SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Next generation sequencing oncology panel, somatic or germline variant detection system

Device Trade Name: FoundationOne® Liquid CDx

Device Procode: PQP

Applicant's Name and Address: Foundation Medicine, Inc.
400 Summer Street
Boston, MA 02210

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P190032/S029

Date of FDA Notice of Approval: May 27, 2026

The original Premarket Approval (PMA) (P190032) for FoundationOne® Liquid CDx (F1LCDx) was approved on August 26, 2020 as a companion diagnostic for *BRCA1* and *BRCA2* alterations in metastatic castration-resistant prostate cancer (mCRPC) patients who may benefit from treatment with RUBRACA® (rucaparib) and *EGFR* activating mutations (Exon 19 deletions and L858R substitution mutation) in patients with advanced and metastatic non-small cell lung cancer (NSCLC) who may benefit from treatment with IRESSA® (gefitinib), TAGRISSO® (osimertinib), and TARCEVA® (erlotinib). Subsequently, additional PMA supplements were approved for expanding the indications for use of F1LCDx since the original approval. See Section VII for more details.

The current supplement was submitted to expand the indication for the F1LCDx test as a companion diagnostic for the indication listed in the table below.

New Indication Being Sought in this PMA supplement submission.

Tumor Type	**Biomarker(s) Detected**	**Therapy**
Prostate cancer	Homologous Recombination Repair (HRR) gene (*BRCA1, BRCA2, ATM, ATR, CDK12, CHEK2, FANCA, MLH1,MRE11A, NBN,PALB2, RAD51C)*	TALZENNA® (talazoparib) in combination with XTANDI® (enzalutamide)

II. INDICATIONS FOR USE

FoundationOne Liquid CDx is a qualitative next generation sequencing based *in vitro* diagnostic test that uses targeted high throughput hybridization-based capture technology to analyze 324 genes and report genomic alterations in 311 genes. These include substitutions, insertions, and deletions (indels) in 311 genes, rearrangements in 8 genes and copy number alterations in 3 genes. FoundationOne Liquid CDx utilizes circulating cell-free DNA (cfDNA) isolated from plasma derived from anti-coagulated peripheral whole blood of cancer patients collected in FoundationOne Liquid CDx cfDNA blood collection tubes included in the FoundationOne Liquid CDx Blood Sample Collection Kit. The test is intended to be used as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling.

Table 1: Companion diagnostic indications

Tumor Type	Biomarker(s) Detected	Therapy
Breast Cancer	*PIK3CA* mutations	ITOVEBI™ (inavolisib) in combination with palbociclib and fulvestrant
	PIK3CA mutations C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y	PIQRAY® (alpelisib)
Colorectal cancer (CRC)	*BRAF* V600E	BRAFTOVI ® (encorafenib) in combination with cetuximab
Non-small cell lung cancer (NSCLC)	*ALK* Rearrangements	ALECENSA® (alectinib)
	BRAF V600E	BRAFTOVI® (encorafenib) in combination with MEKTOVI® (binimetinib)
	EGFR Exon 19 deletions and *EGFR* Exon 21 L858R substitution	*EGFR* tyrosine kinase inhibitors approved by FDA*
	MET single nucleotide variants (SNVs) and indels that lead to *MET* exon 14 skipping	TABRECTA® (capmatinib)
		TEPMETKO® (tepotinib)**
	ROS1 fusions**	ROZLYTREK® (entrectinib)
Prostate cancer	*BRCA1*, *BRCA2, ATM* alterations	LYNPARZA® (olaparib)
	BRCA1, *BRCA2* alterations	AKEEGA® (niraparib + abiraterone acetate)
		LYNPARZA® (olaparib) in combination with abiraterone
		RUBRACA® (rucaparib)
	Homologous Recombination Repair	TALZENNA ®

Tumor Type	Biomarker(s) Detected	Therapy
	(HRR) gene *(BRCA1, BRCA2, ATM, ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C)* alterations	(talazoparib) in combination with XTANDI® (enzalutamide)
Solid Tumors	*NTRK1/2/3* fusions**	ROZLYTREK® (entrectinib)

*For the most current information about the therapeutic products in this group, go to: https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools#Group_Labeling

** When considering eligibility for ROZLYTREK® based on the detection of *NTRK1/2/3* and *ROS1* fusions, or for TEPMETKO® based on the detection of *MET* SNVs and indels that lead to *MET* exon 14 skipping, testing using plasma specimens is only appropriate for patients for whom tumor tissue is not available for testing.

Additionally, FoundationOne Liquid CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms.

A negative result from a plasma specimen does not mean that the patient's tumor is negative for genomic findings. Patients with the tumor types above who are negative for the mutations listed in Table 1 (see ** footnote under Table 1 for NTRK1/2/3 and ROS1 fusions for ROZLYTREK® and MET SNVs and indels that lead to MET exon 14 skipping for TEPMETKO®) should be reflexed to routine biopsy and their tumor mutation status confirmed using an FDA- approved tumor tissue test, if feasible.

Genomic findings other than those listed in Table 1 are not prescriptive or conclusive for labeled use of any specific therapeutic product.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the F1LCDx labeling.

V. DEVICE DESCRIPTION

The F1LCDx assay is performed using circulating cell-free DNA (cfDNA) isolated from plasma derived from anti-coagulated peripheral whole blood from patients with solid malignant neoplasms. The assay employs a single DNA extraction method to obtain cfDNA from plasma isolated from whole blood. Extracted cfDNA undergoes whole-genome shotgun library construction and hybridization- based capture of 324 cancer-related genes. All coding exons of 309 genes are targeted; select intronic or non- coding regions are targeted in fifteen of these genes (refer to Table 2 for the complete list of genes reported by F1LCDx).

Hybrid-capture selected libraries are sequenced with deep coverage using the NovaSeq® 6000 platform. Sequence data are processed using a custom analysis pipeline designed to detect genomic alterations in 311 genes. These include base substitutions and indels in 311 genes, copy number variants in three genes, and

genomic rearrangements in eight genes. A subset of targeted regions in 75 genes is baited for enhanced sensitivity.

Table 2: Complete List of Genes Interrogated by FoundationOne Liquid CDx[1]

ABL1 [Exons 4-9]	*ACVR1B*	***AKT1 [Exon 3]***	*AKT2*	*AKT3*	***ALK [Exons 20-29, Introns 18, 19]***	*ALOX12B*	*AMER1 (FAM123B)*	***APC***	***AR***
ARAF [Exons 4, 5, 7, 11, 13, 15, 16]	*ARFRP1*	*ARID1A*	*ASXL1*	***ATM***	***ATR***	*ATRX*	*AURKA*	*AURKB*	*AXIN1*
AXL	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*	*BCOR*	*BCORL1*	*BCR* [Introns 8, 13, 14]*
***BRAF [Exons 11-18**, Introns 7-10]*	***BRCA1** [Introns 2, 7, 8, 12, 16, 19, 20]*	***BRCA2** [Intron 2]*	*BRD4*	*BRIP1*	*BTG1*	*BTG2*	***BTK [Exons 2, 15]***	*C11orf30 (EMSY)*	*C17orf39 (GID4)*
CALR	*CARD11*	*CASP8*	*CBFB*	*CBL*	***CCND1***	*CCND2*	*CCND3*	*CCNE1*	*CD22*
CD70	*CD74* [Introns 6-8]*	*CD79A*	*CD79B*	***CD274 (PD-L1)***	*CDC73*	***CDH1***	***CDK12***	***CDK4***	***CDK6***
CDK8	*CDKN1A*	*CDKN1B*	***CDKN2A***	*CDKN2B*	*CDKN2C*	*CEBPA*	*CHEK1*	***CHEK2***	*CIC*
CREBBP	***CRKL***	*CSF1R*	*CSF3R*	*CTCF*	*CTNNA1*	***CTNNB1 [Exon 3]***	*CUL3*	*CUL4A*	*CXCR4*
CYP17A1	*DAXX*	*DDR1*	***DDR2 [Exons 5, 17, 18]***	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	***EGFR [Introns 7**, 15, 24-27]***	*EP300*
EPHA3	*EPHB1*	*EPHB4*	***ERBB2***	***ERBB3 [Exons 3, 6, 7, 8, 10, 12, 20, 21, 23, 24, 25]***	*ERBB4*	*ERCC4*	*ERG*	***ERRFI1***	***ESR1 [Exons 4-8]***
ETV4 [Intron 8]*	*ETV5* [Introns 6,7]*	***ETV6* [Introns 5, 6]***	*EWSR1* [Introns 7-13]*	***EZH2 [Exons 4, 16, 17, 18]***	*EZR* [Introns 9 - 11]*	*FAM46C*	*FANCA*	*FANCC*	*FANCG*
FANCL	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*	*FGF19*	*FGF23*	*FGF3*	*FGF4*
FGF6	***FGFR1** [Introns 1,5, **Intron17]***	***FGFR2** [Intron 1, **Intron 17]***	***FGFR3 [Exons 7, 9 (alternative designation exon 10),14, 18, Intron 17]***	*FGFR4*	*FH*	*FLCN*	*FLT1*	***FLT3 [Exons 14, 15, 20]***	***FOXL2***
FUBP1	*GABRA6*	*GATA3*	*GATA4*	*GATA6*	***GNA11 [Exons 4, 5]***	*GNA13*	***GNAQ [Exons 4, 5]***	***GNAS [Exons 1, 8]***	*GRM3*
GSK3B	*H3F3A*	*HDAC1*	*HGF*	*HNF1A*	***HRAS [Exons 2, 3]***	*HSD3B1*	*ID3*	***IDH1 [Exon 4]***	***IDH2 [Exon 4]***
IGF1R	*IKBKE*	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	***JAK2 [Exon 14]***	***JAK3 [Exons 5, 11, 12, 13, 15, 16]***
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	***KIT [Exons 8, 9, 11, 12, 13, 17, Intron 16]***	*KLHL6*	*KMT2A (MLL) [Introns 6, 8-11, Intron 7]*

KMT2D (MLL2)	***KRAS***	*LTK*	*LYN*	*MAF*	***MAP2K1 (MEK1) [Exons 2, 3]***	***MAP2K2 (MEK2) [Exons 2-4, 6, 7]***	*MAP2K4*	*MAP3K1*	*MAP3K13*
MAPK1	*MCL1*	***MDM2***	*MDM4*	*MED12*	*MEF2B*	*MEN1*	*MERTK*	***MET***	*MITF*
MKNK1	*MLH1*	***MPL [Exon 10]***	*MRE11A*	*MSH2 [Intron 5]*	*MSH3*	*MSH6*	*MST1R*	*MTAP*	***MTOR [Exons 19, 30, 39, 40, 43-45, 47, 48, 53, 56]***
MUTYH	*MYB* [Intron 14]*	***MYC [Intron 1]***	*MYCL (MYCL1)*	***MYCN***	***MYD88 [Exon 4]***	*NBN*	***NF1***	*NF2*	*NFE2L2*
NFKBIA	*NKX2-1 (TTF-1)*	*NOTCH1*	*NOTCH2 [Intron 26]*	*NOTCH3*	***NPM1 [Exons 4-6, 8, 10]***	***NRAS [Exons 2, 3]***	*NSD3 (WHSC1L1)*	*NT5C2*	***NTRK1 [Exons 14, 15, Introns 8-11]***
NTRK2 [Intron 12]	***NTRK3 [Exons 16, 17]***	*NUTM1* [Intron 1]*	*P2RY8*	***PALB2***	*PARK2*	*PARP1*	*PARP2*	*PARP3*	*PAX5*
PBRM1	*PDCD1 (PD-1)*	***PDCD1L G2 (PD-L2)***	***PDGFRA [Exons 12, 18, Introns 7, 9, 11]***	***PDGFRB [Exons 12-21, 23]***	*PDK1*	*PIK3C2B*	*PIK3C2G*	***PIK3CA [Exons 2, 3, 5-8, 10, 14, 19, 21 (Coding Exons 1, 2, 4-7, 9, 13, 18, 20)]***	*PIK3CB*
PIK3R1	*PIM1*	*PMS2*	*POLD1*	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*
PRKCI	*PTCH1*	***PTEN***	***PTPN11***	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*	*RAD51B*
RAD51C	*RAD51D*	*RAD52*	*RAD54L*	***RAF1 [Exons 3, 4, 6, 7, 10, 14, 15, 17, Introns 4-8]***	*RARA [Intron 2]*	***RB1***	*RBM10*	*REL*	***RET [****Introns 7, 8,* ***Exons 11, 13-16, Introns 9-11]***
RICTOR	*RNF43*	***ROS1 [Exons 31, 36-38, 40, Introns 31-35]***	*RPTOR*	*RSPO2* [Intron 1]*	*SDC4* [Intron 2]*	*SDHA*	*SDHB*	*SDHC*	*SDHD*
SETD2	*SF3B1*	*SGK1*	*SLC34A2* [Intron 4]*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	***SMO***	*SNCAIP*
SOCS1	*SOX2*	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*	***STK11 (LKB1)***	*SUFU*
SYK	*TBX3*	*TEK*	*TERC* {ncRNA}*	***TERT* {Promoter}***	*TET2*	*TGFBR2*	*TIPARP*	*TMPRSS2* [Introns 1-3]*	*TNFAIP3*
TNFRSF14	***TP53***	*TSC1*	*TSC2*	*TYRO3*	*U2AF1*	***VEGFA***	*VHL*	*WHSC1*	*WTI*
XPO1	*XRCC2*	*ZNF217*	*ZNF703*						

[1]While the F1LCDx assay interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select non-coding coverage (indicated with an *), F1LCDx reports alterations only in 311 genes (309 genes with coding coverage and 2 genes with non-coding coverage). F1LCDx also reports Rearrangements in 13 genes from non-coding region, only when the partner gene is approved for reporting, e.g., CD74 in a ROS1-CD74 fusion. Select genes and select exons (indicated in bold) are baited for increased sensitivity.

The reporting of rearrangements and copy number alterations as part of the tumor mutation profiling claim are restricted to those genes included in Table 3, below.

Table 3: Genes for which copy number alterations and rearrangements are reported for tumor profiling by F1LCDx

Alteration Type	Genes
Copy Number Alterations	*BRCA1, BRCA2, ERBB2*
Rearrangements	*ALK, BRCA1, BRCA2, NTRK1, NTRK2, NTRK3*

The test report includes variants reported in the following levels:

Level 1: Companion Diagnostics (CDx)
Clinical evidence should be presented from a prospectively designed clinical trial. Results can also be presented from a retrospective clinical bridging study demonstrating that the clinical endpoints are preserved using plasma samples in trials where enrollment was based on tissue test results. For follow-on markers, a clinical concordance study demonstrating non-inferiority to the original FDA-approved cfDNA-based companion diagnostic device is required. In addition to the clinical validation, analytical validation for each specific Level 1 CDx biomarker should be presented.

