

Foundation Medicine

The Challenges of getting an NGS assay to the EU market

February 27, 2018



**FOUNDATION
MEDICINE**

Thomas Holtschke, Director QA, FMI Germany GmbH

Forward Looking Statement

These slides and materials, including any accompanying oral presentation, contain forward-looking statements about our business. You should not place undue reliance on forward-looking statements as these statements are based upon our current expectations, forecasts and assumptions and are subject to significant risks and uncertainties. These statements may be identified by words such as “may,” “will,” “should,” “could,” “expect,” “intend,” “plan,” “anticipate,” “believe,” “estimate,” “predict,” “potential,” “forecast,” “continue” or the negative of these terms or other words or terms of similar meaning. Risks and uncertainties that could cause our actual results to differ materially from those set forth in any forward-looking statements include, but are not limited to, the matters listed under “Risk Factors” in our Annual Report on Form 10-K for the twelve months ended December 31, 2016, which is on file with the Securities and Exchange Commission, as well as other risks detailed in our subsequent filings with the Securities and Exchange Commission. These reports are available at www.sec.gov or by contacting our investor relations department at ir@foundationmedicine.com.

Statements and information, including forward-looking statements, speak only to the date they are provided (unless an earlier date is indicated), and we do not undertake any obligation to publicly update any statements or information, including forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.



Foundation Medicine

WHO WE ARE

Foundation Medicine is a molecular information company that's leading a transformation in cancer care.



Our NGS based assays provide biomarker information to help match patients to approved targeted therapies, immunotherapies, and clinical trials — giving doctors and patients powerful actionable insights for navigating therapies.

Foundation Medicine



History and Milestones



2010

Company Founded



2012

FoundationOne[®]
launched



2013

FoundationOne[®]Heme
launched



2016

FoundationACT[®]
launched,
FoundationFocus[™]
CDxBRCA - first FDA-
approved companion
diagnostic



2017

FDA approves
FoundationOne CDx -
the first broad
companion diagnostic
for solid tumors

- Laboratories located in Cambridge, MA, Morrisville, NC and Penzberg, Germany
- US Laboratories are CLIA, CAP, and NYSDOH certified and accredited
- Has processed >200,000 samples
- Partial coverage by numerous national health insurance providers
- Roche acquired majority stake in 2015



Transformational Shift in Oncology

Why use Next Generation Sequencing (NGS) in Cancer Diagnostics?

500+

Genes Involved in
Oncogenesis

200+

Biomarker Tests

55+

FDA Approved Targeted
Therapies

850+

Targeted Compounds in
Development

3,200+

Active Clinical
Trials

500+

BioPharmas Developing
Targeted Therapies

1

Brain per
Human (even per
Oncologist and
Pathologist)

