December 13, 2018

Medical Device Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Program 01, Diagnostic program
Term Name	Software for gene variants analysis (for comprehensive genomic profiling for cancer) Software for analysis of somatic variants (for eligibility identification of antineoplastic agents) (to be newly established)
Brand Name	FoundationOne CDx Cancer Genomic Profile
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	March 16, 2018 (Application for marketing approval)

Results of Deliberation

In the meeting held on December 13, 2018, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and concluded that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not designated as a medical device subject to a use-results survey. The product should be approved with the following conditions. The product is classified as a specially controlled medical device, and not classified as a specially designated maintenance-and-management-required medical device. The product is not classified as a biological product or a specified biological product.

Conditions of Approval of the Marketing Application

1. The applicant is required to take necessary measures to ensure that physicians with adequate knowledge and experience in cancer genomic medicine determine the patient's eligibility for and timing of genetic testing in accordance with the latest guidelines developed by related academic societies and that the physicians use the product at medical institutions capable of providing diagnosis and treatment based on cancer genomic profiling in a manner that fulfills the requirements of the guidance on designation of core hospitals for cancer genomic medicine.

2. The applicant is required to perform appropriate procedures and controls for protecting personal information concerning tumor tissue specimens sent to the laboratory and associated information

and to implement up-to-date data security and privacy measures for preventing unauthorized access to relevant data and information.

3. The applicant is required to perform quality control of input data as described in the Remarks column of the Application Form. Any changes to the quality control of input data as described in the Remarks column of the Application Form (excluding minor changes defined by the Ordinance of the Ministry of Health, Welfare and Labour, as specified under Article 23-2-5, Paragraph 11 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics [PMD Act]) must be approved by the Minister of Health, Welfare and Labour pursuant to Article 23-2-5, Paragraph 11 of the PMD Act. Note that the provisions of Article 23-2-5, Paragraph 13; Article 23-2-6; and Article 23-2-7 of the PMD Act are applicable mutatis mutandis to the approval of said changes.

Review Report

November 19, 2018
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following medical device submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

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Term Name	Software for gene variants analysis (for comprehensive genomic profiling for cancer) Software for analysis of somatic variants (for eligibility identification of antineoplastic agents) (to be newly established)
Brand Name	FoundationOne CDx Cancer Genomic Profile
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	March 16, 2018
Items Warranting Special Mention	Expedited review
Reviewing Office	Office of *In Vitro* Diagnostics, Office of Medical Devices I

Review Results

November 19, 2018

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Brand Name	FoundationOne CDx Cancer Genomic Profile
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	March 16, 2018
Items Warranting Special Mention	Expedited review

Results of Review

FoundationOne CDx Cancer Genomic Profile (hereinafter referred to as "F1CDx") is an analysis software program that provides information on genetic mutations (hereinafter referred to as "mutations") on the basis of comprehensive genomic profiling of 324 cancer-related genes collected from patients with solid tumors. Such information may assist physicians developing treatment plans and determining treatment options for individual patients. Tumor tissue specimens (including cytology specimens) are sent from ordering medical institutions in Japan to Foundation Medicine, Inc. (FMI), a US testing laboratory, in which the specimens are subjected to targeted gene sequencing. The obtained sequence data were analyzed in an automated fashion by the genetic testing system using F1CDx (hereinafter referred to as "F1CDx System") to detect base substitutions, insertion and deletion alterations (indels), copy number alterations, and fusion genes (rearrangements) that may inform treatment options, to determine the microsatellite instability (MSI) status, and to calculate the tumor mutational burden (TMB) score. The sequence data analysis is followed by the data review process that checks the quality of specimens, etc. and then by generation of an extensible markup language (XML) file summarizing all information obtained. The XML file is presented to the ordering physician or other healthcare professionals in Japan through a telecommunication line. F1CDx outputs information on mutations that may inform treatment options for individual patients, information on other mutations that may be helpful in developing treatment plans, MSI status, TMB score, and others.

The Expert Meeting for Cancer Genomic Medicine Promotion Consortium (hereinafter referred to as "Expert Meeting") is held to discuss the promotion of cancer genomic medicine that enables the optimal therapy to be identified for individual patients with cancer according to genomic information derived from tumor tissue of each patient. In line with recommendations from the Expert Meeting, a system for diagnosis and treatment of cancer is being developed centered on core hospitals for cancer genomic medicine, and the Center for Cancer Genomics and Advanced Therapeutics (C-CAT) was

established to facilitate the accumulation and provision of cancer genomic information. The Clinical Practice Guidance for Next-Generation Sequencing in Cancer Diagnosis and Treatment (Edition 1.0) jointly issued by the Japanese Society of Medical Oncology, the Japan Society of Clinical Oncology, and the Japanese Cancer Association (hereinafter referred to as “Trilateral Academic Society Guidance”) describes their current position on utilization of gene panel testing in cancer genomic medicine. The Pharmaceuticals and Medical Devices Agency (PMDA) considers that the implementation structure for cancer genomic medicine recommended by the Expert Meeting and the relevant academic societies’ position described in the above guidance currently represent the optimal approaches determined by specialists in cancer genomic medicine with consideration to needs for personalized medicine in clinical settings in Japan. Once gene panel testing is introduced into clinical practice in Japan to obtain comprehensive information on cancer-related gene mutations (comprehensive genomic profiling [CGP]), its clinical utility can be sufficiently promising. On the assumption that the above implementation structure, etc. have already been in place, PMDA evaluated the clinical performance of F1CDx System as gene panel testing on the basis of the appropriateness of the selected targeted genes, the appropriateness of sensitivity for detection of the target mutations, and the appropriateness of generation and contents of reports of sequencing test results.