Level 2: cfDNA Biomarkers with Strong Evidence of Clinical Significance in cfDNA
For a Level 2 claim of cfDNA biomarkers with strong evidence of clinical significance, clinical validation needs to be from evidence presented with FDA-approved liquid biopsy companion diagnostic biomarkers for the specific tumor type at the biomarker or variant level. Such claims should also be supported by analytical performance for each biomarker from at least limit of detection (LoD), precision/ reproducibility, and accuracy studies.

Level 3A: Biomarkers with Evidence of Clinical Significance in Tissue Supported by Strong Analytical Validation Using cfDNA and Concordance Between cfDNA and Tissue
Clinical evidence can be provided from tissue-based companion diagnostics. This should also be supported by analytical validation (LoD, precision, analytical accuracy, and concordance study to a tissue-based test) for the specific tumor type at the biomarker or variant level, using a representative approach for SNVs and indels. Evidence evaluating concordance between cfDNA- and tissue-samples for FDA-approved tissue markers should be demonstrated using an FDA-approved tissue test or a validated tissue test.

Level 3B: Biomarkers with Evidence of Clinical Significance in Tissue Supported by Analytical Validation Using cfDNA
Clinical evidence can be provided from tissue-based companion diagnostics, with analytical validation supported by a representative approach for SNVs and indels from key analytical studies (such as LoD, accuracy, and precision).

Level 4: Other Biomarkers with Potential Clinical Significance
Biomarkers not categorized into Levels 1, 2, or 3 can be included under Level 4 for informational purposes or to be used to direct patients toward clinical trials for which they may be eligible. Such claims can be supported by clinical rationale for inclusion in

the panel. Such rationale could also include peer-reviewed publications for genes/ variants in tissue, variant information from well curated public databases, or *in vitro* pre-clinical models. Analytical validation should be supported by a representative approach for SNVs and indels from key analytical studies (such as LoD, accuracy, and precision).

FoundationOne® Liquid CDx cfDNA Blood Specimen Collection Kit Contents
The test includes a blood specimen collection kit, which is sent to ordering laboratories. The shipping kit contains the following components:

- Specimen preparation and shipping instructions
- Two FoundationOne® Liquid CDx cfDNA Blood Collection Tubes (8.5 mL nominal fill volume per tube)
- Return shipping label

Instruments
The F1LCDx assay is intended to be performed with the serial number-controlled instruments indicated in Table 4, below. All instruments are qualified by Foundation Medicine, Inc. (Foundation Medicine or FMI) under Foundation Medicine's Quality System.

Table 4: Instruments for use with the F1LCDx assay

Instrument
Illumina NovaSeq 6000
Thermo Fisher Scientific Kingfisher Flex DW and 96
Hamilton STARlet STAR Liquid Handling Workstation

Test Process
All assay reagents including blood collection tubes included in the F1LCDx assay process are qualified by Foundation Medicine and are compliant with the medical device Quality System Regulation (QSR).

A. Specimen Collection and Preparation
Whole blood specimens are collected in F1LCDx cfDNA Blood Collection Tubes (BCT) provided as a component of the F1LCDx specimen collection kit. Prior to cfDNA isolation, the plasma is collected from whole blood by centrifugation, which separates the plasma from the buffy coat (white blood cells) and red blood cells. The plasma layer is removed from the buffy coat to avoid contamination of cellular DNA into the plasma sample. A residual volume of plasma remains in the tube to avoid disturbing the buffy coat. A second spin of the separated plasma at high-speed further pellets cell debris and protein.

B. DNA Extraction
Following the separation of plasma from whole blood, cfDNA is isolated from plasma using the KingFisher Flex Magnetic Particle Processor, which uses an efficient and automated method to purify cfDNA. The KingFisher Instrument uses magnetic rods to move nucleic acid through purification phases of

binding, washing, and elution to yield high purity cfDNA. After isolating cfDNA, the Agilent 4200 TapeStation is used to quantify cfDNA.

C. Library Construction

Library Construction (LC) begins with the normalization of cfDNA. The samples are purified, using AMPure® XP Beads (Agencourt®). Solid-phase reversible immobilization (SPRI) purification is used after library construction with the NEBNext® kits (NEB), including mixes for end repair with blunt-end and 5'- phosphorylate the cfDNA fragments using T4 Polynucleotide Kinase and T4 DNA Polymerase. This step prepares the 3'- end for dA-addition while also preparing the 5'-end of the DNA fragment for ligation. Second, dA-addition will incorporate a single dAMP to the 3'-end of the End-Repaired material. After dA addition, a universal Y-adaptor is ligated onto each end of the DNA fragment using a DNA ligase. These steps are performed in 96-well plates (Eppendorf) on a liquid handling workstation (Hamilton STAR) using the "with-bead" protocol to maximize reproducibility and library yield. Dual-indexed (Foundation Medicine customized six base pair barcodes) sequencing libraries are PCR amplified with a high-fidelity DNA polymerase (HiFi™, Kapa) for ten cycles, and SPRI purified. Process matched control (PMC) is prepared and added to the plate with other cfDNA samples at the beginning of LC.

D. Hybrid Capture

Solution hybridization is performed using a >50-fold molar excess of a pool of individually synthesized 5'-biotinylated DNA 120 base pair oligonucleotides (Integrated DNA Technology) for baits. The baits target regions from 324 cancer- related genes including all coding exons of 309 genes and only select introns or non- coding regions in 15 genes. Baits were designed by appointing overlapping 120 bp DNA sequence intervals covering target exons (60 bp overlap) and introns (20 bp overlap), with a minimum of three baits per target; single nucleotide polymorphism (SNP) targets were allocated one bait each. Intronic baits were filtered for repetitive elements as defined by the University of California at Santa Cruz (UCSC) Genome Repeat Masker track. Hybrid selection of targets demonstrating reproducibly low coverage was boosted by increasing the number of baits for these targets.

A 25 µl fixed volume of library from the LC step, blocking DNA (adaptor block, Cot, Salmon Sperm DNA) and the bait reagents are combined and the mixture is lyophilized in a 96-well plate. The library is then re-suspended in buffer and the samples are incubated at 95°C for 5 minutes to denature dsDNA libraries to ssDNA libraries. The incubation temperature is then reduced to 65°C for 2-4 hours to facilitate the hybridization of ssDNA libraries to the bait set. After the 65°Cincubation, the library-bait duplexes are captured on paramagnetic MyOne™ streptavidin beads (Invitrogen) and off-target library is removed by washing two times with Wash Buffer 1 at 65°C and three times with Wash Buffer 2 at 48°C. The PCR master mix is added to

directly amplify the captured library from the washed beads. After amplification, the samples are SPRI purified and quantified by PicoGreen.

E. Sequencing

Sequencing on the Illumina NovaSeq 6000 platform employs on-board cluster generation (OBCG) using patterned flow cell technology to generate monoclonal clusters via exclusion amplification (ExAmp) from a single DNA template. The clusters are then sequenced using sequencing by synthesis (SBS) chemistry. The NovaSeq system is capable of sequencing up to two flow cells at a time. During OBCG, a single DNA template is introduced into each of the primer substrate layered nano-wells of the flow cell, where the template is immediately and rapidly amplified by ExAmp. This rapid amplification prevents other DNA templates from binding, ensuring a monoclonal cluster is formed in each nano-well. The procedure allows for fixed size and spacing of the clusters which results in improved and more accurate resolution.

A growing nucleotide chain is created on the flow cell by incorporating fluorescently labeled, 3'-blocked deoxynucleotide triphosphates (dNTPs). After excitation by a laser, the camera captures the emission color of the incorporated, fluorescently labeled nucleotide. The 3'-block is then removed, reverting the nucleotide to its natural form, which allows the polymerase to add another base to the growing double strand of DNA. With each successive SBS cycle, a new fluorescently labeled 3'- blocked dNTP is added. SBS allows for millions of discrete clusters of clonal copies of DNA to be sequenced in parallel.

F. Sequence Analysis

Sequence data are analyzed using mainly proprietary software developed by Foundation Medicine. External tools used include: 1) BWA (Burrows-Wheeler Aligner) v0.7.17, for aligning sequence reads to the genomic reference, 2) SAMtools v1.6 for utility operations, 3) Picard tools v1.56 for metrics calculations, and 4) Biopython for the pairwise2 sequence alignment module.

Reads from each Illumina flow cell are demultiplexed (sorted into sets of reads deriving from distinct samples), and their fragment barcodes (FBCs) are extracted and encoded into the read names. For each sample, read pairs with matching, valid FBCs are aligned and processed together to: 1) identify clusters of reads originating from the same original fragment; 2) merge overlapping read pairs into single reads, where possible; and 3) generate consensus reads representing all information in the set of reads for each cluster, encoding positions with mismatches (errors) with base quality 20. The consensus reads are then aligned to the reference genome to generate the 'consensus' binary alignment map (BAM).

- **Short Variant (Base Substitutions and Indels) Detection**
  For the detection of short variants (e.g., substitutions and small indels) in each target region of interest, a de novo assembly is performed. This is done using proprietary software to generate a de Bruijn graph including all k-mers in reads mapping to a particular locus. The graph is parsed to identify paths that originate and terminate in reference nodes from the locus. Increased k-mer sizes may be used to account for ambiguities, cycles, and other problematic regions within the graph. The result of the graph traversal is a set of candidate variants. For each variant, there is a set of k-mers supporting the variant and a set of k-mers that would support the reference or another variant at the location.

  Each candidate variant is then scanned against reads in the locus to identify which reads support either the candidate variant or a different variant or reference at the location. The cluster membership of the supporting reads is then assessed to determine which clusters show unambiguous support for the variant and which have conflicting assignments, indicating that the variant may have arisen as an error in sequencing or library preparation.

  After identifying the supporting reads for each candidate short variant, the AP analyzes the short variant candidates and calculates metrics used to evaluate the quality of the variant call. The final variant calls are made based on a series of quality control filters, which will reject a call based on the intrinsic sample noise, the expected noise level for the particular variant, and other known error modes (e.g., sequence homology).

- **Rearrangement Detection**
  The same assembly procedure used to detect short variants is also leveraged to detect rearrangements. Paths in the de Bruijn graph described above that originate in reference nodes of the locus but do not return to that locus are further analyzed as rearrangement candidates. Such paths correspond to sequences that are anchored in the locus of interest, but that diverge to sequences not normally found in that locus. When this exogenous sequence can be mapped unambiguously to another location in the genome, the rearrangement candidate is further evaluated using quality control filters related to sequence repetitiveness, mapping confidence, and the quality and amount of read support. Rearrangement candidates passing all filters are further characterized for functional impact and called as rearrangements.

- **Copy Number Alteration Detection**

Copy number alterations (CNAs) are detected using a comparative panel of normals (PoN)-like method. Normalized target coverage obtained by comparison with a historical set of reference samples (Panel of Normals, or PoN), along with the allele frequencies of targeted SNPs, are used to generate a copy-number model of the targeted genomic regions. This model consists of an overall purity estimate and a copy number state for each distinct genomic segment. Candidates are annotated with regards to functional effect and cancer relevance status. Amplifications are called at segments with ≥ 6 copies (or ≥ 7 for triploid/≥ 8 for tetraploid tumors) and homozygous deletions at 0 copies. Amplifications in ERBB2 are called positive at segments with ≥ 5 copies for diploid tumors. Additional requirements are placed on these calls, including QC metrics for the overall quality and quantity of data supporting the modeled copy-number level. For example, amplifications are required to cover more than 80% of the exons in a gene, and all calls are required to involve at least two consecutive coverage targets.

G. Report Generation

Approved results are annotated by automated software with CDx relevant information and are merged with patient demographic information prior to approval and release by the laboratory director or designee.

H. Internal Process Controls

Process Control

Each assay run includes a control sample run in duplicate. The control sample contains a pool of eleven HapMap cell lines and is used as a positive mutation detection control. 100 different germline SNPs present across the entire targeted region are required to be detected by the analysis pipeline.

Sensitivity Control

The HapMap control pool used as the positive control is prepared to contain variants at 0.1%, 10% mutant allele frequency (MAF) which must be detected by the analysis pipeline to ensure expected sensitivity for each run.

Negative Control

Samples are barcoded molecularly at the library construction (LC) stage. Only reads with a perfect molecular barcode sequence are incorporated into the analysis. The Analysis Pipeline includes an algorithm that analyzes the SNP profile of each specimen to identify potential contamination that may have occurred prior to molecular barcoding.

I. Classification Criteria for CDx Biomarkers Detected by F1LCDx

1. ***CDx classification criteria for Homologous Recombination Repair (HRR) genes for patients with prostate cancer***

1.1. HRR alterations (BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L) to identify patients eligible for TALZENNA ® (talazoparib) in combination with XTANDI® (enzalutamide).

Deleterious or suspected deleterious HRR gene *(BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D*, and *RAD54L*) variants, identified by the rules below in Table 5.

Table 5. Biomarker definition for HRR gene (*BRCA1, BRCA2, ATM, ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C)* Alterations for Talazoparib in combination with Enzalutamide Treatment

Gene	Variant Class	Description
BRCA1 *BRCA2* *ATM* *ATR* *CDK12* *CHEK2* *FANCA* *MLH1* *MRE11A* *NBN* *PALB2* *RAD51C*	Short Variant	Any nonsense, frameshift, or splice site alteration[1] • Any splice alterations within the splice donor or acceptor site[2] • For BRCA2, truncating mutations must occur upstream of bases encoding amino acid 3326 Any of the additional mutations listed in Tables 6 – 10
	Copy Number	Homozygous deletion of one or more exons, regardless of transcript. Only reported for *BRCA1* and *BRCA2*.
	Rearrangement	Any inactivating rearrangement, regardless of transcript

[1] Missense mutations in the start codon (except for those in tables 6-10) and short variant deletions spanning from upstream of the start codon (annotated as M1?) are biomarker negative.
[2] The splice site is defined as the first or last two bases of the intron (except for those in tables 6-10).

