Breakthrough Designation: Industry Perspective

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FOUNDATION MEDICINE

1. Overview of Breakthrough Designation Program
2. Case Study: FoundationOne® CDx
3. Challenges

Overview of Breakthrough Device Program

Breakthrough Devices Program

- Goal:
  - Provide patients and health care providers with timely access to medical devices the provide more effective treatment or diagnosis of life-threatening or debilitating conditions.
  - Expedite development and review of devices

- Benefits:
  - Interactive and timely communication
  - Pre/Post-market balance of data collection
  - FDA Sr. Management engagement
  - Priority review

Eligibility for Breakthrough Devices

Devices subject to premarket approval applications (PMAs), premarket notification (510(k)) or requests for De Novo designation are eligible for breakthrough device designation if both of the following criteria are met:

Criteria	Description	Refer to Guidance
First Criterion	The device provides for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions	Section III.B.1
Second Criterion	The device also meets **at least one** of the following:	
	a. Represents Breakthrough Technology	Section III.B.2.a
	b. No Approved or Cleared Alternatives Exist	Section III.B.2.b
	c. Offers Significant Advantages over Existing Approved or Cleared Alternatives	Section III.B.2.c
	d. Device Availability is in the Best Interest of Patients	Section III.B.2.d

https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/ucm441467.htm

Request Submission Process

Any time prior to marketing submission…earlier in the process is probably better

Submit as Q-submission using “Designation Request for Breakthrough Device”. Keep other feedback requests separate.

Include:

-Device Description

-Proposed IU

-Regulatory History

-**How the device meets statutory requirements (previous slide)**

-Type of marketing submission planned

Decision: 30 Days

Case Study: FoundationOne® CDx

Rapidly Evolving Field Requires Agile Regulatory Strategy

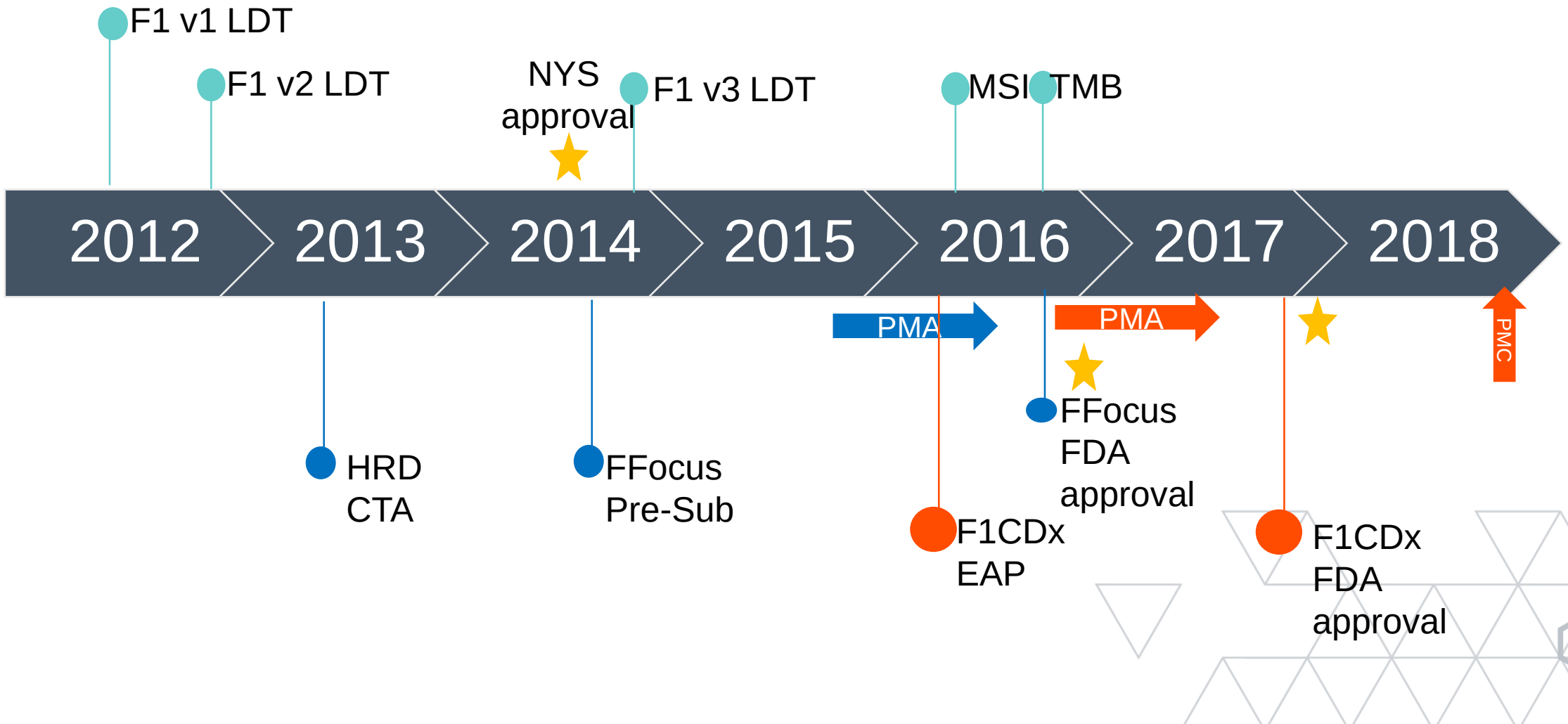
Example: F1CDx Intended Use Evolution

FoundationOne CDx™ (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels) and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed Table 1 in accordance with the approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for cancer patients with solid malignant neoplasms. The F1CDx test is a single-site assay performed at Foundation Medicine, Inc.

Table 1. Companion diagnostic indications

Indication	Biomarker	Therapy
Non-small cell lung cancer (NSCLC)	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	Gilotrif® (afatinib), Iressa® (gefitinib), or Tarceva® (erlotinib)
	EGFR exon 20 T790M alterations	Tagrisso® (osimertinib)
	ALK rearrangements	Alecensa® (alectinib), Xalkori® (crizotinib), or Zykadia® (ceritinib)
	BRAF V600E	Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib)
Melanoma	*BRAF* V600E	Tafinlar® (dabrafenib) or Zelboraf® (vemurafenib)
	BRAF V600E and V600K	Mekinist® (trametinib) or Cotellic® (cobimetinib) in combination with Zelboraf® (vemurafenib)
Breast cancer	*ERBB2* (HER2) amplification	Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumab-emtansine), or Perjeta® (pertuzumab)
Colorectal cancer	*KRAS* wild-type (absence of mutations in codons 12 and 13)	Erbitux® (cetuximab)
	KRAS (exons 2, 3, and 4) and *NRAS* (exons 2, 3, and 4)	Vectibix® (panitumumab)
Ovarian cancer	*BRCA1/2* alterations	Rubraca® (rucaparib)