F1CDx System is designed to analyze 324 genes selected to cover genes whose mutations are found in patients with solid tumors. The targeted genes include those reportedly related to molecular-targeted therapies for which companion diagnostics or biomarkers have been approved or are being developing, or and those reportedly associated with tumor development, growth, or suppression. On the basis of the above information, PMDA has concluded that the selected targeted genes appropriately cover all genes and their variants that are currently adequate for CGP.

To prove the appropriateness of the sensitivity for detection of the target mutations, the applicant submitted the supporting data for accuracy, precision, specificity, the limit of blank, the limit of detection, interfering substances, effect of tissue type, and performance of F1CDx System as a companion diagnostic system. Representative variants including base substitutions, indels, copy number alterations, and fusion genes were selected to evaluate the performance of F1CDx System detecting those variants for CGP. Comparator assays were chosen to evaluate the accuracy of F1CDx System, because only a limited number of approved companion diagnostics, etc. are available in and outside Japan. The above approaches were considered acceptable. PMDA concluded that F1CDx System has clinical performance that meets requirements for CGP of specimens from patients who have no treatment options. PMDA also concluded that F1CDx System possesses a sufficient clinical performance as a companion diagnostic system to identify patients with solid tumors who may benefit from treatment with specific therapy, because studies demonstrated analytical concordance between F1CDx System and other companion diagnostics approved in Japan.

PMDA also concluded that the result report generation process, including the analysis process through to report output, was appropriately managed according to the mutation detection criteria, data quality criteria, and report output criteria. In the analysis process of F1CDx System, clinically known and

public databases (DBs) (e.g., COSMIC, dbSNP, and ExAC) are searched in determining the categories of detected mutations to be described in the reports. The category of each variant will be updated on the basis of publicly known information and according to predefined criteria. Thus, there is no problem with classification of variants. The categories of some variants in the DBs are defined and changed in accordance with the in-house criteria of FMI. However, the assigned categories and their changes will not have a direct impact on the development of treatment plans because the output results of the F1CDx assay will be reviewed by specialists at the core hospitals in Japan before the development of treatment plans. On the basis of the above, PMDA concluded that there was no problem with the quality of mutation information presented by F1CDx System and that changes to the information need not be checked each time they are made after commercialization of F1CDx.

The proposed statement for the intended use of F1CDx was modified for the following reasons: (1) the intended patient population should be decided in accordance with relevant guidelines appropriate for each cancer type and (2) the positioning of CGP for each cancer type may change as more findings accumulate in the future.

On the basis of the above overall evaluation and the conclusion of the Expert Discussion, PMDA concluded that the efficacy and safety of F1CDx were demonstrated by the data submitted.

As a result of its review, PMDA has concluded that F1CDx may be approved for the following intended use, with the following conditions, and that the results should be presented to the Committee on Medical Devices and *In-vitro* Diagnostics for further deliberation.

Intended Use

- F1CDx is intended to provide comprehensive genomic profiling of tumor tissues from patients with solid tumors.
- F1CDx is intended to serve as a companion diagnostic to identify patients who may benefit from treatment with therapeutic drugs listed in the table below.

Alterations	Cancer type	Associated drugs
EGFR exon 19 deletions and *EGFR* exon 21 L858R alterations	Non-small cell lung cancer	Afatinib maleate, erlotinib hydrochloride, gefitinib, osimertinib mesilate
EGFR exon 20 T790M alterations		Osimertinib mesilate
ALK fusion genes		Alectinib hydrochloride, crizotinib, ceritinib
BRAF V600E and V600K alterations	Malignant melanoma	Dabrafenib mesilate, trametinib dimethyl sulfoxide, vemurafenib
ERBB2 copy number alterations (*HER*2 gene amplification positive)	Breast cancer	Trastuzumab (genetical recombination)
KRAS/*NRAS* wild-type	Colorectal cancer	Cetuximab (genetical recombination), panitumumab (genetical recombination)

Conditions of Approval

1. The applicant is required to take necessary measures to ensure that physicians with adequate knowledge and experience in cancer genomic medicine determine the patient's eligibility for and

timing of genetic testing in accordance with the latest guidelines developed by related academic societies and that the physicians use the product at medical institutions capable of providing diagnosis and treatment based on cancer genomic profiling in a manner that fulfills the requirements of the guidance on designation of core hospitals for cancer genomic medicine.