Table 6. List of short variants in *BRCA1

M1I	C47S	T1685A	W1718C	P1812A
M1R	C47Y	T1685I	S1722F	A1823T
M1T	C61Y	H1686R	V1736A	V1833M
M1V	C61G	V1688del	V1736G	W1837C
M18K	C61S	M1689R	G1738E	W1837G
M18T	C64G	T1691I	G1738R	W1837R
L22S	C64R	T1691K	D1739G	V1838E

C24R	C64Y	D1692Y	D1739V	Y1853C
I26N	C64W	D1692H	G1748D	splice site 212+3A>G
T37K	R71G	D1692N	R1753T	splice site 213-11T>G
T37R	R71K	A1693del	K1759N	splice site 213-12A>G
C39R	R71M	C1697R	L1764P	splice site 302-3C>G
C39Y	R71T	R1699Q	I1766S	splice site 4675+3A>T
C39G	S770L	R1699W	I1766N	splice site 4986+3G>C
C39W	R1495K	L1705P	G1770V	splice site 4986+5G>A
H41R	R1495M	G1706E	M1775K	splice site 4986+6T>C
C44F	R1495T	G1706R	M1775R	splice site 4986+6T>G
C44S	E1559K	A1708E	L1780P	splice site 5074+3A>G
C44Y	E1559Q	V1714G	C1787S	splice site 5194-12G>A
C47F	A1623G	S1715N	C1787_G1788>SD	splice site 5406+4A>G
C47R	S1655F	S1715R	G1788V	

Table 7. List of short variants in *BRCA2

M1R	K1530N	R2659G	D2723G	D3095E
M1I	R2336H	R2659K	D2723H	D3095G
M1V	R2336P	R2659T	D2723V	N3124I
M1T	R2336L	Y2660D	G2724W	N3187K
D23N	T2412I	E2663K	Y2726C	splice site 316+4delA
D23Y	L2510P	E2663V	G2748D	splice site 316+5G>A
S142I	R2602T	S2670L	R2784W	splice site 8487+3A>G
S142N	H2623R	I2675V	G2793R	splice site 8754+3G>C
V159M	W2626C	L2686P	Q2829R	splice site 8754+4A>G
G173R	W2626R	L2688P	A2911E	splice site 8754+5G>A
V211I	I2627F	T2722K	E3002K	splice site 8954-5A>G
V211L	L2647P	T2722R	R3052W	
Y600C	L2653P	D2723A	G3076V	

Table 8. List of short variants in *ATM

M1I	E2039K	A2622V	F2827C	splice site 331+5G>A
M1L	A2067D	D2625_A2626>EP	R2832C	splice site 8418+5_8418+8delGTGA
M1T	R2227C	V2662D	S2855_V2856>RI	
P292L	Y2470D	D2708N	D2913Y	
D2016G	A2524P	V2716A	R3008C	
R2032K	R2547_S2549del	G2765S	R3008H	

Table 9. List of Short Variants in *CHEK2*

R117G	K373E

G151S	A392V

Table 10. List of Short Variants in *FANCA, MLH1, RAD51C*

Gene	Short Variant
FANCA	F320L, F1263del
MLH1	R265C
RAD51C	L219S

**Note: This biomarker definition includes ATM and BRCA1/2 inactivating mutation lists that may change over time as a result of periodic review of new evidence, in accordance with FDA-approved variant classification procedures.*

1.2. *HRR alterations (BRCA1, BRCA2, ATM) to identify patients eligible for LYNPARZA® (olaparib).*

Deleterious or suspected deleterious HRR gene *(BRCA1, BRCA2, ATM)* variants, identified by the rules below in Table 11.

Table 11. Biomarker definition for HRR gene (*BRCA1, BRCA2, ATM*) Alterations for Olaparib treatment

Gene	Variant Class	Description
BRCA1 *BRCA2* *ATM*	Short Variant	Any inactivating short variant alteration meeting the definition in table 5. Any of the *BRCA1*, *BRCA2*, or *ATM* additional mutations listed in Tables 6 – 8
	Copy Number	Homozygous deletion meeting the definition in table 5.
	Rearrangement	Inactivating rearrangements meeting the definition in table 5.

1.3. HRR alterations (BRCA1, BRCA2) eligible for AKEEGA® (niraparib + abiraterone acetate), LYNPARZA® (olaparib) in combination with abiraterone, or RUBRACA ® (rucaparib).

Deleterious or suspected deleterious HRR gene *(BRCA1, BRCA2)* variants, identified by the rules below in Table 12.

Table 12. Biomarker definition for HRR gene (*BRCA1, BRCA2*) Alterations for treatment with Niraparib+ abiraterone acetate, or Olaparib in combination with abiraterone, or Rucaparib

Gene	Variant Class	Description

BRCA1 *BRCA2*	Short Variant	Any inactivating short variant alteration meeting the definition in table 5. Any of the *BRCA1* or *BRCA2* additional mutations listed in Tables 6 – 7
	Copy Number	Homozygous deletion meeting the definition in table 5.
	Rearrangement	Inactivating rearrangements meeting the definition in table 5.

2. CDx classification criteria for EGFR alterations

- Base substitutions resulting in EGFR L858R
- In-frame deletions occurring within EGFR Exon 19

3. ALK rearrangements to identify patients eligible for treatment with ALECENSA® (alectinib):

CDx positivity for an *ALK* rearrangement is based on the following variant classification criteria:

- The *ALK* rearrangement must have pathogenic driver status (FMI driver status of "known" or "likely")
- AND the disease type must be NSCLC
- AND one of the following two conditions must hold:
    1. The partner gene is *EML4*, or
    2. The *ALK* breakpoint occurs within *ALK* intron 19

4. SNVs and indels that lead to MET exon 14 skipping to identify patients eligible for treatment with TABRECTA® (capmatinib) and TEPMETKO®:

A SNV or indel in *MET* shall be considered to result in skipping of exon 14 if one or more of the following criteria are met:

1. Deletions greater than or equal to 5 bp that affect positions -3 to -30 in the intronic region immediately adjacent to the splice acceptor site at the 5′ boundary of *MET* exon 14.
2. Indels affecting positions -1 or -2 at the splice acceptor site of the 5′ boundary of *MET* exon 14.
3. Base substitutions and indels affecting positions 0, +1, +2, or +3 at the splice donor site of the 3′ boundary of *MET* exon 14.

5. Biomarker Rules for Rearrangements that Lead to NTRK1, NTRK2, or NTRK3 Fusions:

Rearrangements in *NTRK1*, *NTRK2*, or *NTRK3* shall be considered CDx biomarker positive, that is, to lead to a *NTRK1*, *NTRK2*, or *NTRK3* RNA fusion, if the following criterion is met:

- In-strand rearrangement events that may lead to an *NTRK1*, *NTRK2* or *NTRK3* RNA fusion with a previously reported or novel partner gene in which the kinase domain is not disrupted. This also includes rearrangement events that result in reciprocal fusions (*NTRK* may be on either the 5' or the 3' end of the detected fusion).

In this regard out-of-strand events are considered as non-fusion rearrangements and are classified as CDx biomarker negative. Intragenic fusions in which genomic rearrangement events are wholly internal to the *NTRK1*, *NTRK2*, or *NTRK3* genes (i.e., *NTRK1-NTRK1*, *NTRK2-NTRK2*, *NTRK3-NTRK3* events) are also considered biomarker negative. Unidentified partners (encoded as N/A) or LINC non-coding partners are also considered CDx biomarker negative.

6. ***Biomarker Rules for Rearrangements that Lead to ROS1 Fusions:***
Rearrangements in *ROS1* shall be considered CDx biomarker positive, i.e., to lead to *ROS1* RNA fusion, if the following condition is met:

   - In-strand rearrangement events that may lead to a *ROS1* RNA fusion with another protein coding gene in which the *ROS1* kinase domain is not disrupted. *ROS1* must be on the 3′ end of the detected fusion.

   In this regard, out-of-strand events are considered as non-fusion rearrangements and are classified as CDx biomarker negative. Intragenic fusions in which genomic rearrangement events are wholly internal to the *ROS1* (i.e., *ROS1-ROS1* events) are also considered biomarker negative. Unidentified partners (encoded as N/A) or LINC non- coding partners are also considered CDx biomarker negative. *ROS1* fusions with novel partners are required to be in frame.

7. ***CDx classification criteria for ITOVEBI™ (inavolisib) in combination with palbociclib and fulvestrant for patients with breast cancer***
Presence of a PIK3CA alteration listed in Table 13.

Table 13. Eligible *PIK3CA* short variants

R88Q	N345D	E453G	E542V	Q546H	H1047L	G1049R
G106A	N345H	E453K	E545A	Q546K	H1047N	G1049S
G106D	N345I	E453Q	E545D	Q546L	H1047P	
G106R	N345K	E453V	E545G	Q546P	H1047Q	
G106S	N345S	E542A	E545K	Q546R	H1047R	
G106V	N345T	E542D	E545L	M1043I	H1047T	

K111N	N345Y	E542G	E545Q	M1043T	H1047Y	
K111R	C420R	E542K	E545R	M1043V	G1049A	

8. ***CDx classification criteria for PIQRAY® (alpelisib) for patients with breast cancer***
   Presence of a *PIK3CA* alteration resulting in H1047R, E545K, E542K, C420R, E545A, E545D [1635G>T only], E545G, Q546E, Q546R, H1047L, or H1047Y.

9. ***BRAF V600E to identify metastatic CRC patients eligible for treatment with BRAFTOVI (encorafenib) in combination with cetuximab and NSCLC patients for treatment with BRAFTOVI (encorafenib) in combination with MEKTOVI (binimetinib)***
   CDx classification criteria for BRAF substitutions:
   - Base substitutions resulting in *BRAF V600E*

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are no FDA-approved CDx alternatives using cfDNA isolated from plasma for the detection of HRR gene alterations to identify patients with prostate cancer eligible for treatment with TALZENNA® (talazoparib) in combination with XTANDI® (enzalutamide).

However, FoundationOne CDx (F1CDx) from Foundation Medicine, Inc. (FMI) is an FDA-approved CDx (P170019/S060) using formalin-fixed, paraffin-embedded (FFPE) tissue specimens for this indication.

There are FDA-approved alternatives for the detection of select CDx and tumor profiling genetic alterations using either cfDNA isolated from plasma samples or FFPE tissue specimens. For additional details see FDA List of Cleared or Approved Companion Diagnostic Devices at: https://www.fda.gov/media/119249/download. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The F1LCDx assay was FDA-approved on August 26, 2020, and subsequently commercialized in the United States. The F1LCDx assay has been marketed in the United States, the European Union, and in several other foreign countries since the approval. On September 21, 2022, the companion diagnostic indication for F1LCDx to identify patients with ovarian cancer harboring BRCA1 or BRCA2 alterations for treatment with RUBRACA (rucaparib) was removed. On May 17, 2024, the companion diagnostic

indication for F1LCDx to identify patients with NSCLC harboring *EGFR* exon 20 insertions for treatment with EXKIVITY (mobocertinib) was removed. The approved PMA supplements that affected the intended use are listed in Table 14.

Table 14. Marketing History

Submission No.	Date of Approval	Biomarker/Update	Patient Population	Drug
P200006	October 26, 2020	*ALK* Rearrangements	NSCLC	ALECENSA® (alectinib)
		PIK3 CA alterations	Breast Cancer	PIQRAY® (alpelisib)
P200016	November 6, 2020	*BRCA1, BRCA2,* and *ATM* alterations	Prostate Cancer	LYNPARZA® (olaparib)
P190032/S001	July 15, 2021	*MET* single nucleotide variants (SNVs) and indels that lead to *MET* exon 14 skipping alterations	NSCLC	TABRECTA® (capmatinib)
P190032/S008	December 19, 2022	*EGFR* Exon 19 deletions and Exon 21 L858R substitution mutation)	NSCLC	FDA-approved EGFR tyrosine kinase inhibitors.
P190032/S004	December 22, 2022	*NTRK1/2/3* fusions	Solid tumors	ROZLYTREK® (entrectinib)
		ROS1	NSCLC	ROZLYTREK® (entrectinib)
P190032/S010	June 8, 2023	*BRAF V600E*	Colorectal cancer (CRC)	BRAFTOVI® (encorafenib) in combination with cetuximab
P190032/S011	October 11, 2023	*BRAF V600E*	NSCLC	BRAFTOVI® (encorafenib) in combination with MEKTOVI® (binimetinib)
P190032/S014	June 28, 2024	*BRCA1 and BRCA2* alterations	Prostate cancer	AKEEGA® (niraparib + abiraterone acetate).
P190032/S016	August 30, 2024	*BRCA1 and BRCA2* alterations	Prostate cancer	LYNPARZA® (olaparib) in combination with abiraterone
P190032/S023	October 10, 2024	*PIK3CA*-mutations	Breast cancer	ITOVEBI® (inavolisib) in combination with palbociclib and fulvestrant

P190032/S015	November 14, 2024	*MET* exon 14 skipping alterations	NSCLC	TEPMETKO® (tepotinib)

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Failure of the device to perform as expected or failure to correctly interpret test results may lead to incorrect F1LCDx assay results, and subsequently, inappropriate patient management decisions. Patients with false positive CDx biomarker results may undergo treatment with one of the therapies listed in the intended use statement 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 targeted therapy. There is also a risk of delayed results, which may lead to delay of treatment with the indicated therapy. For the specific adverse events related to the approved therapeutics, please see approved drug product labels.

For the specific adverse events that occurred in the clinical study, please see the FDA approved package insert for TALZENNA ® (talazoparib) and XTANDI® (enzalutamide) which are available at Drugs@FDA.

IX. SUMMARY OF NON-CLINICAL STUDIES

A. Laboratory Studies

The primary evidence supporting the performance of F1LCDx in detecting HRR gene (*BRCA1, BRCA2, ATM, ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C)* alterations in metastatic castration-resistant prostate cancer patients was from data generated using intended use specimens across the validation studies. In addition to the platform-level validation results, as well as validation results for three (3) HRR genes (*ATM*, *BRCA1*, and *BRCA2*) in mCRPC patients (refer to section IX.A in P190032 and P200016 Summary of Safety and Effectiveness Data, respectively), additional evidence of the performance of F1LCDx in detecting HRR (*ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C*) gene alterations is provided through analytical concordance, precision and confirmation of the limit of detection (LoD) studies using clinical samples. Table 15 below includes a list of genes/variant types that were represented in the key analytical validation studies, in accordance with their prevalence in mCRPC, to support performance of the assay for detection of the variant types in the HRR genes (*ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C*) that were not evaluated in P200016.

Table 15. Variants Used in the Key Analytical Validation Studies

	LoD/Precision			Accuracy		
	RE	ID	SUB	RE	ID	SUB
ATR	1	1	0	0	12	4
CDK12	1	1	1	0	39	11
CHEK2	0	1	1	0	18	16
FANCA	1	1	0	0	3	2
MLH1	1	1	0	0	1	0
MRE11A	1	1	0	0	3	2
NBN	1	0	1	0	4	0
PALB2	1	0	1	0	7	4
RAD51C	1	1	0	0	1	1

RE: rearrangement
ID: insertion/deletion
SUB: base substitutions
The prevalence of RE alterations in these genes ranged from 0% to 0.28% in the TALAPRO-2 trial and an external publicly available prostate cancer database that uses another NGS-based technology.
The prevalence of ID and SUB alterations in these genes ranged from 0.03% to 13.84% in the TALAPRO-2 trial and an external publicly available prostate cancer database that uses another NGS-based technology.

Prostate cancer samples evaluated in the analytical validation studies were prepared using the updated workflow of the Library Construction (LC) and Hybrid Capture (HC) of the F1LCDx assay.

