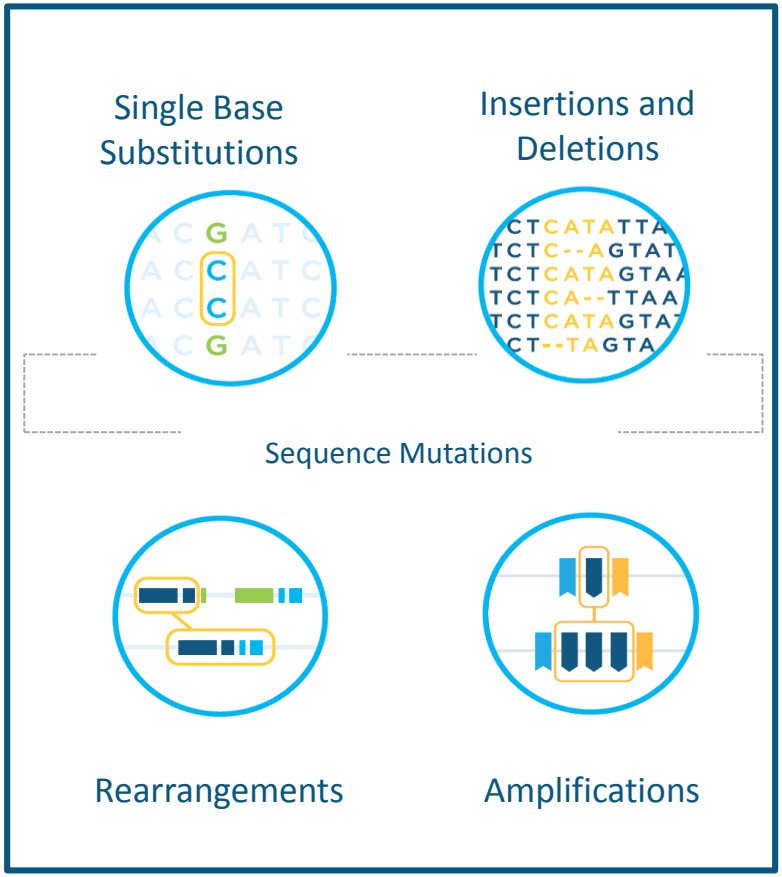
Global Access to NGS

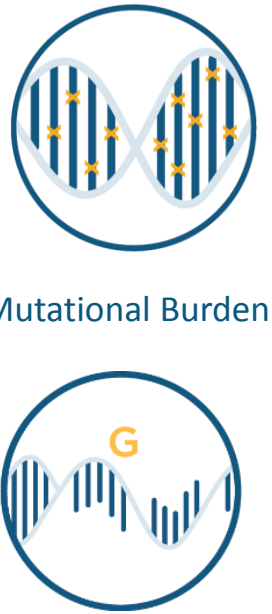
- ✓ IVD Kit Based Portfolio
- ✓ Turn-Key Bioinformatics
- ✓ Installed Sequencer Base
- ✓ Differentiated Dx / Rx Products

Illumina
Sequencer

>10,000 installed units worldwide

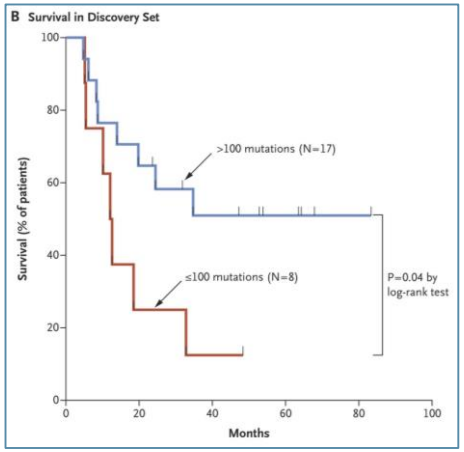




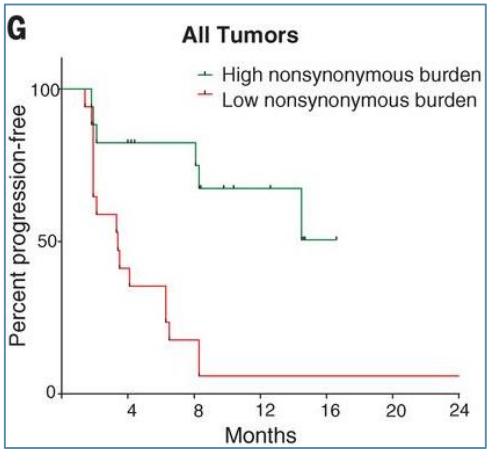


TMB: First Biomarker Truly Requiring NGS?

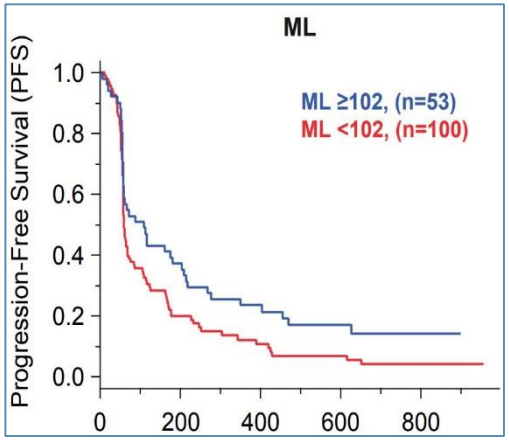
Improved survival in melanoma patients with >100 mutations treated with anti-PD-1/PD-L1[(1)]