Kristen's Story

Making an Impact in Patient's Life

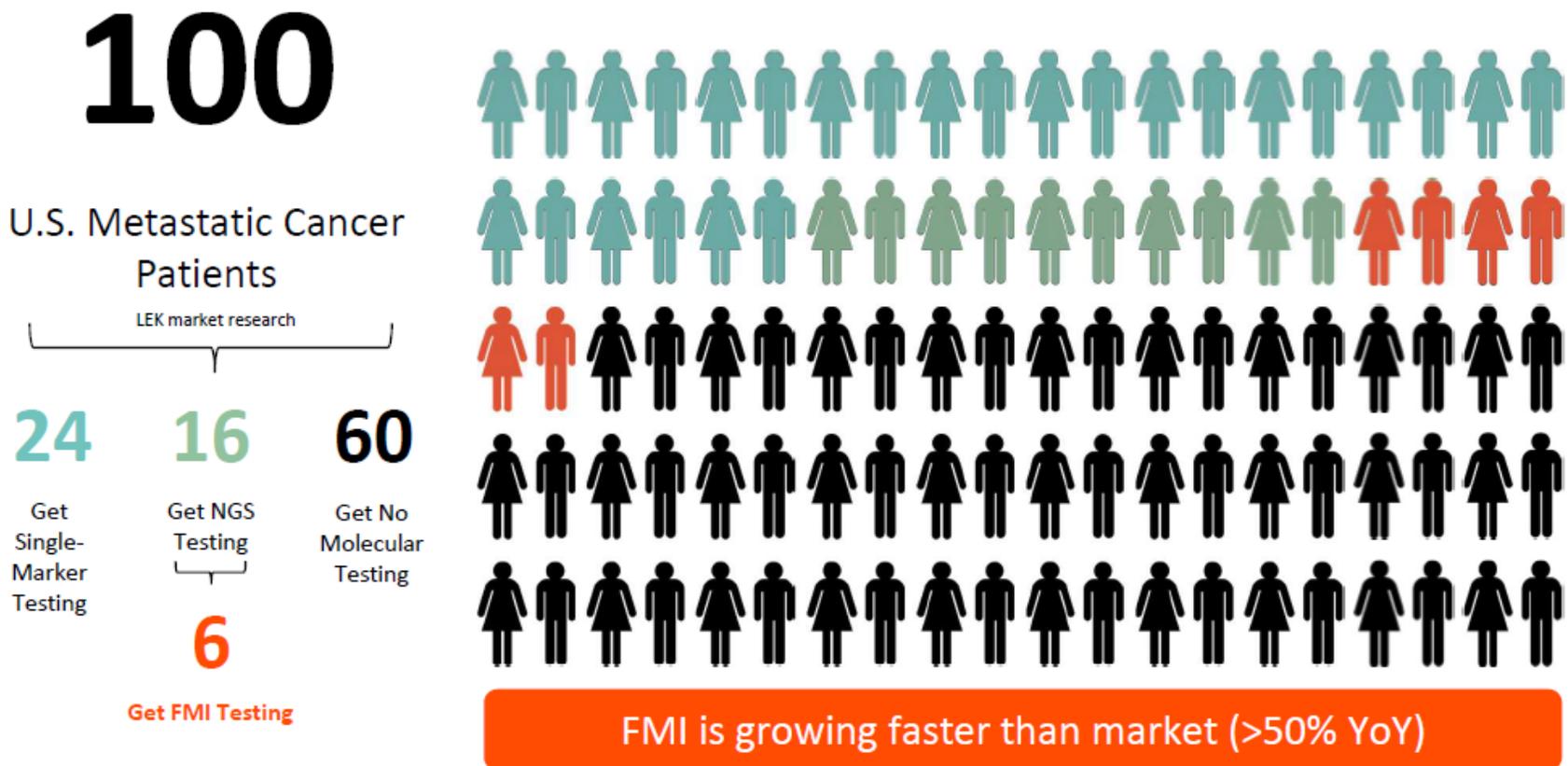


- ▶ 37 year old diagnosed with metastatic colorectal adenocarcinoma in March 2012
- ▶ Received chemotherapy followed by surgery and additional chemotherapy during the year that followed
- ▶ Recurrence of disease with metastasis to bone and lung in April 2014; received additional chemotherapy and cetuximab
- ▶ Progression of disease in February 2015, prior FoundationOne® test revealed an *ERBB2* amplification
- ▶ Foundation Medicine connected Kristen with a clinical trial; she began anti-HER2 therapy a year ago and continues to have a sustained response



Foundation Medicine

Why are we doing this



Foundation Medicine

Available Products

FOUNDATIONONE CDx

FDA/CMS Approved Companion Diagnostic for Lung, Breast, Colorectal and Ovarian Carcinomas and Melanoma

FOUNDATIONONE

Applies next-generation sequencing to identify genomic alterations across 315 cancer-related genes known to be drivers of solid tumors plus select introns of 28 genes

FOUNDATIONONE Heme

Designed to analyze and interpret DNA sequence information of 405 genes and RNA sequence (cDNA) information of 265 commonly rearranged genes in hematologic malignancies

FOUNDATIONACT

A liquid biopsy Assay for Circulating Tumor DNA, interrogating all known classes of genomic alteration across 62 genes. Provides validated, blood-based profiling when tissue biopsy may not be feasible

NEWLY IMPLEMENTED FEATURE OF FOUNDATIONONE®

Microsatellite instability (MSI) + tumor mutational burden (TMB) testing

A single solution for simultaneous assessment of MSI and TMB biomarkers – previously separate and time- and labor-intensive tests. Will provide additional and relevant genomic clues as to which patients may benefit the most from certain immunotherapies

FOUNDATIONICE
INTERACTIVE CANCER EXPLORER

An online portal for oncologists to interact with patient sequencing data which allows comparison of contextualized patient information

FOUNDATION FOCUS BRCA

FDA Approved Companion Diagnostic for Clovis Oncology PARP Inhibitor Rucaprib for treatment of Serious Ovarian Cancer

FoundationOne CDx

FDA-Approval Received on 30th Nov 2017



Comprehensive FDA-Approved
Companion Diagnostic

FIRST AND ONLY IN NGS MARKET

National Coverage Determination:
Coverage for Medicare Patients

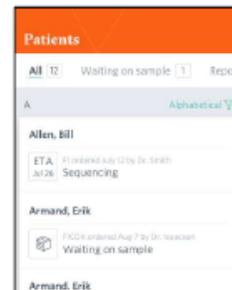


Typical Turnaround Time



SPECIMEN RECEIVED TO
RESULTS REPORTED

Sample Tracking



News & Events

Home > News & Events > Newsroom > Press Announcements

FDA News Release

FDA announces approval, CMS proposes coverage of first breakthrough-designated test to detect extensive number of cancer biomarkers

Agencies' parallel review process makes test for efficient identification of multiple targeted therapy options available to health care professionals, patients and eligible Medicare beneficiaries sooner

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

For Immediate Release

November 30, 2017

Summary

FDA approves test to detect mutations in 324 genes, two genomic signatures. Second to be approved with proposed coverage under FDA/CMS Parallel Review Program.