1. **Analytical Accuracy/Concordance**
   Comparison to an Orthogonal Method
   An analytical accuracy study was conducted previously as part of P200016 to demonstrate the concordance between F1LCDx and an externally validated, ctDNA-based, NGS assay (evNGS) for the detection of *BRCA1*, *BRCA2*, and *ATM* alterations.

   An additional analytical accuracy study was conducted in this sPMA to demonstrate the concordance between F1LCDx and an externally validated NGS assay (evNGS) for the detection of additional HRR gene (*ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C)* alterations.

   In total, 163 clinical samples from prostate cancer patients with valid results from both F1LCDx and the evNGS assay were included in the concordance analysis with representation of *ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C* base substitutions, insertions, and deletions. The study was conducted using 78 biomarker-negative and 85 biomarker positive samples as determined by F1LCDx results during the sample selection step and containing a total of 128 variants. Samples were residual cfDNA specimens from clinical prostate cancer samples from the FMI sample archives, the TALAPRO-2 trial, or processed under previous orthogonal studies.

The F1LCDx and evNGS results for the detection of HRR gene (*ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C)* alterations using evNGS as the comparator assay are provided in the contingency table in Table 16. To align with the product specifications of the evNGS assay, variants below the threshold of 0.5% VAF as detected by the evNGS assay are excluded from analysis. The Positive Percent Agreement (PPA) and Negative Percent Agreement (NPA) using the evNGS assay results as the reference were calculated at the sample level without adjusting for the distribution of samples selected using F1LCDx, positive predictive value (PPV) and negative predictive value (NPV) were also estimated conditional on F1LCDx. The statistical analysis in Table 16 showed a PPV of 81.61% with 95% CI (73.06%, 88.75%) and an NPV of 97.37% with 95% CI (90.90%, 99.28%), and a PPA of 97.26% with 95% CI (90.55%, 99.25%) and an NPA of 82.22% with 95% CI (73.06%, 88.75%) unadjusted for prevalence.

Table 16. Contingency Table Comparing the Sample-Level Detection of HRR gene (*ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C)* alterations by F1LCDx and the evNGS

	evNGS+	**evNGS-**	**Total**	
F1LCDx+	71	16	87	PPV: 81.61% [95%CI*:72.19%, 88.35%]
F1LCDx-	2	74	76	NPV:97.37%[95% CI*: 90.90%, 99.28%]
Total	73	90	163	
	PPA:97.26% [95%CI*:90.55%, 99.25%]	NPA:82.22% [95% CI*: 73.06%, 88.75%]		

*95% 2-sided confidence intervals (CI) were calculated using the Wilson score method

The concordance results at the variant level are provided in the contingency table in Table 17. The statistical analysis in Table 17 showed a PPA of 97.89% with 95% CI (92.65%, 99.42%) and a NPA of 99.92% with 95% CI (99.88%, 99.95%) unadjusted for prevalence.

Table 17. Contingency Table Comparing the Variant-Level Detection of HRR gene (*ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C)* alterations by F1LCDx and the evNGS

	evNGS+	evNGS-	Total
F1LCDx+	93	25	118
F1LCDx-	2	31,013	31,0115
Total	95	31,038	31,133
PPA:97.89% [95%CI*:92.65%, 99.42%]			
NPA:99.92% [95% CI*: 99.88%, 99.95%]			

*95% 2-sided confidence intervals (CI) were calculated using the Wilson score method

There were 27 discordant calls between F1LCDx and the evNGS test results from 18 discordant samples. Of the 18 samples, the following was observed:

- Two samples expressed the two variants detected by the evNGS that were not detected by F1LCDx. These two variants detected by the evNGS had corresponding F1LCDx test results exhibiting low tumor fraction.
- Sixteen samples exhibited the 25 variants detected by F1LCDx and not the evNGS. For these 25 alterations, 15 were variants occurring in a repetitive context representing a challenging variant condition for the evNGS assay and 9 were variants detected in F1LCDx that were below the LoD for the evNGS. The remaining alteration was a complex deletion-insertion event that may be impacted by variant calling sensitivity.

2. <u>Analytical Sensitivity</u>

a. Limit of Blank (LoB)

The LoB of F1LCDx was evaluated in the platform LoB study for PMA P190032 (refer to Section IX.A.3.a. in the Summary of Safety and Effectiveness Data for P190032).

An additional LoB study was performed for P190032/S017 to support the updated LC/HC workflow of F1LCDx by collecting plasma cfDNA and corresponding donor-matched white blood cell (WBC) genomic DNA (gDNA) samples from 47 healthy donors with no known cancer diagnosis. A total of 32,273 unique variants were included in the study, including short variants (SV) for all HRR genes and rearrangements (RE) for all HRR genes except for *RAD51C*. Only one biomarker positive HRR variant was detected, CHEK2_1043T>A, in only one of the tested replicates, at 0.17% VAF, which was below the median LoD for short variants. The false positive rate for

CHEK2_1043T>A was 1.0638%. No other CDx biomarker variants in other HRR genes *(i.e., ATR, CDK12, FANCA, MLH1, MRE11A, NBN, PALB2, and RAD51C)* were detected.

b. Limit of Detection (LoD)

The F1LCDx LoD for the detection of HRR gene *(BRCA1, BRCA2, ATM, ATR, CDK12, FANCA, MLH1, MRE11A, NBN, PALB2, and RAD51C)* alterations was established through CDx-specific and confirmation of platform-based LoD studies.

The LoD for *BRCA1*, *BRCA2*, and *ATM* alterations was established through a previously conducted study for the approved PMA P200016. The LoD for the HRR genes (*ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C*) that were not evaluated in P200016 was confirmed through a precision study that used prostate cancer (PC) samples at or near 1x the median platform LoD for SVs (i.e., gene substitutions and indels) and RE previously determined in P190032, as detailed in section 3 below. The LoD confirmation/Precision study also included one sample from colorectal cancer (CRC) harboring a *BRCA1* homozygous deletion (HD) tested at 2x LoD for HD. A summary of the confirmed LoD results is provided in Table 18 below.

Table 18. Confirmation of LoD results for HRR Gene Alterations

Disease Ontology	Gene	Variant Type	Hit Rate (%)	Confirmed LoD	Median Platform LoD (%)	Fold LoD (x)*
PC	*ATR*	RE	94.44	0.52% VAF	0.37	1.42
PC	*CDK12*	SV (substitution)	100.00	0.57%VAF	0.40	1.44
PC	*CDK12*	SV (insertion)	100.00	0.54%VAF	0.40	1.34
PC	*CDK12*	RE	100.00	0.66%VAF	0.37	1.79
PC	*CHEK2*	SV (substitution)	94.44	0.49% VAF	0.40	1.23
PC	*CHEK2*	SV (deletion)	100.00	0.57%VAF	0.40	1.43
PC	*PALB2*	RE	100.00	0.70%VAF	0.37	1.89
PC	*PALB2*	SV (substitution)	96.88	0.55%VAF	0.40	1.36
PC	*FANCA*	RE	97.14	1.21%VAF	0.90	1.35
PC	*FANCA*	SV (insertion)	100.00	1.40%VAF	0.82	1.70
PC	*MLH1*	SV (deletion)	100.00	1.25%VAF	0.82	1.53
PC	*MLH1*	RE	100.00	1.16%VAF	0.90	1.29
PC	*MRE11A*	SV (deletion)	100.00	1.37%VAF	0.82	1.67
PC	*NBN*	SV (substitution)	100.00	1.30%VAF	0.82	1.59
PC	*RAD51C*	SV (insertion)	100.00	1.29%VAF	0.82	1.57
PC	*RAD51C*	RE	94.44	1.22% VAF	0.90	1.35
CRC	*BRCA1*	HD	100.00	61.80%TF	30.40	2.03

* Fold LoD = [Confirmed LoD(%)] / [Median Platform LoD(%)]
TF: tumor fraction

3. Precision and Reproducibility

Site-to-Site Precision

To evaluate the performance of HRR gene alteration detection, a site-to-site precision study was conducted using 18 prostate cancer specimens harboring HRR gene (*ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C*) alterations (biomarker-positive samples) at or near 1x the median platform LoD for short variants (substitutions, indels), and rearrangements. The study also included one clinical specimen from a CRC patient harboring a *BRCA1* HD tested at 2x LoD for HD. Table 19 below lists the biomarker-positive samples included in this study.

Table 19. List of samples and HRR alterations evaluated in the study

Sample ID	Disease Ontology	Gene	Variant Type	Targeted Variant
1	Prostate Cancer	*ATR*	SV (deletion)	p.I774fs*5 (2320delA)
2	Prostate Cancer	*ATR*	RE	ATR- CMSS1 truncation
3	Prostate Cancer	*CDK12*	SV (substitution)	p.Y279 * (837C>G)
		CDK12	SV (insertion)	p.Y913fs* 1 (2738_273 9insA)
4	Prostate Cancer	*CDK12*	RE	CDK12-MICALCL truncation
5	Prostate Cancer	*CHEK2*	SV (deletion)	p.T367fs* 15 (1100delC)
6	Prostate Cancer	*CHEK2*	SV (substitution)	p.L354* (1061T>A)
7	Prostate Cancer	*PALB2*	RE	PALB2-N/A truncation
8	Prostate Cancer	*PALB2*	SV (substitution)	splice site 49-1G>C
9^	Prostate Cancer	*FANCA*	RE	FANCA-N/A truncation
10	Prostate Cancer	*FANCA*	SV (insertion)	p.L432fs*53 (1290G>AT)

11	Prostate Cancer	*MLH1*	SV (deletion)	p.K618fs* 19 (1851delG)
12^	Prostate Cancer	*MLH1*	RE	MLH1- TMPRSS2 truncation
13	Prostate Cancer	*MRE11A*	SV (deletion)	p.E515fs* 8 (1543_154 6delGAAG)
14	Prostate Cancer	*MRE11A*	RE	MRE11A- N/A truncation
15	Prostate Cancer	*NBN*	RE	NBN-N/A truncation
16	Prostate Cancer	*NBN*	SV (substitution)	p.E718* (2152G>T)
17	Prostate Cancer	*RAD51C*	SV (insertion)	p.G149fs* 6 (444_445insT)
18^	Prostate Cancer	*RAD51C*	RE	RAD51C- N/A truncation
19	Colorectal Cancer[#]	*BRCA1*	HD	HD

[#] No PC samples with sufficient mass are available for this variant.
^ Samples selected from the talazoparib clinical program.
An "-*N/A*" partner gene indicates that the partner gene was not identified/ represents intragenic breakpoints

Samples were tested in duplicate across a total of 18 runs. Each run was performed using 2 reagent lots on 3 different Library Construction start days at 3 sites (2 replicates x 2 reagent lots x 3 LC start days x 3 sites) for a total of 36 replicates per sample. A total of 684 sample replicates (18 sample runs x 36 replicates per sample) were included in the study. Of the 684 replicates, 12 replicates failed to meet F1LCDx processing hybrid capture QC metrics. Thus, 672 valid replicates were evaluated.

The 18 PC samples included in the precision study harbored a total of 19 HRR gene alterations targeted at ~1-1.5x LoD. Since there was no matched normal sample for BRCA1 HD, the CRC sample was processed without being diluted, at approximately 2x LoD. All 19 biomarker-positive samples were run at challenging DNA input (close to 20 ng).

Reproducibility was evaluated by processing replicates from the same source sample, under conditions where one factor was changed at a time. The alterations had to be detected in each replicate of the source sample and meet the biomarker

definition to be considered a positive call. The point estimates and 95% two-sided score CIs for reproducibility of each sample are detailed in Table 20. 19 out of the 20 targeted variants were above LoD and 1 variant was below LoD.

Table 20. Reproducibility for All Targeted Variants

Alteration	Variant Type	Observed Average %VAF[1]/ %TF[2]	Median Platform LoD	# of Positive Replicates	# of Valid Replicates	Reproducibility (%)	95% Two-sided Score CI (%)	Fold LoD (x)
ATR-CMSS1	RE	0.52	0.37	34	36	94.44	[81.86, 98.46]	1.42
CDK12_837C>G	SV (substitution)	0.57	0.40	36	36	100.00	[90.36, 100.00]	1.44
CDK12_2738_2739insA	SV (Insertion)	0.54	0.40	36	36	100.00	[90.36, 100.00]	1.34
CDK12-MICALCL	RE	0.66	0.37	35	35	100.00	[90.11, 100.00]	1.79
CHEK2_1100delC	SV (Deletion)	0.57	0.40	36	36	100.00	[90.36, 100.00]	1.43
CHEK2_1061T>A	SV (substitution)	0.49	0.40	34	36	94.44	[81.86, 98.46]	1.23
PALB2-N/A	RE	0.70	0.37	35	35	100.00	[90.11, 100.00]	1.89
PALB2_49-1G>C	SV (substitution)	0.55	0.40	31	32	96.88	[84.26, 99.45]	1.36
FANCA-N/A	RE	1.21	0.90	34	35	97.14	[85.47, 99.49]	1.35
FANCA_1290G>AT	SV (Insertion)	1.40	0.82	36	36	100.00	[90.36, 100.00]	1.70
MLH1_1851delG	SV (Deletion)	1.25	0.82	36	36	100.00	[90.36, 100.00]	1.53
MLH1-TMPRSS2	RE	1.16	0.90	36	36	100.00	[90.36, 100.00]	1.29
MRE11A_1543 1546delGAAG	SV (Deletion)	1.37	0.82	36	36	100.00	[90.36, 100.00]	1.67
MRE11A-N/A	RE	1.05	0.90	29	36	80.56	[64.97, 90.25]	1.17
NBN-N/A	RE	1.16	0.90	31	36	86.11	[71.34, 93.92]	1.29
NBN_2152G>T	SV (substitution)	1.30	0.82	35	35	100.00	[90.11, 100.00]	1.59
RAD51C_444_445insT	SV (insertion)	1.29	0.82	36	36	100.00	[90.36, 100.00]	1.57
RAD51C-N/A	RE	1.22	0.90	34	36	94.44	[81.86, 98.46]	1.35
BRCA1_loss	HD	61.80	30.40	32	32	100.00	[89.28, 100.00]	2.03
ATR_2320delA	SV (Deletion)	0.08	0.40	33	36	91.67%	[78.17, 97.13]	0.19

* Fold LoD = [Observed Average %VAF/TF] / [Median Platform LoD(%)]

[1]VAF is applicable for short variants (substitutions, insertions, deletions) and rearrangements

[2]Tumor fraction (TF) is applicable for homozygous deletions

An "-*N/A*" partner gene indicates that the partner gene was not identified/ represents intragenic breakpoints

One sample with a targeted MRE11A-N/A RE tested at 1.17x LoD demonstrated reproducibility of 80.56%. This sample had three replicates with evidence for the variant observed but filtered from reporting due to insufficient supporting read evidence and four replicates with a qualified QC status due to low coverage, which may impact variant calling sensitivity.
One sample with a targeted NBN-N/A RE tested at 1.29x LoD demonstrated reproducibility of 86.11%. This sample had two replicates with no evidence of variant detected and three replicates with evidence for the variant observed but filtered from reporting due to insufficient supporting read evidence.
One sample with a targeted ATR_2320delA demonstrated reproducibility <95%. This sample had observed reads below the median platform LoD.