2. The applicant is required to perform appropriate procedures and controls for protecting personal information concerning tumor tissue specimens sent to the laboratory and associated information and to implement up-to-date data security and privacy measures for preventing unauthorized access to relevant data and information.

3. The applicant is required to perform quality control of input data as described in the Remarks column of the Application Form. Any changes to the quality control of input data as described in the Remarks column of the Application Form (excluding minor changes defined by the Ordinance of the Ministry of Health, Welfare and Labour, as specified under Article 23-2-5, Paragraph 11 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics [PMD Act]) must be approved by the Minister of Health, Welfare and Labour pursuant to Article 23-2-5, Paragraph 11 of the PMD Act. Note that the provisions of Article 23-2-5, Paragraph 13; Article 23-2-6; and Article 23-2-7 of the PMD Act are applicable mutatis mutandis to the approval of said changes.

Review Report

November 19, 2018

Product Submitted for Approval

Classification Program 01, Diagnostic program

Term Name Software for gene variants analysis (for comprehensive genomic profiling for cancer)
Software for analysis of somatic variants (for eligibility identification of antineoplastic agents) (to be newly established)

Brand Name FoundationOne CDx Cancer Genomic Profile

Applicant Chugai Pharmaceutical Co., Ltd.

Date of Application March 16, 2018

Proposed Intended Use F1CDx is a software program that analyzes mutations in genomic DNA extracted from tumor tissues or cells from patients with solid tumors and then provides the following information in an integrated manner in order to support physicians in making diagnosis and treatment plans:

- Comprehensive profiling of mutations in cancer-related genes (which assists physicians in making diagnosis and treatment plans)
- Microsatellite instability (MSI) status and tumor mutational burden (TMB) score (either of which can be used to support physicians in making treatment plans for patients who are eligible for cancer immunotherapy)
- Test results showing the gene mutations and other alterations listed in the table below (used as an aid for identifying patients with specific cancer types who may benefit from treatment with the targeted therapeutic drugs)

Alterations	Cancer type	Associated therapeutic drugs
EGFR exon 19 deletions and *EGFR* exon 21 L858R alterations	Non-small cell lung cancer	Afatinib maleate, erlotinib hydrochloride, gefitinib
EGFR exon 20 T790M alterations		Osimertinib mesilate
ALK fusion genes		Alectinib hydrochloride, crizotinib, ceritinib
BRAF V600E and V600K alterations	Malignant melanoma	Dabrafenib mesilate, trametinib dimethyl sulfoxide, vemurafenib
ERBB2 copy number alterations (*HER*2 gene amplification positive)	Breast cancer	Trastuzumab (genetical recombination), trastuzumab emtansine (genetical recombination), pertuzumab (genetical recombination), lapatinib tosilate hydrate

Alterations	Cancer type	Associated therapeutic drugs
KRAS/*NRAS* wild-type	Colorectal cancer	Cetuximab (genetical recombination), panitumumab (genetical recombination)

Items Warranting Special Mention

Expedited review

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List of Abbreviations

ALK	Anaplastic Lymphoma Kinase
AR	Androgen Receptor
BAM	Binary Alignment Map
BRAF	v-raf murine sarcoma viral oncogene homolog B1
C-CAT	Center for Cancer Genomics and Advanced Therapeutics
CCD	Comparative Companion Diagnostics
CCND1	Cyclin D1
CDx	Companion Diagnostics
CGP	Comprehensive Genomic Profiling
CLIA	Clinical Laboratory Improvement Amendments
DNA	Deoxyribonucleic Acid
EGFR	Epidermal Growth Factor Receptor
ERBB2	erb-b2 Receptor Tyrosine Kinase 2
FDA	Food and Drug Administration
FFPE	Formalin Fixed Paraffin Embedded
FISH	Fluorescence *in situ* Hybridization
FMI	Foundation Medicine, Inc.
HER2	Human Epidermal Growth Factor Receptor 2
IPsec	Security Architecture for Internet Protocol
KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS Proto-oncogene, GTPase)
MAF	Mutant Allele Frequency
MMR	MisMatch Repair
MSI	Micro Satellite Instability
NPA	Negative Percent Agreement
NRAS	Neuroblastoma RAS viral oncogene homolog (NRAS proto-oncogene, GTPase)
PCR	Polymerase Chain Reaction
PTEN	Phosphatase and tensin homolog
SNP	Single Nucleotide Polymorphism
TMB	Tumor Mutation Burden
VPN	Virtual Private Network
VUS	Variant of Unknown Significance
XML	eXtensible Markup Language

I. Product Overview

FoundationOne CDx Cancer Genomic Profile ("F1CDx") is an analysis software program that provides information on genetic mutations (hereinafter referred to as "mutations") on the basis of comprehensive profiling of 324 cancer-related genes collected from patients with solid tumors. Such information may support physicians in developing treatment plans and determining treatment options for individual patients. Figure 1 shows the flowchart of the analysis process by a genetic testing system using F1CDx ("F1CDx System").