FoundationOne CDx™ Approval



FDA Regulations

- FoundationOne CDx™ has received a Premarket approval (PMA) from the FDA
- PMA is the most stringent type of device marketing application required by FDA.
- The applicant must receive FDA approval of its PMA application prior to marketing the device.
- PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s)



FoundationOne CDx

Overview

FoundationOne CDx™ (F1CDx™) is a broad companion diagnostic (CDx) test using next generation sequencing for the 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) for five tumor indications.

In addition to use as a companion diagnostic, F1CDx provides cancer relevant alterations that may inform patient management in accordance with professional guidelines.

Information generated by this test is an aid in the identification of patients who are most likely to benefit from associated therapeutic products.

The F1CDx assay is a single-site assay performed at Foundation Medicine, Inc.



Performance Characteristics

Concordance Studies

Performance characteristics were established using DNA derived from a wide range of FFPE tissue types; tissue types associated with CDx indications were included in each study.

- **Concordance – Comparison to an externally validated NGS assay (Orthogonal Method)**

The detection of alterations by F1CDx was compared to results of an externally validated NGS assay (evNGS). The comparison between short alterations, including base substitutions and short indels, detected by F1CDx and the orthogonal method included 188 samples from 46 different tumor tissue types

Overall there were 157 overlapping genes between the F1CDx assay and the orthogonal method with Positive Percent Agreement (PPA) ranging between 83.4% - 96.6 % and Negative Percent Agreement (NPA) of 99.9%.

Differences in variants of unknown significance (VUS) alteration calls between the platform were noted, and are expected based on differences in filtering employed by F1CDx and evNGS. As such, the difference observed was due to varying filter thresholds between the two platforms.





Performance Characteristics



Concordance Studies

- **Concordance – Comparison to FoundationOne®**

To support the use of retrospective data generated using the FoundationOne® (F1 LDT), a concordance study was conducted with FoundationOne CDx™ (F1CDx). This study evaluated a test set of 165 specimens. A total of 2325 variants, including 2026 short variants, 266 copy number alterations and 33 rearrangements met the variant inclusion criteria.

Overall the concordance between the F1 LDT and the F1CDx assay showed a minimum Positive Percent Agreement (PPA) of 94.3% and a minimum Negative Percent Agreement (NPA) of 99.8%.

Of the 165 samples, 5 were MSI-H by F1 LDT and 160 were MSS by F1 LDT; there was one discordant sample observed.

The 90% bootstrap CI of the ratio is within the equivalence interval (-0.5, +0.5), thus the TMB scores are considered equivalent.



Pivotal Phase 3 CheckMate -227 Study Demonstrates Superior Progression-Free Survival (PFS) with the Opdivo Plus Yervoy Combination Versus Chemotherapy in First-Line Non-Small Cell Lung Cancer (NSCLC) Patients with High Tumor Mutation Burden (TMB)

First and only Phase 3 trial to evaluate and show a highly statistically significant PFS benefit with an I-O/I-O combination in first-line NSCLC patients with high TMB, regardless of PD-L1 expression

Monday, February 5, 2018 6:59 am EST

PRINCETON, N.J. [Bristol-Myers Squibb Company](#) (NYSE:BMJ) today announced that the ongoing Phase 3 CheckMate -227 study met its co-primary endpoint of progression-free survival (PFS) with the *Opdivo* (nivolumab) plus *Yervoy* (ipilimumab) combination versus chemotherapy in first-line advanced non-small cell lung cancer (NSCLC) patients whose tumors have high (≥ 10 mutations/megabase, mut/mb) tumor mutation burden (TMB), regardless of PD-L1 expression. **In the study, TMB was evaluated using Foundation Medicine's (Nasdaq: FMI) analytically validated assay FoundationOne CDx.** Additionally, based on an interim analysis for overall survival (OS), the Data Monitoring Committee recommended that the study continue. The safety profile was consistent with previously reported findings in first-line NSCLC for the combination schedule of *Opdivo* 3 mg/kg every two weeks and low-dose *Yervoy* (1 mg/kg) every six weeks.

Performance Characteristics

Comparability

- **Tissue Comparability**

A large-scale retrospective analysis was conducted, using 80,715 specimens from 43 tissue types, in order to establish the comparability of assay performance across tumor tissue types. The goal of the study was to establish that assay performance after DNA extraction is independent of the tissue type from which the DNA was extracted.

Thirty-nine of the 43 tissue types had $\geq 90\%$ of specimens passing DNA extraction QC. Specimen DNA extraction pass rates for the remaining four tissue types, lung, pancreas, pelvis and prostate, were 89.6%, 89%, 89%, and 79.7%, respectively. Each of these four tissue types have characteristically small biopsies and may also be more likely to require macro-dissection.