Repeatability was assessed by processing samples with two replicates from the same source sample and plate within each site, reagent lot, and LC start day. The result was considered to be in agreement if the duplicate replicates processed under identical conditions had the same detection status for the targeted variants. The repeatability results for each targeted variant are detailed in Table 21 below.

Table 21. Repeatability for All Targeted Variants

Alteration	Variant Type	# of Agree Pairs	# of Valid Pairs	Repeatability (%)	95% Two-sided Score CI (%)
ATR-CMSS1	RE	16	18	88.89	[67.20, 96.90]
CDK12_837 C>G	SV (substitution)	18	18	100.00	[82.41, 100.00]
CDK12_2738_2739insA	SV (Insertion)	18	18	100.00	[82.41, 100.00]
CDK12-MICALCL	RE	17	17	100.00	[81.57, 100.00]
CHEK2_1100delC	SV (Deletion)	18	18	100.00	[82.41, 100.00]
CHEK2_1061T>A	SV (substitution)	16	18	88.89	[67.20, 96.90]
PALB2-N/A	RE	17	17	100.00	[81.57, 100.00]
PALB2_49-1G>C	SV (substitution)	14	15	93.33	[70.18, 98.81]
FANCA-N/A	RE	16	17	94.12	[73.02, 98.95]
FANCA_1290G>AT	SV (Insertion)	18	18	100.00	[82.41, 100.00]
MLH1_1851delG	SV (Deletion)	18	18	100.00	[82.41, 100.00]
MLH1-TMPRSS2	RE	18	18	100.00	[82.41, 100.00]
MRE11A_1543_1546delGAAG	SV (Deletion)	18	18	100.00	[82.41, 100.00]

Alteration	Variant Type	# of Agree Pairs	# of Valid Pairs	Repeatability (%)	95% Two-sided Score CI (%)
MRE11A-N/A	RE	13	18	72.22	[49.13, 87.50]
NBN-N/A	RE	17	18	94.44	[74.24, 99.01]
NBN 2152G>T	SV (substitution)	17	17	100.00	[81.57, 100.00]
RAD51C 44 4 4 45insT	SV (insertion)	18	18	100.00	[82.41, 100.00]
RAD51C-N/A	RE	16	18	88.89	[67.20, 96.90]
BRCA1_loss	HD	15	15	100.00	[79.61, 100.00]
ATR 2320del A	SV (Deletion)	17	18	94.44	[74.24, 99.01]

B. Animal Studies

No animal studies were conducted using the F1LCDx assay.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The clinical performance of F1LCDx for identification of prostate cancer patients with HRR gene alterations who may benefit from treatment with TALZENNA® (talazoparib) in combination with XTANDI® (enzalutamide) was demonstrated based on results from the TALAPRO-2 clinical trial.

A summary of the clinical study design is presented below:

A. TALAPRO-2 Study Design

TALAPRO-2 is an international, double-blinded, placebo-controlled, randomized Phase 3 study of talazoparib in combination with enzalutamide compared with placebo in combination with enzalutamide in patients with mCRPC, where no systemic cancer treatments have been initiated after documentation of CRPC with the exception of androgen deprivation therapy (ADT) and first-generation anti-androgen agents. Part 1 was open-label and non-randomized and evaluated the safety, tolerability, and pharmacokinetics (PK) of talazoparib in combination with enzalutamide. The primary objective of Part 1 was to determine the starting dose of talazoparib in combination with enzalutamide to be used in Part 2. Part 2 was randomized, double-blinded, and placebo-controlled and evaluated the safety and efficacy of talazoparib in combination with enzalutamide compared with placebo in combination with enzalutamide. The major efficacy outcome measure of Part 2 was radiographic progression-free survival (rPFS) evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 and Prostate Cancer Working Group (PCWG3) (bone) criteria, assessed by Blinded Independent Central Review (BICR). An additional efficacy outcome measure was Overall Survival (OS). Part 2 of the study included 2 cohorts and were 1:1 randomized to talazoparib in combination with enzalutamide versus placebo in combination with enzalutamide.

Part 2 Cohort 1
The first cohort (Cohort 1) enrolled 805 mCRPC patients unselected for HRR status (referred to as an all-comers population). Although patients were unselected for HRR status, HRR deficiency assessment prior to randomization was required for stratification.

Part 2 Cohort 2
After enrollment for Cohort 1 was closed, enrollment into the study continued but was restricted to patients with HRR deficiencies (Cohort 2). Cohort 2 enrolled 230 patients harboring HRR gene alterations that were likely to sensitize the patient's tumor to poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibition (HRR-deficient).

Patients with HRR gene alterations were identified prior to randomization by central testing of tumor tissue or blood samples (liquid biopsy) using primarily the F1CDx

during Cohort 1 of the study, and F1CDx and/or the F1LCDx assays during Cohort 2 of the study.
Of the 805 mCRPC patients enrolled into Cohort 1, 169 patients were HRR-deficient and thus, there were 399 HRR-deficient patients from Cohort 1 and Cohort 2.

Clinical Validation Study Design
The clinical effectiveness of TALZENNA® in combination with XTANDI® among patients with HRR gene alterations as determined by F1LCDx was demonstrated through a clinical validation study using specimens from the TALAPRO-2 clinical trial. The clinical validation study was conducted to: (1) evaluate the efficacy of talazoparib in combination with enzalutamide in mCRPC patients with HRR gene alterations as determined by F1LCDx and (2) assess the robustness of the efficacy evaluated with sensitivity analyses that account for the uncertainty due to missing data for the F1LCDx biomarker status.

The clinical validation for F1LCDx was based on 399 HRR-deficient patients from TALAPRO-2, which included clinical trial patients harboring HRR gene alterations from Cohorts 1 and 2. An additional analysis was conducted on the 805 patients in Cohort 1 of the TALAPRO-2 study unselected for HRR status.
The clinical performance for F1LCDx was assessed through the primary efficacy analysis of HRR gene alteration positive patients as determined by F1LCDx in these populations.

1. **Clinical Inclusion and Exclusion Criteria**

   Inclusion criteria:
   Enrollment in the TALAPRO-2 study was limited to patients who met the following key inclusion criteria:

   - At least 18 years of age. For Japan, at least 20 years of age.
   - Histologically or cytologically confirmed adenocarcinoma of the prostate without small cell or signet cell features. If the patient does not have a prior histological diagnosis, a baseline de novo biopsy must be used to confirm the diagnosis and to support biomarker analysis.
   - Asymptomatic or mildly symptomatic metastatic castration resistant prostate cancer (mCRPC).
   - For enrollment into Part 2 only (optional in Part 1): assessment of DNA damage repair (DDR) mutation status by prospective analysis of blood (liquid biopsy), or tissue (de novo or archival tissue), or historical analysis (with Sponsor pre-approval), of most recent tumor tissue per FoundationOne® testing. (Note: for patients enrolling in Part 1, DDR deficiency testing is optional).
   - For enrollment into Part 2 only (optional for Part 1): Unless prohibited by local regulations or ethics committee decision, consent to a saliva sample collection for retrospective sequencing of the same DDR genes tested on tumor tissue and blood (liquid biopsy), or a subset thereof, and to serve as a germline control in identifying tumor mutations.

- Surgically or medically castrated, with serum testosterone ≤50 ng/dL (≤1.73 nmol/L) at screening. Ongoing androgen deprivation therapy with a gonadotropin releasing hormone (GnRH) agonist or antagonist for patients who have not undergone bilateral orchiectomy must be initiated at least 4 weeks before Day 1 (Part 1) or randomization (Part 2) and must continue throughout the study.
- Metastatic disease in bone documented on bone scan or in soft tissue documented on CT/MRI scan.
- Progressive disease at study entry in the setting of medical or surgical castration.

Exclusion criteria:
Patients were not permitted to enroll in the TALAPRO-2 study if they met any of the following key exclusion criteria:

- Any prior systemic cancer treatment initiated in the non-metastatic CRPC or mCRPC disease state. (ADT and first-generation anti-androgens received in the CRPC disease state are NOT exclusionary).
- Patients whose only evidence of metastasis is adenopathy below the aortic bifurcation.
- Prior treatment with second-generation androgen receptor inhibitors (enzalutamide, apalutamide, and darolutamide), a PARP inhibitor, cyclophosphamide, or mitoxantrone for prostate cancer.
- Prior treatment with platinum-based chemotherapy within 6 months (from the last dose) prior to Day 1 (Part 1) or randomization (Part 2), or any history of disease progression on platinum-based therapy within 6 months (from the last dose).
- Treatment with cytotoxic chemotherapy which includes but is not limited to docetaxel, biologic therapy including sipuleucel-T, or radionuclide therapy received in the castration-sensitive prostate cancer is NOT exclusionary if discontinued in the 28 days prior to Day 1 (Part 1) or randomization (Part 2). Prior treatment with abiraterone in the castration-sensitive settings is not exclusionary if discontinued prior to randomization. Hormonal therapy (eg, bicalutamide, nilutamide, flutamide, estrogens) are not exclusionary if discontinued prior to randomization. Prednisone>10 mg/day (or equivalents) is exclusionary.
- Treatment with any investigational agent within 4 weeks before Day 1 (Part 1) or randomization (Part 2).
- Prior treatment with opioids for pain related to either primary prostate cancer or metastasis within 28 days prior to Day 1 (Part 1) or randomization (Part 2).
- Current use of potent P-gp inhibitors within 7 days prior to Day 1 (Part 1) or randomization (Part 2).
- Known or suspected brain metastasis or active leptomeningeal disease.
- Symptomatic or impending spinal cord compression or cauda equina syndrome.

- Any history of myelodysplastic syndrome, acute myeloid leukemia, or prior malignancy *except* for any of the following:
    - Carcinoma in situ or non melanoma skin cancer.
    - Any prior malignancies ≥3 years before randomization with no subsequent evidence of recurrence or progression regardless of the stage.
    - Stage 0 or Stage 1 cancer <3 years before randomization that has a remote probability of recurrence or progression in the opinion of the investigator.

2. Follow-up Schedule

Patients were followed-up in accordance with the TALAPRO-2 study safety follow-up and long-term follow-up schedules. The F1LCDx clinical validation study involved only testing and analysis of plasma cfDNA samples; as such, no additional patient subject follow-up was conducted with regard to the diagnostic study.

3. Clinical Endpoints

Clinical efficacy of talazoparib in combination with enzalutamide in mCRPC patients with HRR gene alterations by the F1LCDx assay was evaluated by the following primary efficacy endpoint: rPFS, defined as the time from the date of randomization to first objective evidence of radiographic progression as assessed in soft tissue per RECIST 1.1 or in bone (upon subsequent confirmation) per PCWG3 guidelines by BICR, or death, whichever occurred first. The primary efficacy analysis set included F1LCDx+ HRR-deficient patients, who were HRR gene alteration positive by the F1LCDx assay based on the F1LCDx biomarker definition for HRR gene alterations.

B. Accountability of PMA Cohort

The clinical validation study was based on the combined HRR-deficient population in the TALAPRO-2 study as determined by the Clinical Trial Assays (CTA), i.e., HRRm CTA+ population, which consisted of 399 HRR-deficient patients (169 from Cohort 1 and 230 from Cohort 2). Of these 399 HRR-deficient patients, a total of 239 patients had valid results by F1LCDx prospective testing (i.e., on screening- phase samples) and 160 were not tested or did not have valid F1LCDx prospective results. An additional 115 patients had valid results by F1LCDx retrospective testing (i.e., on additional samples collected at screening and tested retrospectively). In total, of the 399 HRR-deficient patients in Cohort 1 and 2 of the study, 354 patients had valid results by either prospective or retrospective F1LCDx and 45 were not tested or did not have valid results by F1LCDx prospective or retrospective testing. Out of the 354 patients with F1LCDx valid results, 287 were HRR+ by F1LCDx and 67 were HRR- by F1LCDx (but positive by other enrolling assays) (Table 22).

An additional analysis was conducted on the 805 patients in Cohort 1 of the TALAPRO-2 study unselected for HRR status (i.e., the all-comers population). Of these 805 patients unselected for HRR status, a total of 688 patients had valid results by either prospective

or retrospective F1LCDx and 117 were not tested or did not have valid results by F1LCDx. Out of the 688 patients with valid F1LCDx results, 194 were HRR+ by F1LCDx and 494 were HRR- by F1LCDx (Table 22).

Table 22. PMA sample accountability in the combined HRRm deficient population in Cohorts 1+2 and the all-comers population (Cohort 1) of the TALAPRO-2 study

Population	Subpopulation	Sample size (%)	
		HRRm population from Cohorts 1+2	All-comers population (Cohort 1)
F1LCDx evaluable	**Overall**	**354 (88.72%)**	**688 (85.47%)**
	• **F1LCDx HRRm (F1LCDx+)**	**287 (71.93%)**	**194 (24.10%)**
	• By prospective testing	201 (50.38%)	20 (2.50%)
	• By retrospective testing	86 (21.55%)	174 (20.50%)
	• **F1LCDx Non-HRRm (F1LCDx-)**	**67 (16.79%)**	**494 (61.37%)**
	• By prospective testing	38 (9.52%)	38 (4.73%)
	• By retrospective testing	29 (7.27%)	456 (56.64%)
F1LCDx unevaluable	**Overall**	**45 (11.28%)**	**117 (14.53%)**
Overall	**Overall**	**399 (100.00%)**	**805 (100.00%)**

C. Study Population Demographics and Baseline Parameters

The distributions of the selected demographic, patient and disease characteristics between the treatment and control arms were compared for the F1LCDx+ HRR-deficient (n=287) population. The results are shown in table 23. In general, most covariates are balanced between the treatment and control arms for the F1LCDx+ HRR-deficient patients.