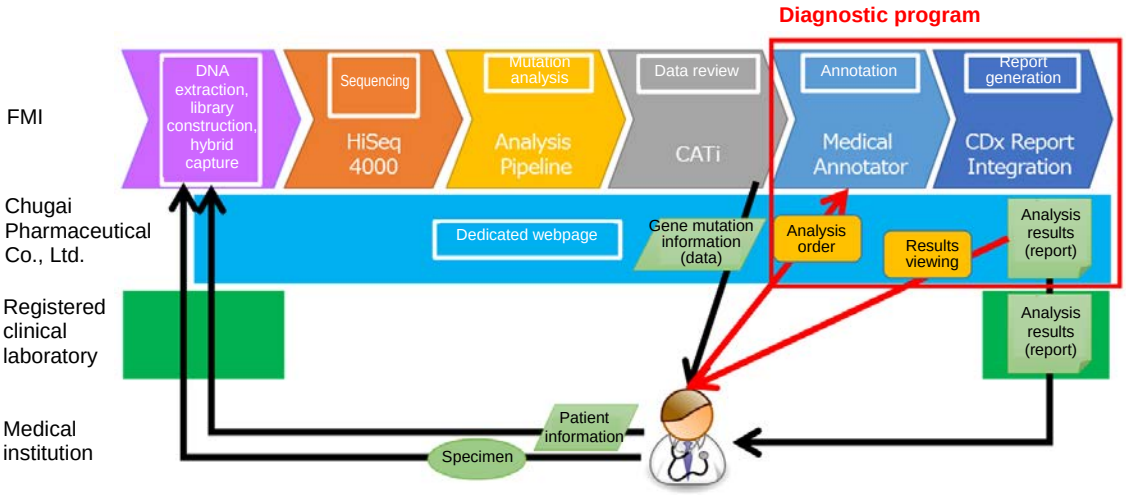

Figure 1. Flowchart of analysis process by F1CDx System

First, formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens (including cytology specimens) of each patient prepared at medical institutions in Japan are sent to Foundation Medicine, Inc. (FMI), a US laboratory, via registered clinical laboratories in Japan (hereinafter referred to as "registered clinical labs"). The analysis process at FMI consists of deoxyribonucleic acid (DNA) extraction from FFPE tumor tissue specimens, library construction (DNA fragmentation, addition of adapter sequences, and amplification by Polymerase Chain Reaction [PCR]), targeted enrichment of genomic DNA region by hybrid capture, and targeted DNA sequencing by a DNA sequencer (Illumina HiSeq 4000). The sequence data obtained are then analyzed in a fully automated manner to detect possibly clinically significant substitutions, insertion and deletion alterations (indels), copy number alterations, and fusion genes, determine microsatellite instability (MSI) status, and calculate a tumor mutational burden (TMB) score. The subsequent data review process checks [redacted][i] resulting in generation of an extensible markup language (XML) file summarizing all information obtained.

The XML file generated after the above processes is presented as an interim report to the ordering physician in Japan through a telecommunication line. After reviewing the presented data, the ordering

[i] [redacted]

physician orders F1CDx to analyze the data as input information by assessing the presence of mutations that may inform treatment options for individual patients and other mutations that may be helpful in developing treatment plans, the MSI status, and the TMB score. Then, F1CDx outputs the results. The analysis results provided by F1CDx are presented to the ordering physician through a telecommunication line. A paper-based report containing the same analysis results is separately sent to the physician via a registered clinical lab.

The analysis report comes with a report containing scientific findings related to mutations detected, information on therapeutic products associated with the mutations, information on clinical studies ongoing in and outside Japan, and others. These are regarded as additional information not within the scope of approval.

II. Summary of the Data Submitted and the Outline of Review Conducted by the Pharmaceuticals and Medical Devices Agency

The data submitted by the applicant in support of the application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

The expert advisors for the Expert Discussion on F1CDx declared that it does not fall under Item 5 of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/20 dated December 25, 2008).

1. History of Development, Use in Foreign Countries, and Other Information

1.A Summary of the submitted data

1.A.(1) History of development

F1CDx System was developed based on laboratory-developed tests, FoundationOne (previous generation of F1CDx, hereinafter referred to as "F1") and FoundationFocus CDx_{BRACA}. The former was commercialized by FMI in 2012 and the latter was approved in 2016 by the Food and Drug Administration (FDA) as a companion diagnostic for rucaparib. F1 is used to identify available treatment options for patients with solid tumors on the basis of the results of analysis of [redacted] genes. In the US, it has been used in [redacted] cases by the end of March 2018. Clinical research of F1 in patients with different cancer types showed that variants that might inform treatment options were detected in 83% to 95% of patients (as of August 17, 2017), of whom 11% to 34% had individual treatment plans developed based on their analysis results.[1-5]

Considering that the previous generation of F1CDx has been used in the above-mentioned overseas clinical research and that the necessity of cancer genomic medicine is being more widely recognized in and outside Japan, the applicant submitted the marketing application for F1CDx providing genomic profiling that may support physicians in developing treatment plans and determining treatment options for individual patients on the basis of the information on mutations detected.