Of specimens entering the assay at LC, 39 of 43 tissue types had $\geq 90\%$ of specimens resulting in a patient report being issued. The four tissue types below 90% include pancreatobiliary, appendix, pericardium, and prostate, and had pass rates of 83%, 88%, 79%, and 84%, respectively. For these four tissue types, the most frequent cause of failure was low tumor purity with no alterations detected.



Performance Characteristics



Analytical Specificity

- **Interfering Substances**

The robustness of the FoundationOne CDx™ (F1CDx) assay process was assessed while evaluating human formalin-fixed paraffin-embedded (FFPE) samples in the presence of exogenous and endogenous interfering substances.

All samples tested at all interfering substance levels met all process requirements and specifications; achieving the acceptance criterion of $\geq 90\%$, indicating that the sample quality was not impacted by the interfering substances at the levels evaluated.

- **In silico Analysis – Hybrid Capture Bait Specificity**

This analysis showed that all regions that may harbor alterations associated with companion diagnostic claims consistently have high quality (MQS ≥ 30), deep coverage $\geq 250X$.

- **Carryover/Cross-contamination**

No carryover or cross-contamination was observed when alternating positive and negative samples for BRCA1 and BRCA2 variants, assessed in a checker-board pattern



Performance Characteristics

Precision: Repeatability and Reproducibility

- **Reagent Lot-to-Lot Reproducibility**
- **Instrument-to-Instrument Reproducibility**

In this study based on 47 samples, repeatability and reproducibility of alterations associated with CDx claims and platform-wide alterations, including agreement for MSI, TMB, and MAF of short variants, were evaluated.

Repeatability between intra-run aliquots (run on the same plate under the same conditions) and reproducibility of inter-run aliquots (run on different plates under different conditions) were assessed and compared across three different sequencers and three different reagent lots, across multiple days of performance by multiple operators.

Across all samples, the pre-sequencing process failure is 1.5%, and the no call rate is 0.18% for MSI, 6.38% for TMB (all) and 0.22% for TMB (>10 mut/Mb).

Within the assessment of repeatability and reproducibility for CDx variants, all variants from all samples were 100% concordant. Percent of negative calls at each CDx variant location for wild-type samples was 100%.

Performance Characteristics

Analytical Sensitivity

- **Limit of Detection (LoD) and Limit of Blank (LoB)**

The LoB of zero was confirmed through the assessment of alterations within the LoB samples, with a percentage of false-positive results less than 5% (type I error risk $\alpha=0.05$). Seventy-five (75) samples were used for the assessment of LoB. For all the alterations evaluated for LoD, the LoB of zero was confirmed. A similar study was conducted for BRCA alterations (PMA P160018) with no false-positive BRCA calls observed, thus confirming the LoB of zero for BRCA.



Performance Characteristics

Stability

- **Reagent Stability, DNA Amplification and Reagent Lot Interchangeability**

Identical reagents with the same specifications are used following the same protocols for both the FoundationFocus CDxBRCA Assay and FoundationOne CDx™ (F1CDx). The claimed reagent stability is 4 months for the library construction (LC) and hybrid capture (HC) kits, and 3 months for the sequencing kits.

- **DNA Stability**

Stability of DNA was evaluated through a retrospective review of data generated using the FoundationOne LDT assay. Samples from 47 unique clinical specimens from 21 different tissues of origin were evaluated.

Duration of DNA storage at time of testing ranged from 48 to 464 days, with a median of 184 days and a mean of 199 days. A total of 199 of 200 alteration calls were concordant.

- **FFPE Sample Stability**

The FFPE Slide Stability Study is an ongoing study with data summarized for T0, T1 (30 days), and T2 (6 months) Based on five tumor samples including ovarian, lung, colorectal cancer, melanoma and breast cancer that contained a variety of DNA alterations FFPE slides are considered stable for at least 6 months. Further assessment at Months 12 and 15 will evaluate stability of FFPE slides beyond 6 months..

Performance Characteristics

DNA Extraction and Guard Banding/Robustness

- **DNA Extraction**

The performance of DNA extraction from FFPE tumor specimens was evaluated. The DNA extraction procedure for the FoundationOne CDx™ (F1CDx) assay was assessed by testing FFPE specimens including two samples per tissue type for ten different tumor tissue types including lung, breast, ovarian, melanoma, colorectal, brain, hepatic, pancreatic, thyroid, and bladder with different representative types of alterations.

Average DNA yield was calculated across twelve (12) replicates for each sample. All average DNA yields were significantly above the minimum requirement of 55 ng, with the minimum being 758.3 ng.

- **Guard banding/Robustness**

Guard banding studies were performed to evaluate the impact of process variation with regard to the measurement of DNA concentration at various stages of the process. A total of 255 samples were processed; ninety (90) to assess DNA input into LC, ninety (90) to assess DNA input into HC, and seventy-five (75) to assess DNA input into sequencing.