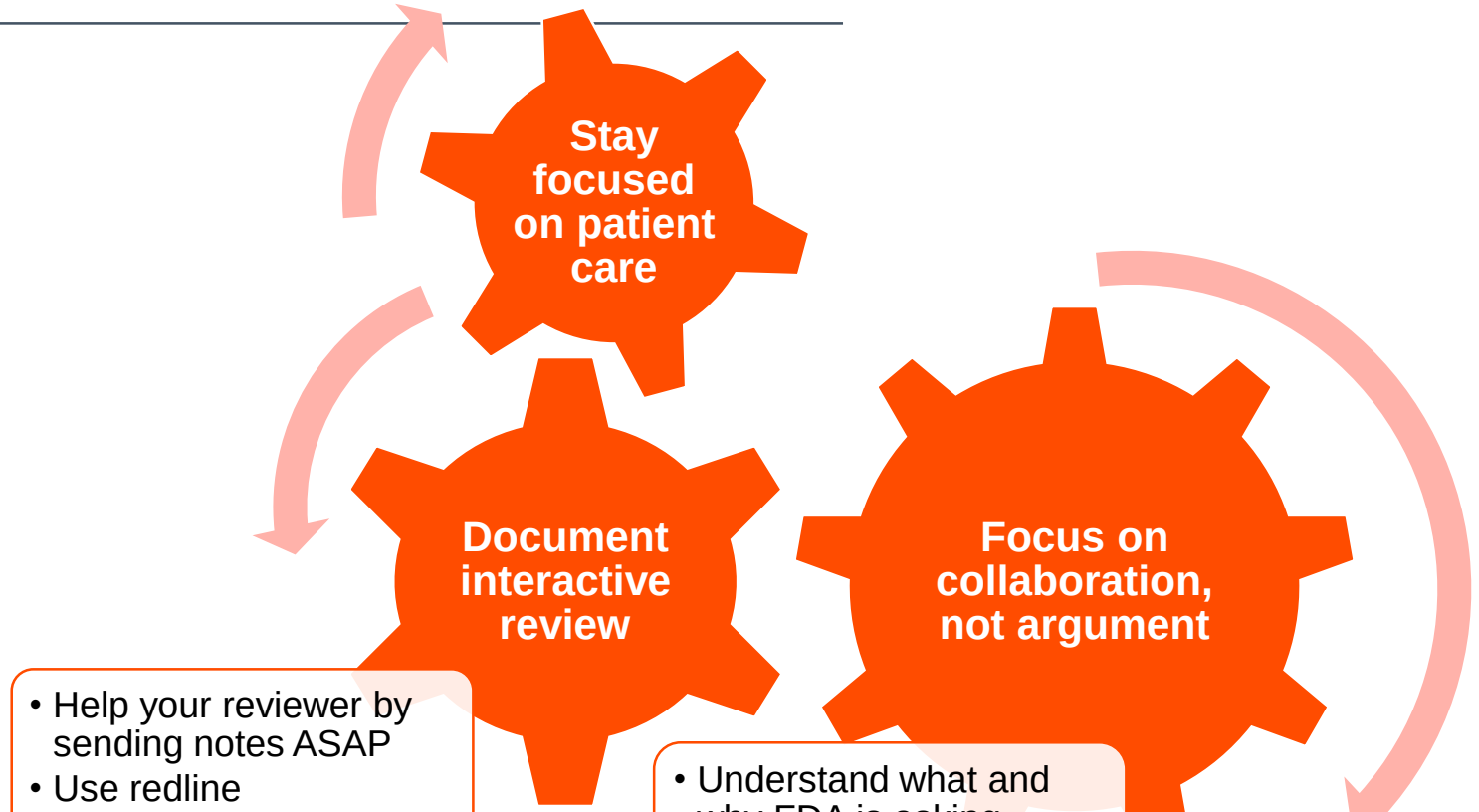
FMI Product Approval History



F1CDx Eligibility

Requirement	FoundationOne CDx
Provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions	F1CDx is a companion diagnostic for cancer therapies.
A. Represents breakthrough technologies; B. No cleared or approved alternative available; C. Significant advantages over existing alternatives; or D. Availability is in the best interest of patients	• At the time of request, no comprehensive genomic profiling assays with CDx indications were available • Available CDx assays were typically for a single gene or alteration requiring a physician to potentially order multiple tests • Limited tissue availability for use with approved assays could have lead to missed therapy options

Successful FDA Review



- Help your reviewer by sending notes ASAP
- Use redline

- Understand what and why FDA is asking
- Consider that FDA may be helping you
- We are scientists, they are scientists