Table 23. Demographic and patient characteristics for F1LCDx HRR-deficient population

Covariate	Summary Statistics/Category	Treatment Group (N=142)	Placebo Group (N=145)	P value
Previous treatment status	No Prior NHT or Taxane	84 (59.15%)	90 (62.07%)	0.631
	Prior NHT or Taxane	58 (40.85%)	55 (37.93%)	
	(Missing)	0 (0.00%)	0 (0.00%)	
	Total	142 (100.00%)	145 (100.00%)	
Age	min	51.00	44.00	0.765
	Q1	64.00	64.00	
	median	70.00	71.00	

Covariate	Summary Statistics/Category	Treatment Group (N=142)	Placebo Group (N=145)	P value
	mean	69.94	69.99	
	Q3	76.00	76.00	
	max	90.00	90.00	
	SD	8.45	8.61	
	(Missing)	0 (0.00%)	0 (0.00%)	
Age group	< 65	38 (26.76%)	38 (26.21%)	0.954
	>= 75	45 (31.69%)	44 (30.34%)	
	65 to < 75	59 (41.55%)	63 (43.45%)	
	(Missing)	0 (0.00%)	0 (0.00%)	
	Total	142 (100.00%)	145 (100.00%)	
BMI	min	18.60	18.00	0.562
	Q1	24.10	24.90	
	median	27.30	27.80	
	mean	28.03	28.45	
	Q3	30.60	30.90	
	max	44.50	59.40	
	SD	4.72	5.67	
	(Missing)	1 (0.70%)	2 (1.38%)	
Baseline use of a bone protecting agent	No	118 (83.10%)	123 (84.83%)	0.749
	Yes	24 (16.90%)	22 (15.17%)	
	(Missing)	0 (0.00%)	0 (0.00%)	
	Total	142 (100.00%)	145 (100.00%)	
Baseline circulating tumor cells (CTC) count (continuous)	min	0.00	0.00	0.511
	Q1	0.00	0.00	
	median	3.00	2.00	
	mean	45.54	41.60	
	Q3	16.75	14.25	
	max	1218.00	1108.00	
	SD	162.26	145.17	
	(Missing)	28 (19.72%)	21 (14.48%)	
Baseline circulating tumor cells (CTC) count (categorical with cutoff = 5)	<5	62 (43.66%)	75 (51.72%)	0.361
	>=5	52 (36.62%)	49 (33.79%)	
	(Missing)	28 (19.72%)	21 (14.48%)	
	Total	142 (100.00%)	145 (100.00%)	
Baseline circulating	>0	76 (53.52%)	78 (53.79%)	0.588
	0	38 (26.76%)	46 (31.72%)	
tumor cells (CTC) count (categorical with cutoff = 0)	(Missing)	28 (19.72%)	21 (14.48%)	
	Total	142 (100.00%)	145 (100.00%)	
Distribution of disease at screening involved: bone	No	14 (9.86%)	28 (19.31%)	0.044
	Yes	124 (87.32%)	117 (80.69%)	
	(Missing)	4 (2.82%)	0 (0.00%)	
	Total	142 (100.00%)	145 (100.00%)	
Distribution of disease at screening involved: lymph node	No	77 (54.23%)	75 (51.72%)	0.551
	Yes	61 (42.96%)	70 (48.28%)	
	(Missing)	4 (2.82%)	0 (0.00%)	
	Total	142 (100.00%)	145 (100.00%)	
	No	123 (86.62%)	133 (91.72%)	0.545

Covariate	Summary Statistics/Category	Treatment Group (N=142)	Placebo Group (N=145)	P value
Distribution of disease at screening involved: other soft tissue	Yes	15 (10.56%)	12 (8.28%)	
	(Missing)	4 (2.82%)	0 (0.00%)	
	Total	142 (100.00%)	145 (100.00%)	
Distribution of disease at screening involved: visceral disease (liver)	No	130 (91.55%)	141 (97.24%)	0.247
	Yes	8 (5.63%)	4 (2.76%)	
	(Missing)	4 (2.82%)	0 (0.00%)	
	Total	142 (100.00%)	145 (100.00%)	
Distribution of disease at screening involved: visceral disease (lung)	No	121 (85.21%)	123 (84.83%)	0.497
	Yes	17 (11.97%)	22 (15.17%)	
	(Missing)	4 (2.82%)	0 (0.00%)	
	Total	142 (100.00%)	145 (100.00%)	
Distribution of disease at screening involved: visceral disease (lung or liver)	No	115 (80.99%)	121 (83.45%)	1.000
	Yes	23 (16.20%)	24 (16.55%)	
	(Missing)	4 (2.82%)	0 (0.00%)	
	Total	142 (100.00%)	145 (100.00%)	
Disease localization at screening	Bone only	56 (39.44%)	59 (40.69%)	0.046
	Both bone and soft tissue	68 (47.89%)	58 (40.00%)	
	None	3 (2.11%)	0 (0.00%)	
	Soft tissue only	15 (10.56%)	28 (19.31%)	
	(Missing)	0 (0.00%)	0 (0.00%)	
	Total	142 (100.00%)	145 (100.00%)	
Eastern Cooperative Oncology Group (ECOG) performance status	0	88 (61.97%)	85 (58.62%)	0.630
	1	54 (38.03%)	60 (41.38%)	
	(Missing)	0 (0.00%)	0 (0.00%)	
	Total	142 (100.00%)	145 (100.00%)	
Geographic region	Asia	27 (19.01%)	20 (13.79%)	0.279
	European Union/GBR	67 (47.18%)	82 (56.55%)	
	North America	13 (9.15%)	16 (11.03%)	
	Rest of the world	35 (24.65%)	27 (18.62%)	
	(Missing)	0 (0.00%)	0 (0.00%)	
	Total	142 (100.00%)	145 (100.00%)	
	High [8-10]	107 (75.35%)	101 (69.66%)	0.246
Gleason score category 1	Low [2-4]	1 (0.70%)	0 (0.00%)	
	Medium [5-7]	31 (21.83%)	41 (28.28%)	
	(Missing)	3 (2.11%)	3 (2.07%)	
	Total	142 (100.00%)	145 (100.00%)	
Gleason score category 2	<=6	5 (3.52%)	5 (3.45%)	0.679
	7	27 (19.01%)	36 (24.83%)	
	8	31 (21.83%)	27 (18.62%)	
	9-10	76 (53.52%)	74 (51.03%)	
	(Missing)	3 (2.11%)	3 (2.07%)	
	Total	142 (100.00%)	145 (100.00%)	

Covariate	Summary Statistics/Category	Treatment Group (N=142)	Placebo Group (N=145)	P value
Histopathological classification	ADENOCARCINOMA	142 (100.00%)	144 (99.31%)	1.000
	ADENOCARCINOMA WITH NEUROENDOCRINE FEATURES	0 (0.00%)	1 (0.69%)	
	(Missing)	0 (0.00%)	0 (0.00%)	
	Total	142 (100.00%)	145 (100.00%)	
Number of bone metastases at screening	0	21 (14.79%)	30 (20.69%)	0.039
	1-4	46 (32.39%)	43 (29.66%)	
	5-9	39 (27.46%)	22 (15.17%)	
	10-20	14 (9.86%)	26 (17.93%)	
	>20	22 (15.49%)	24 (16.55%)	
	(Missing)	0 (0.00%)	0 (0.00%)	
	Total	142 (100.00%)	145 (100.00%)	
Baseline pain score by Brief Pain Inventory-Short Form (BPI-SF)	0-1	92 (64.79%)	85 (58.62%)	0.331
	2-3	50 (35.21%)	59 (40.69%)	
	>3	0 (0.00%)	1 (0.69%)	
	(Missing)	0 (0.00%)	0 (0.00%)	
	Total	142 (100.00%)	145 (100.00%)	
Baseline serum Prostate-Specific Antigen (PSA) (ng/mL)	min	0.31	0.04	0.911
	Q1	6.94	7.95	
	median	24.39	21.73	
	mean	96.59	76.20	
	Q3	72.77	74.10	
	max	3412.00	1055.00	
	SD	316.88	153.83	
	(Missing)	1 (0.70%)	0 (0.00%)	
Race	ASIAN	28 (19.72%)	22 (15.17%)	0.733
	BLACK OR AFRICAN AMERICAN	4 (2.82%)	4 (2.76%)	
	MULTIPLE	0 (0.00%)	1 (0.69%)	
	NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0 (0.00%)	1 (0.69%)	
	WHITE	105 (73.94%)	104 (71.72%)	
	(Missing)	5 (3.52%)	13 (8.97%)	
	Total	142 (100.00%)	145 (100.00%)	
Race group	ASIAN	28 (19.72%)	22 (15.17%)	0.438
	NON-ASIAN	109 (76.76%)	110 (75.86%)	
	(Missing)	5 (3.52%)	13 (8.97%)	
	Total	142 (100.00%)	145 (100.00%)	
Renal impairment at baseline	Mild (60-89)	67 (47.18%)	61 (42.07%)	0.550
	Moderate (30-59)	16 (11.27%)	17 (11.72%)	
	Normal (>=90)	53 (37.32%)	64 (44.14%)	
	(Missing)	6 (4.23%)	3 (2.07%)	
	Total	142 (100.00%)	145 (100.00%)	
Time from primary diagnosis to	min	5.59	5.49	0.957
	Q1	16.39	17.89	
	median	31.21	26.83	
	mean	49.01	46.18	

Covariate	Summary Statistics/Category	Treatment Group (N=142)	Placebo Group (N=145)	P value
randomization in months	Q3	69.78	64.44	
	max	216.57	190.85	
	SD	46.29	42.21	
	(Missing)	5 (3.52%)	9 (6.21%)	
TNM stage at diagnosis: M	M0	63 (44.37%)	61 (42.07%)	0.762
	M1	36 (25.35%)	29 (20.00%)	
	M1A	3 (2.11%)	5 (3.45%)	
	M1B	24 (16.90%)	26 (17.93%)	
	M1C	3 (2.11%)	6 (4.14%)	
	MX	12 (8.45%)	15 (10.34%)	
	(Missing)	1 (0.70%)	3 (2.07%)	
	Total	142 (100.00%)	145 (100.00%)	
TNM stage at diagnosis: N	N0	53 (37.32%)	53 (36.55%)	0.643
	N1	65 (45.77%)	60 (41.38%)	
	NX	22 (15.49%)	28 (19.31%)	
	(Missing)	2 (1.41%)	4 (2.76%)	
	Total	142 (100.00%)	145 (100.00%)	
TNM stage at diagnosis: T	T0	1 (0.70%)	1 (0.69%)	0.358
	T1	4 (2.82%)	13 (8.97%)	
	T2	29 (20.42%)	26 (17.93%)	
	T3	65 (45.77%)	60 (41.38%)	
	T4	21 (14.79%)	22 (15.17%)	
	TX	20 (14.08%)	21 (14.48%)	
	(Missing)	2 (1.41%)	2 (1.38%)	
	Total	142 (100.00%)	145 (100.00%)	
TNM stage at study entry: M	M0	1 (0.70%)	0 (0.00%)	0.238
	M1	74 (52.11%)	66 (45.52%)	
	M1A	6 (4.23%)	14 (9.66%)	
	M1B	46 (32.39%)	43 (29.66%)	
	M1C	14 (9.86%)	18 (12.41%)	
	MX	0 (0.00%)	1 (0.69%)	
	(Missing)	1 (0.70%)	3 (2.07%)	
	Total	142 (100.00%)	145 (100.00%)	
TNM stage at study entry: N	N0	50 (35.21%)	51 (35.17%)	0.384
	N1	66 (46.48%)	58 (40.00%)	
	NX	24 (16.90%)	33 (22.76%)	
	(Missing)	2 (1.41%)	3 (2.07%)	
	Total	142 (100.00%)	145 (100.00%)	
TNM stage at study entry: T	T0	9 (6.34%)	5 (3.45%)	0.164
	T1	1 (0.70%)	7 (4.83%)	
	T2	23 (16.20%)	18 (12.41%)	
	T3	37 (26.06%)	30 (20.69%)	
	T4	20 (14.08%)	24 (16.55%)	
	TX	50 (35.21%)	58 (40.00%)	
	(Missing)	2 (1.41%)	3 (2.07%)	
	Total	142 (100.00%)	145 (100.00%)	
Type of progression at study entry	Bone only	6 (4.23%)	7 (4.83%)	0.485
	Bone+soft tissue	2 (1.41%)	6 (4.14%)	
	PSA only	67 (47.18%)	70 (48.28%)	
	PSA+bone	29 (20.42%)	31 (21.38%)	
	PSA+bone+soft tissue	17 (11.97%)	8 (5.52%)	

Covariate	Summary Statistics/Category	Treatment Group (N=142)	Placebo Group (N=145)	P value
	PSA+soft tissue	17 (11.97%)	18 (12.41%)	
	Soft tissue only	4 (2.82%)	5 (3.45%)	
	(Missing)	0 (0.00%)	0 (0.00%)	
	Total	142 (100.00%)	145 (100.00%)	
Weight	min	45.90	49.00	0.484
	Q1	72.34	73.20	
	median	80.50	83.80	
	mean	84.18	85.52	
	Q3	94.00	93.80	
	max	134.50	177.70	
	SD	17.44	19.06	
	(Missing)	0 (0.00%)	0 (0.00%)	

In the clinical validation study, demographics and baseline characteristics were compared between the F1LCDx evaluable (n=354) and F1LCDx unevaluable (n=45) population in the HRR-deficient population of the TALAPRO-2 study (n=399). The F1LCDx unevaluable population included patients with positive HRR gene alteration status by non-F1LCDx assay [F1CDx, historical F1/F1CDx, or Interactive Web Response System (IWRS)] prior to randomization per the biomarker definition for clinical trial enrollment and had unevaluable HRR gene alteration status by F1LCDx. The demographics and disease characteristics for the F1LCDx evaluable and F1LCDx unevaluable patients are provided in Table 24. Differences in characteristics of the F1LCDx evaluable and F1LCDx unevaluable populations were identified by covariate analysis. In general, the majority of the demographics and baseline characteristics for the F1LCDx evaluable and F1LCDx unevaluable patients were similar, except for differences in a few unbalanced variables most of which were included in the sensitivity analysis imputation model.