All samples passed the Success Rate (95% CI) for the Number of Concordant comparisons, except for all HC samples failed at the input level of 0.25 µg and as a result, there is no data available to present for that level.

Clinical Studies

CDx claims were based on a non-inferiority (NI) statistical testing approach using the enrichment design presented in the paper by Li (2016), when the concordance study sample is not a random sample from the companion diagnostic (F1CDx) intended use population and a reference standard is not available.

To assess clinical concordance, F1CDx was compared to FDA-approved CDxs (CCD).

- **FoundationOne CDx™ Concordance Study for EGFR Exon19delL858R**

Clinical validity of FoundationOne CDx™ (F1CDx) as a companion diagnostic used for identifying patients with advanced NSCLC who may be eligible for treatment with Gilotrif® (afatinib), Iressa® (gefitinib), or Tarceva® (erlotinib) was established by retrospectively testing 282 samples from NSCLC patients.

- **FoundationOne CDx™ Concordance Study for EGFR T790M**

Two separate concordance analyses were performed: one included samples with complete records only (N = 227), and the second analysis was with all the 312 samples, where missing data was handled by multiple imputation.

Clinical Studies

- **FoundationOne CDx™ Concordance Study for ERBB2 (HER2)**

A study was performed using 317 pre-screened retrospective samples obtained from patients with advanced breast cancer

- **FoundationOne CDx™ Concordance Study for ALK**

The study was performed using 175 tumor samples from patients with histologically-confirmed nonsmall cell lung cancer (NSCLC).

- **FoundationOne CDx™ Concordance Study for KRAS**

The study was performed using 342 retrospective samples obtained from patients with advanced front-line or later-line colorectal cancer. The samples used for this study were not obtained from a clinical trial and had limited demographic data available.

- **FoundationOne CDx™ Concordance Study for BRAF**

The study was performed using 305 retrospective samples obtained from patients with advanced melanoma.

- **FoundationOne CDx™ Concordance with FoundationFocus CDxBRCA for BRCA1 and BRCA2**

FoundationOne CDx™ (F1CDx) and FoundationFocus CDxBRCA use the same reagents, equipment and procedures with exception of the allowance for a broader range of DNA input into library construction and incremental enhancements to the analysis pipeline for F1CDx. The two changes were shown to have no impact on assay performance through the guard band study

Clinical Studies

Summary

All studies based on non-inferiority NI passed the acceptance criteria specified in each study protocol.

Biomarker	EGFR exon 19 deletions and L858R	EGFR T790M	ALK rearrangements	KRAS	ERBB2(HER2) Amplifications	BRAF V600, BRAF V600E
PPA (positive percent agreement)	98.1% (106/108)	98.9% (87/88)	92.9% (78/84)	100% (173/173)	89.4% (101/113)	99.4% (166/167), 99.3% (149/150)
NPA (negative percent agreement)	99.4% (153/154)	86.1% (93/108)	100% (75/75).	100% (154/154)	98.4% (180/183)	89.6% (121/135)*, 99.2% (121/122)
Comparator Method	cobas® EGFR Mutation Test v2	cobas® EGFR Mutation Test v1 and v2	Ventana ALK (D5F3) CDx Assay, Vysis ALK Break-Apart FISH Probe Kit	therascreen® KRAS RGQ PCR Kit	Dako HER2 FISH PharmDx® Kit	cobas® BRAF V600 Mutation Test

Conclusions drawn

Based on Preclinical and Clinical Studies

- **Effectiveness Conclusion**

All seven clinical concordance studies based on non-inferiority (NI) statistical testing approach passed the acceptance criteria specified in each study protocol.

- **Safety Conclusion**

Failure of the device to perform as expected or failure to correctly interpret test results may lead to incorrect test results, and subsequently, inappropriate patient management decisions in cancer treatment. Patients with false positive results may undergo treatment with one of the therapies without clinical benefit, and may experience adverse reactions associated with the therapy. Patients with false negative results may not be considered for treatment with the indicated therapy. There is also a risk of delayed results, which may lead to delay of treatment with indicated therapy.