Challenges

Comprehensive Genomic Profile + Broad CDx Claim = Huge Validation Effort

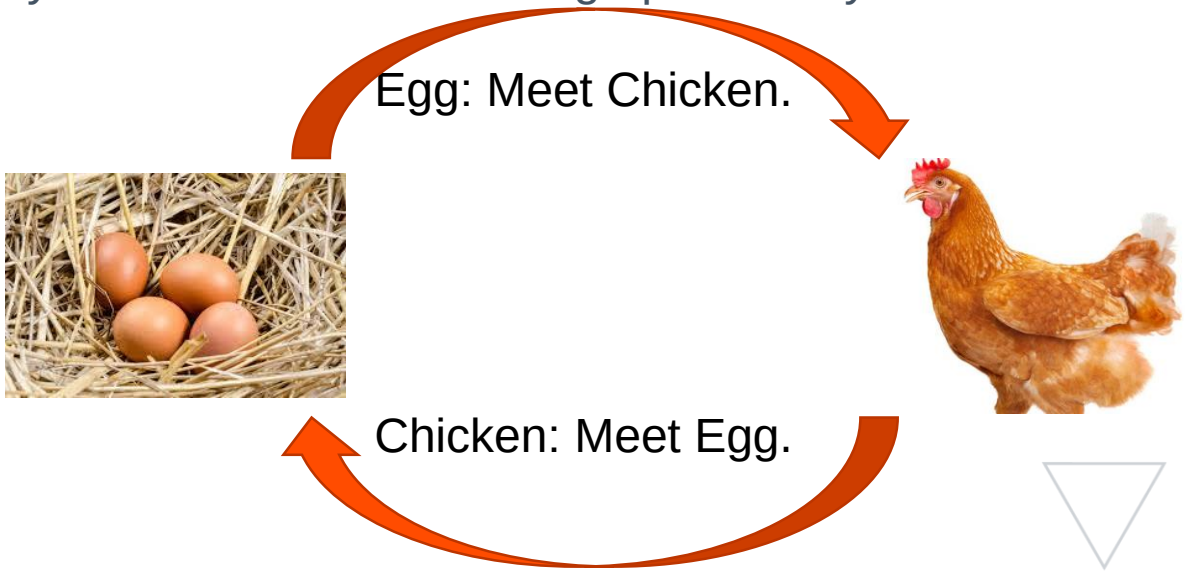
- ~6,000 samples run on complex assay (~7-10 days)
- Cover multiple tumor types
- Include CDx associated alterations as well as representative alterations
  - Substitutions and Indels
  - Alterations in GC rich regions
  - Long indels in homopolymer regions
  - CNVs of various gene sizes, copy number and tumor content
  - Variety of fusions
- Multiple comparator assays and laboratories required

Challenge #1: Sample Availability

- CDx claim can be established using clinical trial samples and data: no problem if the CDx was the CTA…if not, likely a significant challenge to find material for bridging
- CDx claim can be established as follow-on using procured samples and concordance to CDx
  - ~150 biomarker positive, ~150 negative
  - Non-inferiority requires two test results from approved CDx for each sample
  - Infeasible to procure sufficient positive samples for rare biomarkers
- Volume of sample for analytical validation
- How many exemplar samples is enough for broadly defined biomarkers?