Table 24. Demographic and Baseline Characteristics for F1LCDx evaluable and unevaluable populations

Baseline/Demographic Characteristics	Summary Statistics/ Category Level	F1LCDx-evaluable N=354	F1LCDx-unevaluable N=45	p-value
Age	min	44.00	41.00	0.558
	Q1	64.00	67.00	
	median	70.00	70.00	
	mean	69.94	68.64	
	Q3	76.00	73.00	
	max	90.00	81.00	
	SD	8.52	8.05	
	(Missing)	0 (0.00%)	0 (0.00%)	
Age group	< 65	93 (26.27%)	8 (17.78%)	0.025
	>= 75	110 (31.07%)	8 (17.78%)	

Baseline/Demographic Characteristics	Summary Statistics/ Category Level	F1LCDx-evaluable N=354	F1LCDx-unevaluable N=45	p-value
	65 to < 75	151 (42.66%)	29 (64.44%)	
	(Missing)	0 (0.00%)	0 (0.00%)	
	Total	354 (100.00%)	45 (100.00%)	
BMI	min	18.00	17.10	0.014
	Q1	24.60	22.20	
	median	27.70	26.10	
	mean	28.19	26.24	
	Q3	30.78	29.20	
	max	59.40	43.00	
	SD	5.10	4.85	
	(Missing)	4 (1.13%)	0 (0.00%)	
Baseline use of a bone protecting agent	No	300 (84.75%)	39 (86.67%)	1.000
	Yes	54 (15.25%)	6 (13.33%)	
	(Missing)	0 (0.00%)	0 (0.00%)	
	Total	354 (100.00%)	45 (100.00%)	
Baseline circulating tumor cells (CTC) count (continuous)	min	0.00	0.00	0.818
	Q1	0.00	0.00	
	median	1.00	1.00	
	mean	36.59	34.28	
	Q3	12.75	5.00	
	max	1218.00	429.00	
	SD	140.65	92.02	
	(Missing)	68 (19.21%)	20 (44.44%)	
Baseline circulating tumor cells (CTC) count (categorical with cutoff = 5)	<5	179 (50.56%)	18 (40.00%)	0.395
	>=5	107 (30.23%)	7 (15.56%)	
	(Missing)	68 (19.21%)	20 (44.44%)	
	Total	354 (100.00%)	45 (100.00%)	
Baseline circulating tumor cells (CTC) count (categorical with cutoff = 0)	>0	168 (47.46%)	14 (31.11%)	0.834
	0	118 (33.33%)	11 (24.44%)	
	(Missing)	68 (19.21%)	20 (44.44%)	
	Total	354 (100.00%)	45 (100.00%)	
Distribution of disease at screening involved: bone	No	51 (14.41%)	8 (17.78%)	0.657
	Yes	296 (83.62%)	37 (82.22%)	
	(Missing)	7 (1.98%)	0 (0.00%)	
	Total	354 (100.00%)	45 (100.00%)	
	No	190 (53.67%)	26 (57.78%)	0.752
	Yes	157 (44.35%)	19 (42.22%)	

Baseline/Demographic Characteristics	Summary Statistics/ Category Level	F1LCDx-evaluable N=354	F1LCDx-unevaluable N=45	p-value
Distribution of disease at screening involved: lymph node	(Missing)	7 (1.98%)	0 (0.00%)	
	Total	354 (100.00%)	45 (100.00%)	
Distribution of disease at screening involved: other soft tissue	No	312 (88.14%)	37 (82.22%)	0.129
	Yes	35 (9.89%)	8 (17.78%)	
	(Missing)	7 (1.98%)	0 (0.00%)	
	Total	354 (100.00%)	45 (100.00%)	
Distribution of disease at screening involved: visceral disease (liver)	No	333 (94.07%)	44 (97.78%)	1.000
	Yes	14 (3.95%)	1 (2.22%)	
	(Missing)	7 (1.98%)	0 (0.00%)	
	Total	354 (100.00%)	45 (100.00%)	
Distribution of disease at screening involved: visceral disease (lung)	No	302 (85.31%)	41 (91.11%)	0.631
	Yes	45 (12.71%)	4 (8.89%)	
	(Missing)	7 (1.98%)	0 (0.00%)	
	Total	354 (100.00%)	45 (100.00%)	
Distribution of disease at screening involved: visceral disease (lung or liver)	No	293 (82.77%)	40 (88.89%)	0.514
	Yes	54 (15.25%)	5 (11.11%)	
	(Missing)	7 (1.98%)	0 (0.00%)	
	Total	354 (100.00%)	45 (100.00%)	
Disease localization at screening	Bone only	138 (38.98%)	19 (42.22%)	0.836
	Both bone and soft tissue	158 (44.63%)	18 (40.00%)	
	None	6 (1.69%)	0 (0.00%)	
	Soft tissue only	52 (14.69%)	8 (17.78%)	
	(Missing)	0 (0.00%)	0 (0.00%)	
	Total	354 (100.00%)	45 (100.00%)	
Eastern Cooperative Oncology Group (ECOG) performance status	0	219 (61.86%)	27 (60.00%)	0.871
	1	135 (38.14%)	18 (40.00%)	
	(Missing)	0 (0.00%)	0 (0.00%)	
	Total	354 (100.00%)	45 (100.00%)	
Geographic region	Asia	62 (17.51%)	18 (40.00%)	<0.001
	European Union/GBR	183 (51.69%)	10 (22.22%)	
	North America	37 (10.45%)	12 (26.67%)	
	Rest of the world	72 (20.34%)	5 (11.11%)	
	(Missing)	0 (0.00%)	0 (0.00%)	
	Total	354 (100.00%)	45 (100.00%)	
Gleason score category 1	High [8-10]	257 (72.60%)	38 (84.44%)	0.161
	Low [2-4]	1 (0.28%)	0 (0.00%)	
	Medium [5-7]	88 (24.86%)	5 (11.11%)	

Baseline/Demographic Characteristics	Summary Statistics/ Category Level	F1LCDx-evaluable N=354	F1LCDx-unevaluable N=45	p-value
	(Missing)	8 (2.26%)	2 (4.44%)	
	Total	354 (100.00%)	45 (100.00%)	
Gleason score category 2	<=6	14 (3.95%)	0 (0.00%)	0.096
	7	75 (21.19%)	5 (11.11%)	
	8	73 (20.62%)	15 (33.33%)	
	9-10	184 (51.98%)	23 (51.11%)	
	(Missing)	8 (2.26%)	2 (4.44%)	
	Total	354 (100.00%)	45 (100.00%)	
Histopathological classification	ADENOCARCINOMA	352 (99.44%)	45 (100.00%)	1.000
	ADENOCARCINOMA WITH NEUROENDOCRINE FEATURES	2 (0.56%)	0 (0.00%)	
	(Missing)	0 (0.00%)	0 (0.00%)	
	Total	354 (100.00%)	45 (100.00%)	
Number of bone metastases at screening	0	65 (18.36%)	9 (20.00%)	0.647
	1-4	114 (32.20%)	12 (26.67%)	
	5-9	74 (20.90%)	7 (15.56%)	
	10-20	48 (13.56%)	9 (20.00%)	
	>20	53 (14.97%)	8 (17.78%)	
	(Missing)	0 (0.00%)	0 (0.00%)	
	Total	354 (100.00%)	45 (100.00%)	
Baseline pain score by Brief Pain Inventory-Short Form (BPI-SF)	0-1	226 (63.84%)	32 (71.11%)	0.476
	2-3	127 (35.88%)	13 (28.89%)	
	>3	1 (0.28%)	0 (0.00%)	
	(Missing)	0 (0.00%)	0 (0.00%)	
	Total	354 (100.00%)	45 (100.00%)	
Baseline serum Prostate-Specific Antigen (PSA) (ng/mL)	min	0.04	1.98	0.795
	Q1	6.60	8.67	
	median	19.60	17.15	
	mean	75.97	66.03	
	Q3	64.81	39.88	
	max	3412.00	713.20	
	SD	226.42	139.12	
	(Missing)	1 (0.28%)	1 (2.22%)	
Race	ASIAN	65 (18.36%)	19 (42.22%)	0.006
	BLACK OR AFRICAN AMERICAN	10 (2.82%)	1 (2.22%)	
	MULTIPLE	1 (0.28%)	0 (0.00%)	

Baseline/Demographic Characteristics	Summary Statistics/ Category Level	F1LCDx-evaluable N=354	F1LCDx-unevaluable N=45	p-value
	NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	2 (0.56%)	0 (0.00%)	
	WHITE	252 (71.19%)	21 (46.67%)	
	(Missing)	24 (6.78%)	4 (8.89%)	
	Total	354 (100.00%)	45 (100.00%)	
Race group	ASIAN	65 (18.36%)	19 (42.22%)	0.001
	NON-ASIAN	265 (74.86%)	22 (48.89%)	
	(Missing)	24 (6.78%)	4 (8.89%)	
	Total	354 (100.00%)	45 (100.00%)	
Renal impairment at baseline	Mild (60-89)	160 (45.20%)	16 (35.56%)	0.219
	Moderate (30-59)	38 (10.73%)	3 (6.67%)	
	Normal (>=90)	146 (41.24%)	25 (55.56%)	
	(Missing)	10 (2.82%)	1 (2.22%)	
	Total	354 (100.00%)	45 (100.00%)	
Time from primary diagnosis to randomization in months	min	5.49	8.31	0.023
	Q1	17.21	13.01	
	median	29.34	21.16	
	mean	46.82	32.03	
	Q3	63.40	39.36	
	max	216.57	125.50	
	SD	43.83	27.80	
	(Missing)	20 (5.65%)	0 (0.00%)	
TNM stage at diagnosis: M	M0	150 (42.37%)	18 (40.00%)	0.890
	M1	73 (20.62%)	10 (22.22%)	
	M1A	11 (3.11%)	0 (0.00%)	
	M1B	73 (20.62%)	11 (24.44%)	
	M1C	11 (3.11%)	2 (4.44%)	
	MX	32 (9.04%)	4 (8.89%)	
	(Missing)	4 (1.13%)	0 (0.00%)	
	Total	354 (100.00%)	45 (100.00%)	
TNM stage at diagnosis: N	N0	139 (39.27%)	13 (28.89%)	0.075
	N1	149 (42.09%)	18 (40.00%)	
	NX	59 (16.67%)	14 (31.11%)	
	(Missing)	7 (1.98%)	0 (0.00%)	
	Total	354 (100.00%)	45 (100.00%)	
TNM stage at diagnosis: T	T0	2 (0.56%)	0 (0.00%)	0.673
	T1	19 (5.37%)	1 (2.22%)	

Baseline/Demographic Characteristics	Summary Statistics/ Category Level	F1LCDx-evaluable N=354	F1LCDx-unevaluable N=45	p-value
	T2	72 (20.34%)	8 (17.78%)	
	T3	158 (44.63%)	18 (40.00%)	
	T4	48 (13.56%)	9 (20.00%)	
	TX	51 (14.41%)	9 (20.00%)	
	(Missing)	4 (1.13%)	0 (0.00%)	
	Total	354 (100.00%)	45 (100.00%)	
TNM stage at study entry: M	M0	2 (0.56%)	0 (0.00%)	0.771
	M1	166 (46.89%)	17 (37.78%)	
	M1A	25 (7.06%)	3 (6.67%)	
	M1B	120 (33.90%)	19 (42.22%)	
	M1C	36 (10.17%)	4 (8.89%)	
	MX	1 (0.28%)	0 (0.00%)	
	(Missing)	4 (1.13%)	2 (4.44%)	
	Total	354 (100.00%)	45 (100.00%)	
TNM stage at study entry: N	N0	131 (37.01%)	17 (37.78%)	0.810
	N1	154 (43.50%)	17 (37.78%)	
	NX	64 (18.08%)	9 (20.00%)	
	(Missing)	5 (1.41%)	2 (4.44%)	
	Total	354 (100.00%)	45 (100.00%)	
TNM stage at study entry: T	T0	17 (4.80%)	0 (0.00%)	0.490
	T1	9 (2.54%)	1 (2.22%)	
	T2	53 (14.97%)	5 (11.11%)	
	T3	96 (27.12%)	11 (24.44%)	
	T4	49 (13.84%)	10 (22.22%)	
	TX	125 (35.31%)	16 (35.56%)	
	(Missing)	5 (1.41%)	2 (4.44%)	
	Total	354 (100.00%)	45 (100.00%)	
Type of progression at study entry	Bone only	16 (4.52%)	2 (4.44%)	0.197
	Bone+soft tissue	9 (2.54%)	0 (0.00%)	
	PSA only	170 (48.02%)	27 (60.00%)	
	PSA+bone	76 (21.47%)	4 (8.89%)	
	PSA+bone+soft tissue	28 (7.91%)	3 (6.67%)	
	PSA+soft tissue	43 (12.15%)	5 (11.11%)	
	Soft tissue only	12 (3.39%)	4 (8.89%)	
	(Missing)	0 (0.00%)	0 (0.00%)	
	Total	354 (100.00%)	45 (100.00%)	
Weight	min	45.90	45.00	0.013

Baseline/Demographic Characteristics	Summary Statistics/ Category Level	F1LCDx-evaluable N=354	F1LCDx-unevaluable N=45	p-value
	Q1	73.43	70.00	
	median	82.05	76.80	
	mean	84.94	77.93	
	Q3	94.00	87.40	
	max	177.70	124.70	
	SD	17.82	15.03	
	(Missing)	0 (0.00%)	0 (0.00%)	

D. Safety and Effectiveness Results

1. Safety Results

The safety with respect to treatment with talazoparib in combination with enzalutamide was addressed during the review of the talazoparib in combination with enzalutamide NDA (No. NDA 211651/S-010) and is not addressed in detail in this Summary of Safety and Effectiveness Data. The evaluation of safety was based on the analysis of adverse events (AEs), clinical laboratory evaluations, physical examinations, and vital signs. Please refer to Drugs@FDA for complete safety information on TALZENNA® (talazoparib) in combination with XTANDI® (enzalutamide).

2. Effectiveness Results

The effectiveness of F1LCDx to identify patients with HRR gene alterations who may benefit from treatment with talazoparib in combination with enzalutamide is supported by the evaluation of the mCRPC patient population enrolled in TALAPRO-2 harboring HRR gene alterations. The efficacy analysis and sensitivity analysis of missing results are presented below.

i. Clinical Efficacy Results

The TALAPRO-2 study demonstrated that treatment with talazoparib in combination with abiraterone resulted in a clinically meaningful and statistically significant improvement in rPFS compared with placebo + enzalutamide in the HRR-deficient (HRRm) population (n=399).

The clinical validity of F1LCDx for the detection of HRR gene alterations in mCRPC patients was based on the F1LCDx+ subset based on the CDx biomarker definition (n=287) within the HRRm population from the TALAPRO-2 study. As presented in Table 25, in the F1LCDx HRRm population, the median rPFS was 22.14 months (95% two-sided CI: [16.59, non-estimable (NE)]) in the experimental treatment group and 11.07 months (95% two-sided CI: [10.91, 16.43]) in the placebo group as estimated by the Kaplan-Meier method. The estimated HR based on

stratified Cox regression models and the Breslow tie handling method was 0.48 (95% two-sided CI: [0.34, 0.69]) comparing the treatment group versus the placebo group.