- **Risk-Benefit Determination**

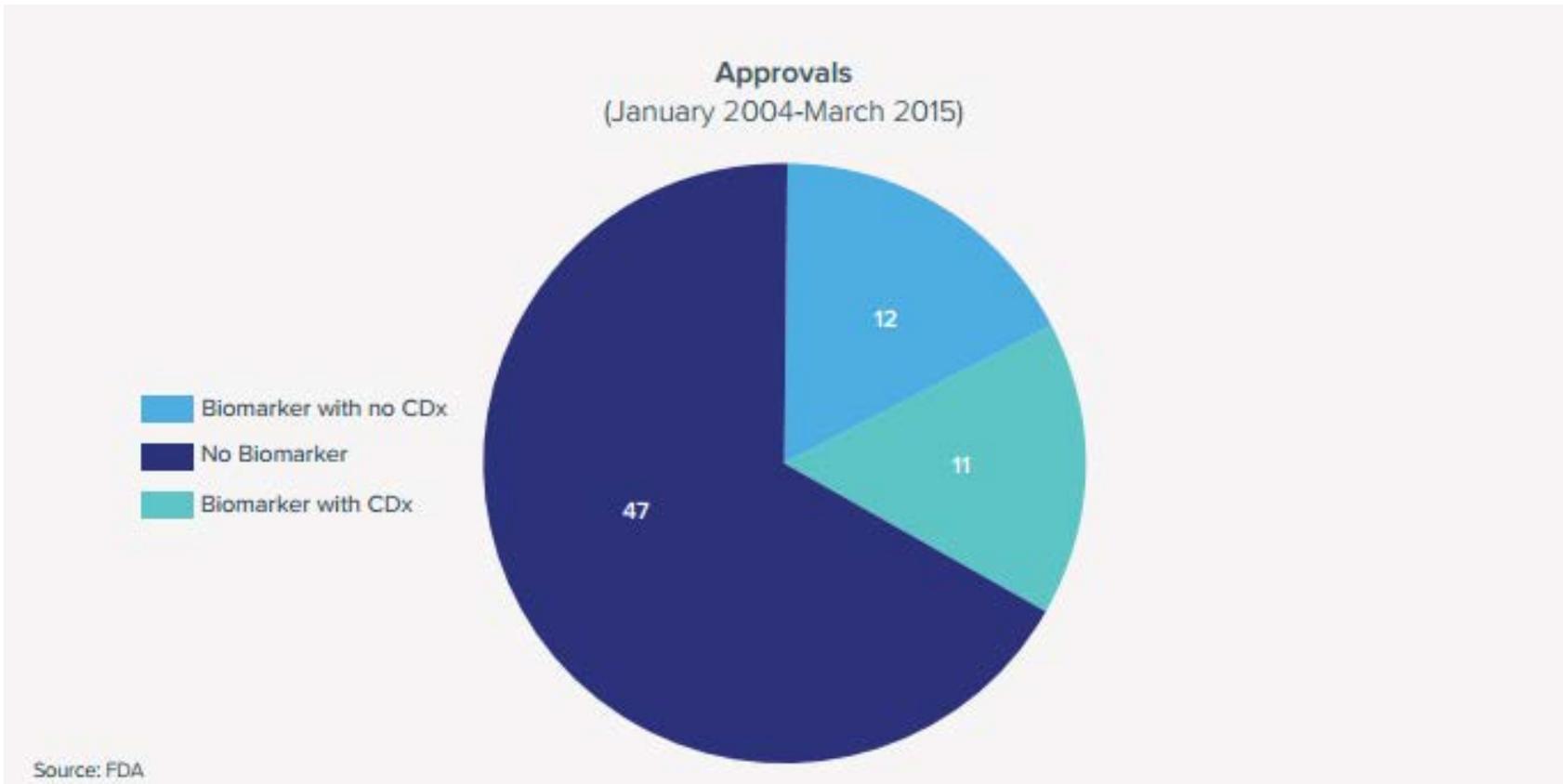
In conclusion, the data support that for the F1CDx assay, and the indications noted in the intended use statement, the probable benefits outweigh the probable risks.