Challenge #2: Limited Orthogonal Methods

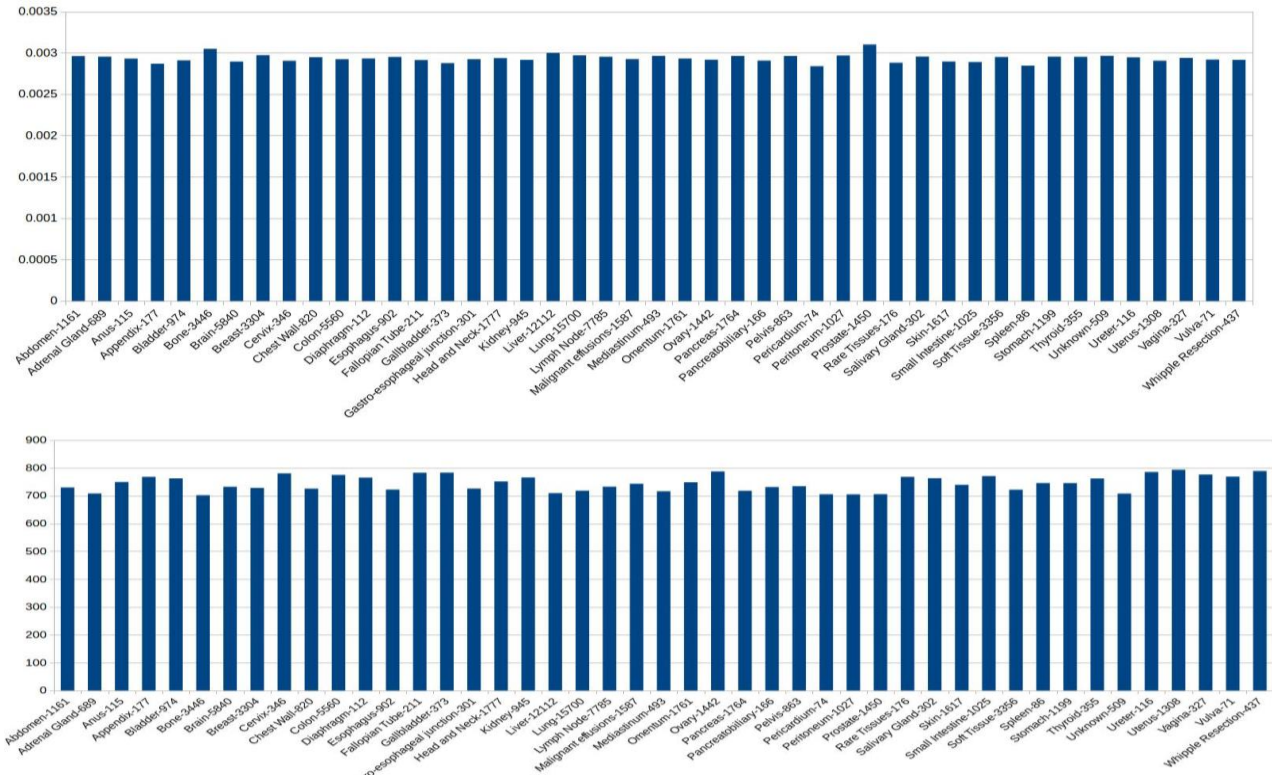
- Many newer biomarkers are novel and no “gold standard” exists
- If another assay is identified, validation rarely meets FDA standards
  - Most LDTs rely on “representative” approach for large panels
- Other laboratories my not have sufficient through-put or may not be amenable to working with a competitor



Challenge #3: Pan Tumor Validation

- Tumor types associated with CDx represented in all AV studies
- Broad range of tumor types represented in NGS Concordance
- Retrospective study to prove that “DNA is DNA”

QC Metric Name	QC Specification for F1CDx	Range of Mean QC Performance Across Tissue Types	Range of QC Pass Rate Across Tissue Types	Tissue types with ≥90% QC Pass Rate
Overall report Pass/Qualified rate	Pass rate: ≥90% specimens entering assay	N/A (see pass rate)	79%-98%	39/43 (90.6%)
Library Construction (LC) Yield	≥545 ng	7050–8643 ng	98-100%	43/43 (100%)
Quantity of DNA library after Hybridization Capture (HC)	≥140 ng	434-576 ng	97-100%	43/43 (100%)
Median Exon Coverage	≥250X	702-793X	96-100%	43/43 (100%)
Percent of target >100X coverage	≥95% target at ≥100X coverage	99.0%-99.8% targets	98%-100%	43/43 (100%)
Sequencing error rate	<1%	0.0028-0.0031	100%	43/43 (100%)
Noisy copy number data	N/A (not specified in product requirements)	N/A (see pass rate)	93.8-100%	43/43 (100%)



Thank you