1.A.(2) Use in foreign countries

F1CDx System was approved in the US in November 2017 for the following intended use: F1CDx is intended to be used for detecting mutations in *epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), v-raf murine sarcoma viral oncogene homolog B1 (BRAF), erb-b2 receptor tyrosine kinase 2 (ERBB2), v-Ki-ras2 kirsten rat sarcoma viral oncogene homolog (KRAS), neuroblastoma RAS viral oncogene homolog (NRAS)*, *BRCA1*, and *BRCA2* genes; developing treatment plans based on MSI status and TMB score; obtaining comprehensive genomic profile to help medical experts to develop treatment strategies in accordance with relevant academic society guidelines. F1CDx has been used in [redacted] cases by October 26, 2018. In the EU, F1CDx obtained the CE mark for the same intended use as of June 5, 2018. F1CDx was under preparation for commercialization as of October 26, 2018, and there is no experience of use in the EU.

As of October 26, 2018, F1CDx is not approved in any countries other than the US and EU.

1.A.(3) Malfunction report for F1CDx

No malfunction of F1CDx was reported overseas as of October 26, 2018.

2. Data Relating to Design and Development

2.(1) Performance and safety specifications

2.(1).A Summary of the submitted data

Specifications for [redacted] has been included in the performance specifications of F1CDx. To assure the quality of input data, specifications for [redacted], [redacted], [redacted], and [redacted] have been established for quality control [redacted] of input data described in the Remarks column of the attached Application Form.

2.(1).B Outline of the review conducted by PMDA

PMDA reviewed the data relating to the performance and safety specifications established by the applicant and concluded that there was no particular problem with these specifications.

2.(2) Safety

2.(2).A Summary of the submitted data

The safety of F1CDx System was confirmed in the assessment of conformity to the Essential Principles. No safety data were submitted.

2.(2).B Outline of the review conducted by PMDA

After considering the positioning and operational procedures of F1CDx System based on the performance study results later described in Section II.2.(3), PMDA concluded that there was no particular problem with safety.

2.(3) Performance

2.(3).A Summary of the submitted data

The applicant submitted data relating to the quality and performance of assays that generate mutation information (XML file) to be input in F1CDx. The data are presented in Sections 2.(3).A.1) to 2.(3).A.4).

2.(3).A.1) Selection of target genes

A total of 324 genes are selected as target genes to be analyzed by F1CDx System, and their variants found in patients with solid tumors are reportedly related to molecular-targeted drugs that have been approved or are being developed, or to tumor cell growth or suppression.

2.(3).A.2) Sequence analysis

The sequence data provided by a DNA sequencer are analyzed by special software developed by FMI (Analysis Pipeline). The analysis process by Analysis Pipeline consists of 3 automated processes. In the primary analysis process, binary base call (BCL) files are generated from image data and converted to a QSEQ file for each read. In the secondary analysis process, Analysis Pipeline segregates data for each specimen from the whole data according to the specimen-specific barcode sequence and generates a FASTQ file with the quality information of each read added to the base sequence information. After that, the sequence data are mapped to the reference sequence (hg19), and then a Binary Alignment Map (BAM) file added with [redacted] and other information is generated. The tertiary analysis process consists of i) detection of base substitutions, ii) detection of indels, iii) detection of copy number alterations, iv) detection of fusion genes, v) QC analysis, vi) determination of MSI status, vii) calculation of TMB score, and viii) data aggregation. Throughout this process, the BAM file generated is cross-checked against the reference file.

At FMI, alterations are classified based on the information from external databases (DBs) (e.g., COSMIC, dbSNP, and ExAC) and an in-house DB (FMI DB), as well as [redacted] and according to the definitions shown in Table 1, and described as [redacted]. In the steps of i) to iv) in the tertiary analysis process, [redacted], alterations classified as “Known” or “Likely,” or variants classified as “Unknown” are output as mutations when they meet the criteria in Table 2.

Table 1. Classification of alterations

Category	Definition
Known	Alterations listed in COSMIC or other DBs referenced by Analysis Pipeline to identify cancer-related genes, or those that should be classified as "Known" in accordance with [redacted]
Likely	Alterations that have no documented evidence of being directly associated with cancer, but are listed as those having functional significance as determined by other alteration analysis.
Unknown	Variants that have not enough evidence to be classified as "Known" or "Likely," but are not typical single nucleotide polymorphism (SNP)

Table 2. Criteria for alteration detection

Alteration type	Acceptance criteria
Base substitution	Mutant allele frequency (MAF) ≥5% (≥1% in hotspot locations[ii])
Insertion/deletion alteration	MAF ≥5% (≥3% in hotspot locations[ii])
Copy number alteration	Tumor purity ≥20% Gene amplification: ≥6 copies for diploid (or ≥5 copies in *ERBB2*), ≥7 copies for triploid, ≥8 copies for tetraploid Homozygous deletion: 0 copies
Fusion genes (genomic rearrangements[iii])	≥5 read-pairs aligned on different chromosomes or ≥10 Mbp apart (≥3 read-pairs for known fusion genes) Truncations[iv], deletions[v], duplications[vi], and rearrangements[vii] that meet this criterion are also detected.