Higher TMB correlated with increased PFS in NSCLC patients treated with Keytruda[(3)]



Across tumor types, patients treated with Keytruda with >100 mutations had improved PFS[(6)*]



[1]*Snyder et al. NEJM 2014 (Melanoma)*
[2]*Le et al. NEJM 2015 (CRC)*
[3]*Rizvi et al. Science 2015 (NSCLC)*
[4]*Hugo et al. Cell 2016 (Melanoma)*

[5]*Rosenberg et al. Lancet 2016 (Urothelia)l* [7.] *Carbone et al. NEJM 2017 (NSCLC).*
[6]*Cristescu et al. ASCO-SITC 2017 (pan-cancer)*

[7]*Carbone et al. NEJM 2017 (NSCLC)*

Full IVD Implementation Model

- Advantages
  - Easier separation of IVD, Lab QMS
  - Enables global market access
  - Protects the clinical lab from FDA oversight
  - Does not unduly burden the clinical lab
- Disadvantages
  - Still need to parse out common and separated QMS elements
  - Need to maintain dual QMS systems and certifications
  - Build and maintain two very different business models

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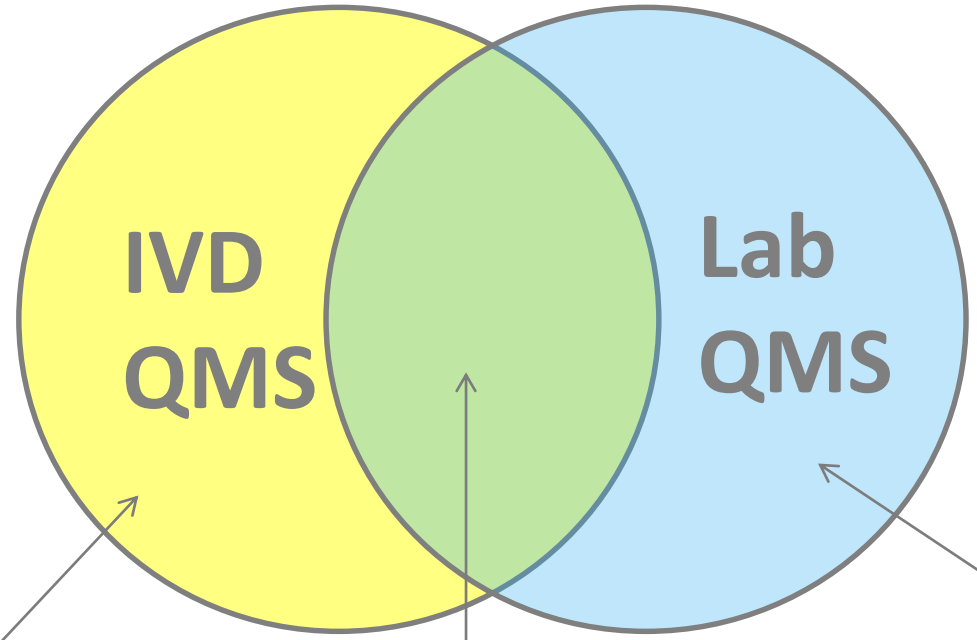
Tips and Recommendations

Example: separated and shared parts of the QMS



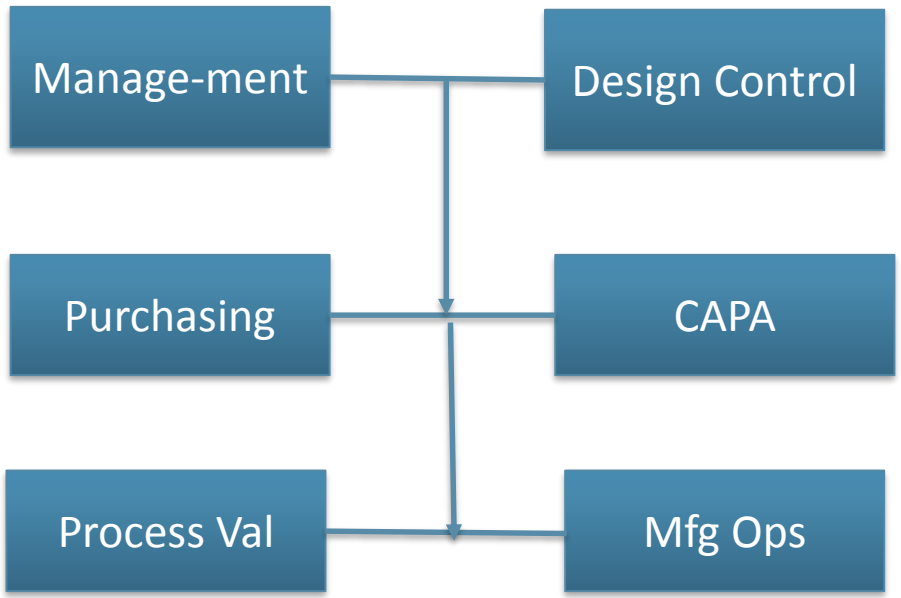
Manufacturing
Process Validation
Design Control
NCR handling

Purchasing
Complaints*
CAPA
Management
Audits
Equipment calibration

Accessioning
Patient and Doctor
Communications
Proficiency Testing
Lab Ops

Tips for building the QMS

- Decide what is common
- Define the “device”
- Distinguish mfg ops from lab ops
- Build as needed (example:)



Tips for building the QMS

- Iterate
- Facilitate user ownership
- Right-size it

Thank you!

- PGDx Regulatory and Quality Team
- Michael Wienholt (QS consultant)

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