Table 25. Efficacy analyses for F1LCDx HRRm population from Cohorts 1 and 2 in TALAPRO-2

	Total HRRm population (CTA+) n=399*		**F1LCDx**			
			HRRm population (CTA+|F1LCDx+) n=287		**Non- HRRm population (CTA+|F1LCDx-) n=67**	
	Talazoparib/ enzalutamide N =200	**Placebo/ enzalutamide** N = 199	**Talazoparib/ enzalutamide** N = 142	**Placebo/ enzalutamide** N = 145	**Talazoparib/ enzalutamide** N=37	**Placebo/ enzalutamide** N=30
rPFS Events, n (%)	66 (33)	104 (52)	53 (37)	74 (51)	7 (19)	12 (40)
Median rPFS (95% CI), months	NE(21.9, NE)	13.8 (11.0, 16.7)	22.14 (16.59, NE)	11.07 (10.91, 16.43)	NE (NE, NE)	27.40 (19.52 , NE)
Hazard ratio (95% CI)[a]	0.45 (0.33, 0.61)		0.48 (0.34, 0.69)		0.49 (0.19, 1.25)	

* Combined HRR-deficient population in the TALAPRO-2 study from Cohorts 1 and 2 (i.e., from drug primary efficacy population-169 from Cohort 1 and 230 from Cohort 2) based on prospective testing results only.
[a]Calculated using a stratified univariable Cox proportional hazards model

As presented in Table 25, patients without HRR alterations as determined by F1LCDx (n=67) had an estimated rPFS HR of 0.49 (95% two-sided CI: [0.19, 1.25)]. The efficacy observed in the F1LCDx negative subpopulation could be driven by patients in this subset being biomarker-positive by the tissue assay (F1CDx), which was a consequence of the biomarker testing strategy for patient stratification in Cohort 1 of the clinical trial.

In addition to the efficacy analysis based on Cohorts 1 and 2 to support the therapeutic approval, to further evaluate the clinical validity of F1LCDx, an additional efficacy analysis was conducted in the all-comers population of the TALAPRO-2 study (n=805, Cohort 1) using all available samples (i.e., by prospective or retrospective testing) with valid results. In the F1LCDx HRRm population from Cohort 1 (n=194), the median rPFS was 21.88 months (95% two-sided CI: [16.59, non-estimable (NE)]) in the experimental treatment group and 13.77 months (95% two-sided CI: [10.61, 22.47]) in the placebo group as estimated by the Kaplan-Meier method. The estimated HR was 0.59 (95% two-sided CI: [0.40, 0.88]) comparing the treatment group versus the placebo group (Table 26).

Patients in Cohort 1 of the TALAPRO-2 study without HRR alterations as determined by F1LCDx (n=494) had an estimated rPFS HR=0.72 (95% two-sided CI: [0.54, 0.95] (Table 26). The efficacy results in Cohort 1 further supported the clinical validity of F1LCDx for the detection of HRR gene alterations in mCRPC.

Table 26. Efficacy analyses for F1LCDx HRRm population in Cohort 1 (all-comers population) of the TALAPRO-2

	HRRm population (F1LCDx+) n=194		**Non-HRRm population (F1LCDx-) n=494**	
	Talazoparib/ enzalutamide	**Placebo/ enzalutamide**	**Talazoparib/ enzalutamide**	**Placebo/ enzalutamide**
	N = 94	N = 99	N=245	N=245
rPFS Events, n (%)	46 (49)	55 (55)	87 (35)	108 (44)
Median rPFS (95% CI), months	21.88 (16.59, NE)	13.77 (10.61, 22.47)	NE (33.05, NE)	25.13 (21.95 , NE)
Hazard ratio (95% CI)[a]	0.59 (0.40, 0.88)		0.72 (0.54, 0.95)	

*Total HRRm population in Cohort 1 of the TALAPRO-2 study based on prospective and retrospective testing results.
[a]Calculated using a stratified univariable Cox proportional hazards model

ii. Sensitivity Analysis for Missing CDx Results

A sensitivity analysis was conducted to assess the robustness of the clinical efficacy results accounting for the patients in the HRR-deficient (HRRm) population (n=399) with missing F1LCDx status (n=45). Samples were considered missing if they were not tested (n=15), or if they had positive HRR gene alteration status by non-F1LCDx assay (F1CDx, historical F1/F1CDx, or Interactive Web Response System IWRS) prior to randomization per the biomarker definition for clinical trial enrollment and had unevaluable HRR gene alteration status by F1LCDx (n=30). Following imputation, the HR estimated for rPFS based on the Cox proportional hazards model using the complete dataset was 0.43 (95% two-sided CI: [0.41, 0.45]) in the HRRm population as determined by F1LCDx testing.

iii. Concordance between F1LCDx and F1CDx

Patients with HRR gene alterations in TALAPRO-2 were identified prior to randomization by central testing of tumor tissue or blood samples (liquid

biopsy) using primarily the F1CDx and/or the F1LCDx assays. Concordance between F1LCDx and F1CDx was evaluated using all samples from Cohort 1 (i.e., the all-comers population, n=805) of the TALAPRO-2 clinical study (Table 27).
The PPA was 77.87% (95/122) with two-sided 95% confidence interval (69.72%, 84.32%), and NPA was 86.59% with two-sided 95% confidence interval (82.57%, 89.79%) after excluding F1LCDx and F1CDx unevaluable results (i.e., samples not tested or invalid).

Table 27. Concordance Between F1LCDx and F1CDx

		F1CDx			
		HRRm+	HRRm-	Unevaluable	Total
F1LCDx	HRRm+	95	46	53	194
	HRRm-	27	297	170	494
	Unevaluable	10	30	77	117
	Total	132	373	300	805
PPA (95% CI)		77.87% (69.72%, 84.32%)			
NPA (95% CI)		86.59% (82.57%, 89.79%)			

The discordances between F1CDx and F1LCDx were evaluated. Among the 27 patient samples with F1CDx+|F1LCDx- results, 22 samples had low tumor fraction in F1LCDx or variants were detected below the LoD for F1LCDx, 4 samples had no evidence of variant(s) detected by F1LCDx, and 1 sample had insufficient reporting read evidence. The rPFS HR for these patients was 0.09 [95% CI (0.01, 0.77)]. Among the 46 patient samples with F1CDx-|F1LCDx+ results, 29 samples had low tumor purity in F1CDx or variants were detected below the LoD for F1CDx, 6 were reported with a Qualified QC status which may impact variant calling sensitivity, and 11 samples had no evidence of variant(s) detected by F1CDx. The rPFS HR for these patients was 0.72 [95% CI (0.25, 2.02)].

Based on the PPA between F1LCDx and F1CDx, F1LCDx may miss a proportion of patients with mCRPC with HRR gene alterations who may derive benefit from talazoparib in combination with enzalutamide. Therefore, reflex testing using tissue specimens with an FDA approved tissue test will be required, if feasible, if the plasma test is negative.

3. Pediatric Extrapolation

Patients aged 18 years of older were eligible for enrollment into the TALAPRO-2 study if they fulfilled other inclusion criteria. The youngest patient enrolled in the study was 41 years of age. For the TALAPRO-2 study, data from adult patients aged 41 years and older are considered generalizable to the device pediatric population

aged 18-21 years and can be relied on to establish safety and effectiveness within the 18-21 years age group.

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included one investigator who was a full-time or part-time employee of the sponsor and the investigator had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: [0]
- Significant payment of other sorts: [0]
- Proprietary interest in the product tested held by the investigator: [1]
- Significant equity interest held by investigator in sponsor of covered study: [0]

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Molecular and Clinical Genetics Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The effectiveness of F1LCDx to identify prostate cancer patients with HRR gene alterations who may benefit from TALZENNA® (talazoparib) in combination with XTANDI® (enzalutamide) treatment is supported by the results from the clinical validation study. This study was performed using specimens from patients enrolled in the TALAPRO-2 clinical trial with HRR gene altered status. The data from the analytical validation and clinical validation studies support the reasonable assurance of safety and effectiveness of the F1LCDx assay when used in accordance with the indications for use. Data from the TALAPRO-2 trial show that patients who had HRR gene alterations, received benefit from treatment with talazoparib in combination with enzalutamide and support the addition of this CDx indication to F1LCDx. The

clinical validation study demonstrated the ability of F1LCDx to detect HRR gene altered patients that benefit from TALZENNA® (talazoparib) in combination with XTANDI® (enzalutamide).

B. Safety Conclusions

The risks of the device are based on data collected in the analytical studies conducted to support PMA approval as described above. The F1LCDx assay is an *in vitro* diagnostic test, which involves testing of cfDNA extracted from blood or plasma.

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 listed in Table 1 of the intended use statement 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 the indicated therapy.

C. Benefit-Risk Determination

The probable benefits of F1LCDx in identification of HRR gene alterations for patients with metastatic castration resistant prostate cancer, for treatment with TALZENNA® (talazoparib) in combination with XTANDI® (enzalutamide) are based on data collected in the TALAPRO-2 clinical trial and this device clinical validation study. This drug combination is indicated for the first-line treatment of metastatic castration-resistant prostate cancer (mCRPC) in patients with HRR gene alterations using a 12-gene HRR panel (*BRCA1, BRCA2, ATM, ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C*).

The clinical benefit of the F1LCDx assay for the selection of metastatic castration resistant prostate cancer patients with HRR gene alterations, in this clinical setting, was demonstrated in a clinical validation study using samples from patients enrolled in the TALAPRO-2 clinical study, indicating substantial and clinically meaningful benefit in selecting patients more likely to respond to this drug combination, which has substantial clinical relevance given the toxicity profile of this drug combination.

In the F1LCDx+ HRR-deficient population (n=287, i.e., 287 out of 399 HRRm from the drug efficacy population), patients demonstrated substantial clinical benefit with a median radiographic progression-free survival (rPFS) of 22.14 months (95% CI: 16.59, non-estimable) in the talazoparib plus enzalutamide arm compared to 11.07 months (95% CI: 10.91, 16.43) in the placebo plus enzalutamide arm, representing an absolute benefit of approximately 11 months. This represents a clinically meaningful 52% reduction in the risk of disease progression or death (HR=0.48, 95% CI: 0.34, 0.69).

Importantly, the additional analysis with all-comers from Cohort 1 (n=805) provides critical evidence in the actual intent-to-treat population of the device's probable clinical benefit in an unselected population. In this cohort, F1LCDx+ patients (n=194) achieved a median rPFS of 21.88 months (95% CI: 16.59, non-estimable) versus 13.77 months (95% CI: 10.61, 22.47) in the placebo arm (HR=0.59, 95% CI: 0.40, 0.88). In contrast, F1LCDx- patients (n=494) showed a more modest treatment effect with median rPFS not reached in either arm but with HR=0.72 (95% CI: 0.54, 0.95). This differential treatment effect between F1LCDx+ and F1LCDx- populations demonstrates the value of the device in effectively identifying patients most likely to benefit from the combination therapy, which is substantially meaningful, given the toxicity profile of the drug.

Probable Risks:
There is potential risk associated with the use of this device, mainly due to 1) false positive, false negatives, or failure to provide a result, and 2) incorrect interpretation of test results by the user. The risks of the F1LCDx assay are associated with the potential mismanagement of patients resulting from false results of the test. Patients who are determined to be false positive by the test may be exposed to TALZENNA® (talazoparib) in combination with XTANDI® (enzalutamide), a drug that may lead to significant clinical adverse events without probable benefit or may have delayed access to treatments that could be more beneficial. A false negative result may prevent a patient from accessing a potentially beneficial drug.

The risk of false results is partially mitigated by clinical and analytical studies presented above. The F1LCDx does not detect homozygous deletions in non-BRCA HRR genes. In addition, the representation of HRR gene short variants and rearrangements was limited in the analytical validation studies and may not be detected consistently by F1LCDx. To address these issues, we modified two of the existing limitations to mitigate the risks of this test:

The FoundationOne Liquid CDx assay does not report copy number losses/homozygous deletions in *ATM, ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2*, and *RAD51C*. The prevalence of homozygous deletions in these genes ranges from 0-2.83% based on TALAPRO-2 trial data and 0-1.64% based on publicly available prostate cancer databases.

The representation of short variants and rearrangements in *ATM, ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2*, and *RAD51C* was limited in the analytical validation studies.

The risks of false negative results are demonstrated by the subset of patients who were F1CDx+|F1LCDx- (tissue positive but liquid negative). In the all-comers Cohort 1, 27 patients (3.4% of total cohort) fell into this category. While this represents a small proportion of patients, these individuals showed a trend of treatment benefit with HR=0.72 (95% CI: 0.25, 2.02), suggesting they may derive clinical benefit

despite negative liquid biopsy results; thus, this device does have a certain probable risk of false negative results, for responders to the drug combination. The concordance analysis between F1LCDx and F1CDx, conditional on the FFPE based F1CDx device, demonstrated a positive percent agreement of 77.87% (95% CI: 69.72%, 84.32%), indicating that approximately 22% of tissue-positive patients may not be identified by liquid biopsy. This risk is partially mitigated by a recommendation in the F1LCDx technical label that those patients whose plasma generates a negative result for those alterations included in Table 1, including HRR gene (*BRCA1, BRCA2, ATM, ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C*) alterations, should have their tumor mutation status reflexively tested using an FDA-approved tumor tissue test, if feasible.

Additional factors to consider in determining probable risks and benefits for F1LCDx included the availability of alternative tests. Of note, there are no FDA-approved CDx alternatives using cfDNA isolated from plasma for the detection of patients with mCRPC for treatment with TALZENNA® (talazoparib) in combination with XTANDI® (enzalutamide), and this device may meet an unmet clinical need; however, there is an FDA-approved tissue test available for the identification of patients with mCRPC with HRR gene (*BRCA1, BRCA2, ATM, ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C*) alterations for treatment with TALZENNA® (talazoparib) in combination with XTANDI® (enzalutamide). The advantage of F1LCDx over the FDA-approved tissue test is that it offers a non-invasive method to obtain DNA from the cancer, rather than a tissue biopsy, which may be difficult to obtain in mCRPC and may meet an unmet need for patients who cannot otherwise provide a biopsy.

The overall clinical and analytical performance of the device included in this submission demonstrate that the assay is expected to perform with reasonable accuracy, mitigating the potential for false results, and the assay selects patients more likely to have a favorable response to the drug combination, which is especially important given the toxicity profile of the aforementioned combination. In addition, to supplement the premarket data, some post-market studies are planned as summarized in Section XIV, below.

1. Patient Perspective
   This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above, the data support that for the F1LCDx assay, and the indications noted in the intended use statement, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Data from the analytical and clinical studies support the performance of F1LCDx as an aid for the identification of HRR gene alterations in patients with prostate cancer for whom TALZENNA® (talazoparib) in combination with XTANDI® (enzalutamide) may be indicated.

XIV. CDRH DECISION

CDRH issued an approval order for the PMA (P190032/S029) on May 27, 2026.

Foundation Medicine, Inc. (FMI) must provide the following software information in a post-approval report within 6 months of approval of this PMA supplement:

FMI will provide evidence, acceptable to FDA, that performance expectations with the currently deployed Genomics Platform Analysis Pipeline (AP), including the version at the time of the submission of your sPMA (v3.39.0), are representative of the performance in the clinical and analytical validation studies in P190032/S029. Such evidence may include regression testing using the clinical and analytical datasets to perform in silico reanalysis of the results obtained in the clinical and analytical validation studies in this supplement and confirmation that there is little or no deviation in the quality metrics for each of the samples to support the accuracy and precision of F1LCDx remain the same.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality Management System (QMSR) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

None.