In the process vi), MSI status is determined according to a change in the length of selected 95 intronic homopolymer repeat loci. In the process vii), synonymous and non-synonymous variants present at ≥5% allele frequency are counted, and potential germline alterations are filtered out according to published databases including dbSNP and ExAC and using somatic-germline/zygosity (SGZ) algorism. Furthermore, known and likely driver mutations are filtered to exclude bias of the data set. Then, TMB score is calculated from the total number of remaining variants and the size of the target region. These analysis results and the QC metrics determined in the process v) are aggregated in the process viii) and output as an XML file.

The XML file output is reviewed by trained bioinformaticians using FMI custom-developed software ([redacted]). In this process, [redacted] is performed. Final alteration category and data quality information are saved as an XML file. The results of review by FMI bioinformaticians have been shown to be consistent across them.[viii]

[ii] Locations where potential driver mutations frequently occur as indicated by evidence reported in publications, etc. These locations are listed by gene as reference file, etc. of Analysis Pipeline.

[iii] In this report, fusion genes are primarily described as representative alterations of clinical significance. However, in the description of performance evaluation, etc., of alterations, including truncations, deletions, duplications, and rearrangements, the term "genomic rearrangement" is also used.

[iv] Includes 3'- or 5'- terminal deletion

[v] Deletion of some internal exons

[vi] Duplication of some exons

[vii] Rearrangements with an unclear structure or possibly damaging mutations

[viii] Concordance tests among 3 randomly selected bioinformaticians demonstrated the following:

2.(3).A.3) Generation of analysis report

The XML file generated in the sequence analysis process is presented to the ordering physicians through a telecommunication line. Upon receipt of an order from the ordering physician, Medical Annotator software analyzes the XML file data as input information to identify the baseline disease characteristics of the patient and to detect any mutations associated with companion diagnostic claims and drug-resistant mutations. The analysis results are presented in the analysis report with mutations associated with companion diagnostic claims being displayed as "CDx Associated Findings" and other mutations that may be helpful in developing treatment plans (e.g., precautions for mutations classified as Known or Likely, MSI status, TMB score, and some drug-resistant mutations) as "Other alterations and biomarkers identified." The report presented to ordering physicians does not contain a classification of Known or Likely. Variants classified as Unknown are displayed as variants of unknown significance (VUS) in Appendix of the analysis report.

2.(3).A.4) Analytical performance

To support the analytical performance of F1CDx system, the applicant submitted the data for accuracy, precision, specificity, the limit of blank, the limit of detection, the interfering substances, effect of tissue type, comparability with the previous generation of this system, and performance as a companion diagnostic system. The results were summarized below.

2.(3).A.4).(a) Accuracy

- Base substitutions, and insertion/deletion alterations (indels)

  A total of 188 specimens derived from 46 types of cancers, including lung, breast, colorectal, skin, and orphan cancers, were analyzed with F1CDx System and an external gene panel (University of Washington OncoPlex Cancer Gene Panel)[6] whose analytical performance had been validated in the US, as a comparator to determine the concordance between the 2 assay methods in detecting alterations in156 target genes common to the assay methods (Table 3).

Table 3. Concordance between F1CDx System and University of Washington OncoPlex Cancer Gene Panel (UW)

	F1CDx System+/ UW+	F1CDx System−/ UW+	F1CDx System+/ UW−	F1CDx System−/ UW−	PPA [95% CI]	NPA [95% CI]
All short variants	1282	73	375	284,218	94.6% [93.3%-95.8%]	99.9% [99.9%-99.9%]
Substitutions	1111	39	334	242,540	96.6% [95.4%-97.6%]	99.9% [99.8%-99.9%]
Indels	171	34	41	41,678	83.4% [77.6%-88.2%]	99.9% [99.9%-99.9%]

- Gene mutations associated with companion diagnostic claims were reviewed using 18 positive specimens and 22 negative specimens. All bioinformaticians gave the same results.
- For mutations other than the gene mutations associated with companion diagnostic claims, 20,076 calls for 717 alterations in 28 specimens were reviewed and compared. The bioinformaticians gave the same results for 20,072 calls, with an overall concordance of 99.98%.
- The overall concordance in MSI status was 100% in 134 eligible runs among assays using 46 specimens.

- Fusion genes

  The accuracy of F1CDx System in detecting *ALK* fusion genes was assessed (this assessment also intended to evaluate the performance of F1CDx System as a companion diagnostic system; see (i) described later). In accordance with the report by Li,[7] the non-inferiority of the concordance between F1CDx System and Ventana OptiView ALK (D5F3) as comparator companion diagnostic (CCD) 1 or Vysis ALK Break Apart FISH probe kit as CCD2 to the concordance between CCD1 and CCD2 was assessed. Considering the differences in the concordance and test principles between F1CDx System and the comparators, the non-inferiority margin was 15%.