F1CDx Next Steps

- Currently FDA approved Companion Diagnostics Assay
- Single Site

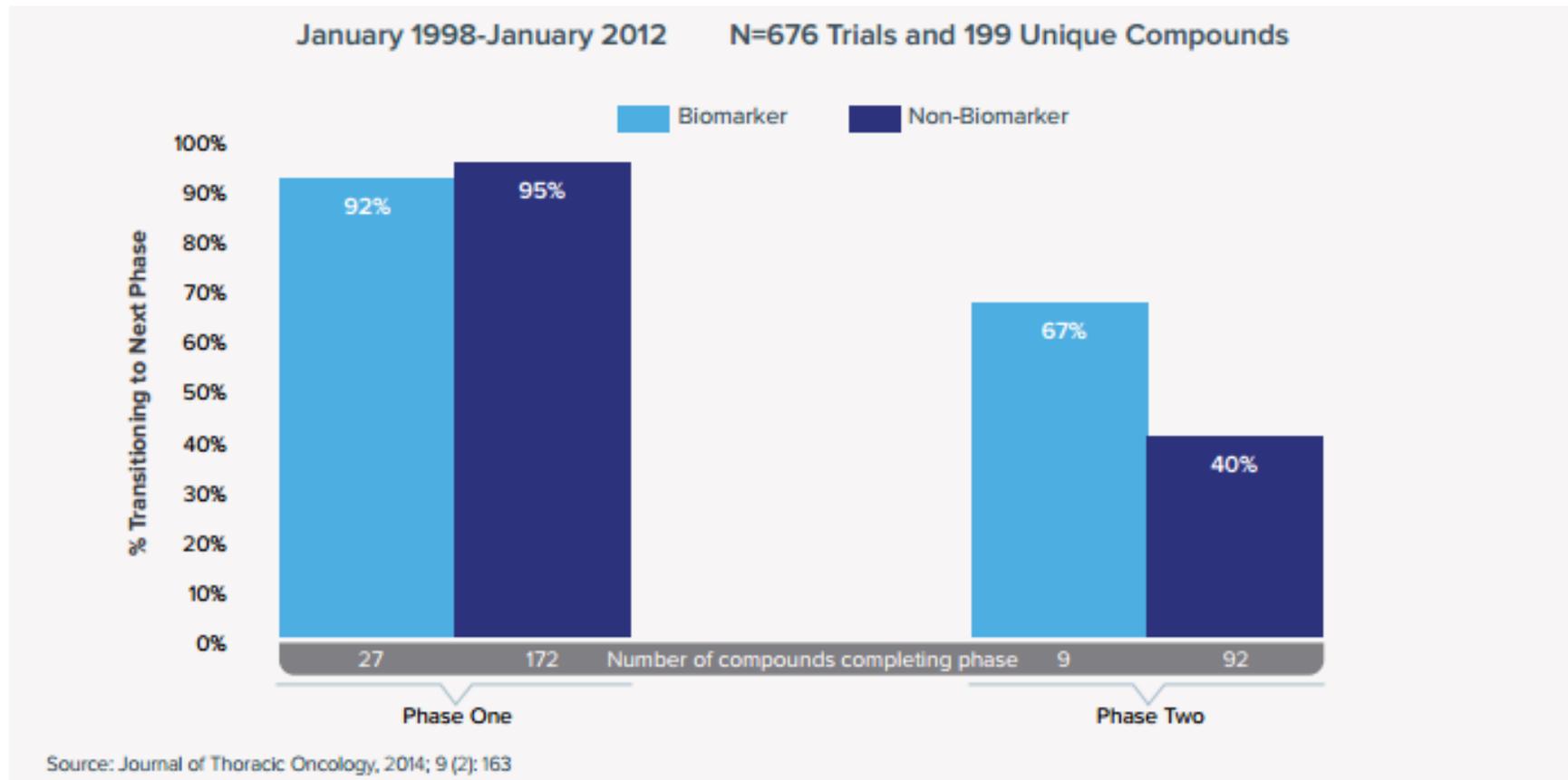
- Close out of the ongoing studies
- Expansion to multiple (global) sites
- CE marking for EU activities
- Further expansion to newly approved Test Systems

New oncology therapeutics launched with either a companion diagnostic (CDx) or a biomarker continue to be a minority