  Table 4 shows the results from 175 specimens that provided all data. The difference between the positive percent agreement (PPA) comparing F1CDx System to CCD1 and that comparing CCD2 to CCD1 was 5.43%, while that between the negative percent agreement (NPA) comparing F1CDx System to CCD1 and that comparing CCD2 to CCD1 was −6.02%. The difference between the PPA comparing F1CDx System to CCD2 and that comparing CCD1 to CCD2 was −8.40%, while that between the NPA comparing F1CDx System to CCD2 and that comparing CCD1 to CCD2 was −1.63%. The above results showed the non-inferiority of F1CDx System to the comparator assay methods.

Table 4. Concordance results in detection of *ALK* fusion genes

	CCD1+			CCD1−		
	CCD2+	CCD2−	Total	CCD2+	CCD2−	Total
F1CDx +	78	1	79	3	0	3
F1CDx −	6	7	13	5	75	80
Total	84	8	92	8	75	83

- Copy number alteration

  The accuracy of F1CDx System in detecting copy number alterations in *human epidermal growth factor receptor 2 (HER2)* gene was assessed (this assessment also intended to evaluate the performance of F1CDx System as a companion diagnostic system; see 2.(3).A.4).(i) described later). In accordance with the report by Li,[7] the non-inferiority of the concordance between F1CDx System and HER2 FISH pharmDx “Dako” (first run as CCD1 and second replicate run as CCD2) to the concordance between CCD1 and CCD2 was assessed. Considering the differences in the concordance and test principles between F1CDx System and the comparator, the non-inferiority margin was 20%.

  Table 5 shows the results in 317 specimens that provided all data. The difference between the PPA comparing F1CDx System to CCD1 and that comparing CCD2 to CCD1 was 8.0%, while that between the NPA comparing F1CDx System and CCD1 and that comparing CCD2 to CCD1 was −1.56%. The difference between the PPA comparing F1CDx System to CCD2 and that comparing CCD1 to CCD2 was 1.99%, while that between the NPA comparing F1CDx System to CCD2 and that comparing CCD1 to CCD2 was −0.14%. The above results showed the non-inferiority of F1CDx System to the comparator assay methods.

Table 5. Concordance results in detection of *HER2* copy number alterations

	CCD1+			CCD1−		
	CCD2+	CCD2−	Total	CCD2+	CCD2−	Total
F1CDx +	101	2	103	3	3	6
F1CDx −	12	10	22	6	180	186
Total	113	12	125	9	180	192

The PPAs of F1CDx System to CCD1 and CCD2 were 82.4% and 78.4%, respectively. An additional analysis of discordant specimens revealed a trend toward discordance in specimens with a low HER2/CEP17 ratio and a small copy number of *HER2* gene as determined by the comparator assay method tend to be discordant. For this reason, the applicant has planned to advise in the instructions for use that additional testing with an approved *HER2* gene detection kit should be performed for patients who have a copy number of *HER2* gene equal to 4.

- MSI testing

  The concordance between F1CDx System and mismatch repair (MMR) protein immunostaining or PCR was assessed with F1, the previous generation of F1CDx System, using colorectal cancer- and endometrial cancer-derived specimens (N = 30 for concordance assessment with MMR protein immunostaining, N = 40 for concordance assessment with PCR). The concordance was 100% (30 of 30 specimens) with MMR protein immunostaining and 95% (35 of 37 specimens) with PCR.

- TMB score

  A total of 89 clinical specimens were analyzed to assess a correlation between the TMB score calculated from whole exome sequencing data that were measured at Broad Institute certified by the Clinical Laboratory Improvement Amendments (CLIA) and TMB score determined by F1CDx System. The correlation coefficient was 0.92; the Spearman correlation coefficient was 0.87.

2.(3).A.4).(b) Precision

- Repeatability

  The repeatability of F1CDx System in detection of gene mutations associated with companion diagnostic claims was determined on the basis of the concordance between the results of 2 replicate analyses. All mutations from 18 specimens were 100% concordant. For mutations other than the gene mutations associated with companion diagnostic claims, the repeatability was assessed on the basis of the lower bound of two-sided 95% confidence interval (CI) of the overall weighted-average concordance. A study was performed for 443 substitutions, 188 indels, 55 copy number duplications, 13 copy number deletions, and 18 genomic rearrangements detected in the analysis. The lower bound of the 95% CI of the overall percent agreement was 99.1% to 99.9%.