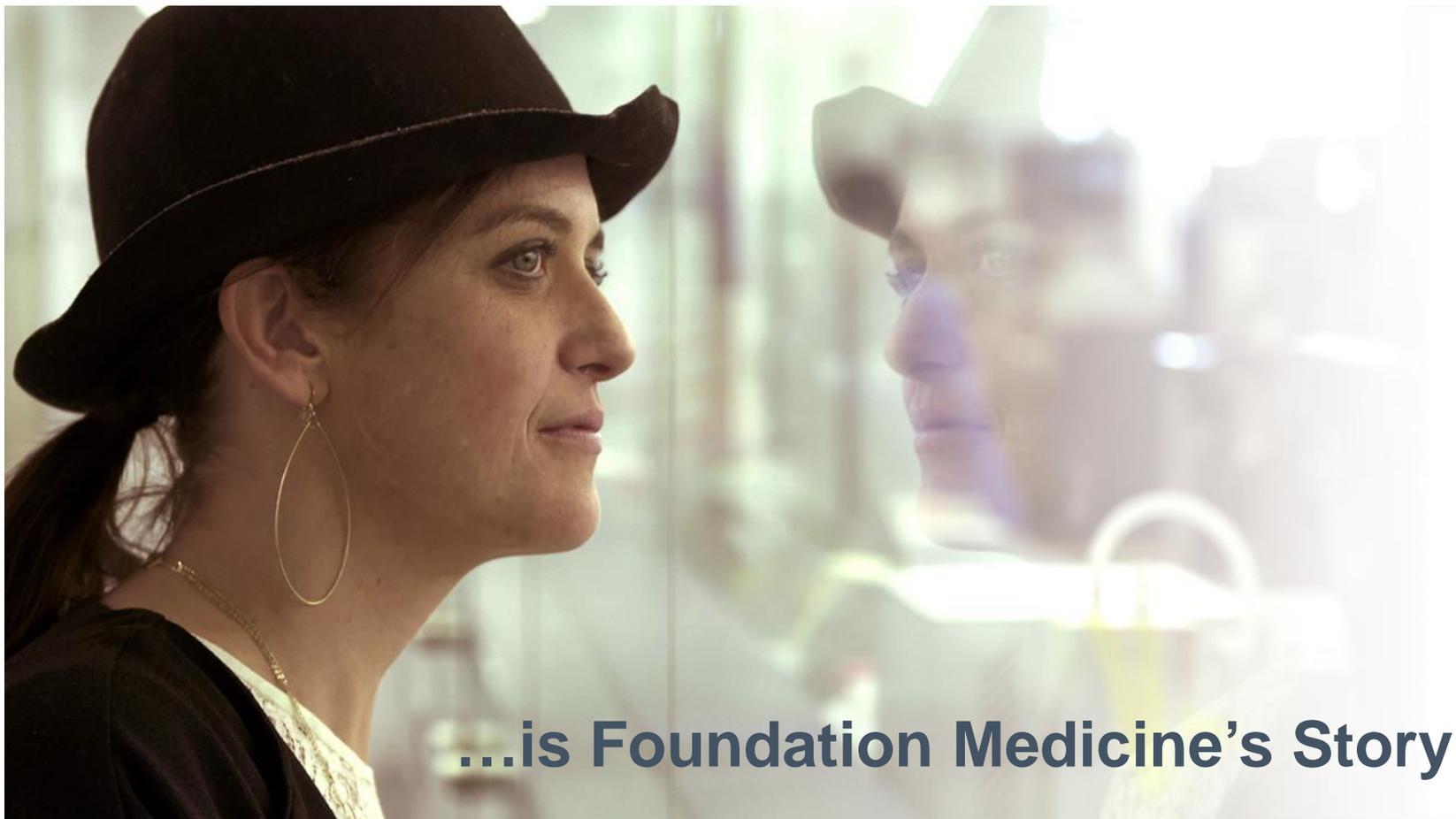


Trials employing biomarkers for patient selection have a higher probability of success

Non-Small Cell Lung Clinical Trial Success for Molecules With and Without Biomarkers



Kristen's Story...

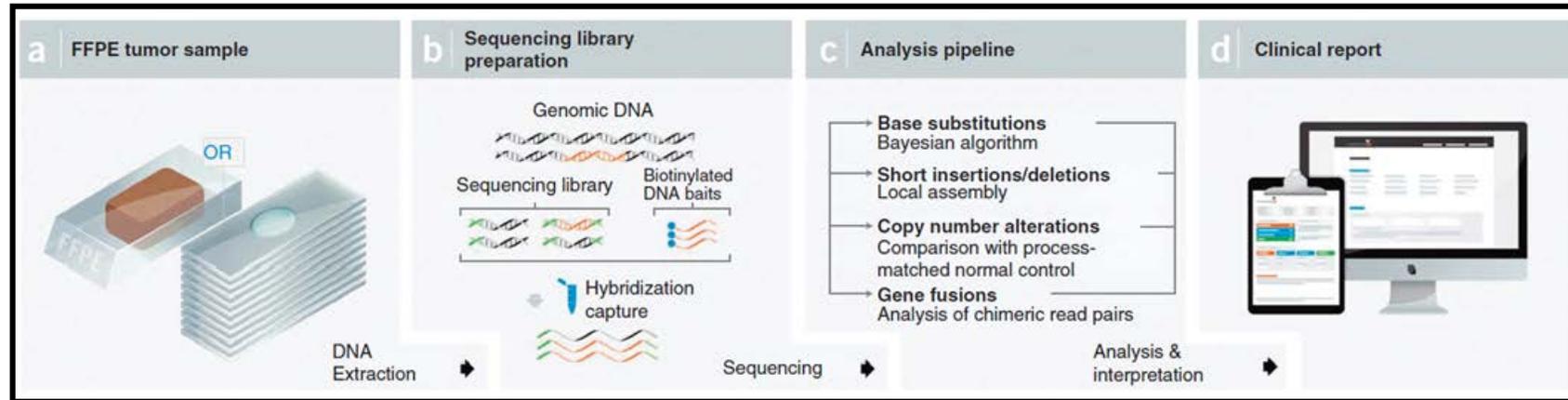




***Thank
you***

The FMI Workflow

Overview



Sample requirements:

- Surface area $\geq 25 \text{ mm}^2$
- Sample volume $\geq 1 \text{ mm}^3$
- Tumor content $\geq 20\%$

Laboratory process:

- $\geq 50 \text{ ng dsDNA}$
- Library construction
- Hybridization capture
- Illumina HiSeq 4000 platform

Analysis methods:

- Customized computational biology algorithms
- Manual secondary review

Report curation:

- Clinically relevant genomic alterations
- FDA-approved therapies in patient tumor type
- FDA-approved therapies in other tumor types
- Available clinical trials