- Intermediate precision

  The intermediate precision of F1CDx System was assessed on the basis of the PPA obtained under different conditions, with sources of variability of different test dates, laboratory technicians, sequencers, and reagent lots. For evaluation of intermediate precision in detecting the gene mutations associated with companion diagnostic claims, 1417 eligible data were obtained from 18

specimens. The PPA was 100%. For 717 mutations other than the gene mutations associated with companion diagnostic claims, the pairwise agreement (PPA and NPA) were measured among 3 different sequencers and among 3 different reagent lots. The PPA among the different sequencers was 86.6% to 100%, with an NPA of 99.3% to 100%. The PPA among the different reagent lots was 85.9% to 100%, with an NPA of 99.3% to 100%. Table 6 shows the PPA by alteration type.

Table 6. [redacted] precision in detection of alterations (substitutions, indels, copy number alterations, and genomic rearrangements)

Alteration type	Number of alterations	Number of comparisons	Number of concordant comparisons	PPA	Lower bound of 95% CI	Upper bound of 95% CI
Substitutions	443	439,899	439,649	99.9%	99.9%	100%
Indels	188	186,684	186,319	99.8%	99.8%	99.8%
Copy number alterations	68	67,524	67,300	99.7%	99.6%	99.7%
Genomic rearrangements	18	17,874	17,851	99.9%	99.8%	99.9%
Total	717	711,981	711,119	99.8%	99.8%	99.8%

- Repeatability and intermediate precision of MSI
  The repeatability of F1CDx System was assessed on the basis of the PPA among 16 to 18 replicate analyses using 46 specimens. The intermediate precision of F1CDx System was assessed on the basis of the PPA among 34 to 36 runs using 46 specimens under different conditions. The PPA was 100% in the repeatability evaluation and 100% in the intermediate precision evaluation.

- Repeatability and intermediate precision of TMB
  The repeatability and intermediate precision of F1CDx System were assessed on the basis of the correlation coefficient that was determined by 35 to 36 replicate analyses using 12 specimens with a TMB score of ≥10. The correlation coefficient was 1.5% to 21.2% in the repeatability evaluation and 1.8% to 23.8% in the intermediate precision evaluation.

2.(3).A.4).(c) Specificity

The targeted region specificity of the capture probe (bait set) used to capture library DNA containing the targeted regions included in F1CDx was assessed as follows:

- The coverage of the targeted regions of mutations associated with companion diagnostic claims in detection of base substitutions, indels, copy number alterations, and fusion genes was determined using 300 specimens. The results showed that 99.3% to 100% of individual bases had ≥250-fold median and mean depths of coverage.

- Targeted regions including coding regions of 309 genes as well as introns or non-coding regions of 35 genes were used to assess whether high mapping quality and deep coverage can be provided by F1CDx. The mean depth of coverage for the targeted regions included in F1CDx with a mapping quality score of ≥30% was determined using 2 HapMap control specimens used in the evaluation of the limit of detection. The results showed that 99.45% of individual bases in the targeted coding regions had ≥100-fold coverage. In the introns and non-coding regions, 91.45% of individual bases had ≥100-fold coverage. Of 220 introns with no confirmed coverage of ≥100-fold, 187 (85%) are

registered as repetitive sequences in the UCSC Genome Browser or as repetitive sequences in germ cells in the Database of Genomic Variants.

- The depth of coverage in the targeted regions was determined using 3407 specimens used in the studies of concordance with the external gene panel testing, and the evaluation of precision and the limit of detection. The results showed that 99.9% of individual bases from 3404 specimens had ≥250-fold median coverage.

2.(3).A.4).(d) Limit of blank

The percentage of false-positive calls was determined by 4 replicate analyses using 19 mutation-negative DNA specimens. A total of 75 runs, excluding 1 with ineligible data, provided negative calls, confirming the limit of blank of 0%.

2.(3).A.4).(e) Limit of detection

To assess the limit of detection for the gene mutations associated with companion diagnostic claims and the other mutations, specimens were prepared at 6 levels of MAF or tumor purity. The specimens were analyzed 13 times per level, resulting in a total of 1482 data points across the specimens, including negative specimens. Table 7 shows the results of the limit of detection for the gene mutations associated with companion diagnostic claims determined by the hit rate approach.

Table 7. Limit of detection for gene mutations associated with companion diagnostic claims

Mutation	Limit of detection
EGFR L858R alteration	2.4% (MAF)
EGFR exon 19 deletion	5.1% (MAF)
EGFR T790M alteration	2.5% (MAF)
KRAS G12/G13 substitution	2.3% (MAF)
BRAF V600E/K alteration	2.0% (MAF)
ALK fusion genes	2.6% (tumor purity)
ERBB2 copy number alteration	25.3% (tumor purity)

Other than the gene mutations associated with companion diagnostic claims, 227 mutations were analyzed. Tables 8 and 9 show the results.

Table 8. Limit of detection for substitutions and indels other than gene mutations associated with companion diagnostic claims (MAF)

Alteration type	Subcategory	N	Range of MAF (%)
Substitutions	Known[ix]	21	1.8-7.9
	Other	166	5.9-11.8
Indels at non-homopolymer context (including insertions up to 42 bp and deletions up to 276 bp)	Known	3	4.5-6.5
	Other	17	6.0-10.2
Indels at homopolymer context	5 bp repeat	8	10.0-12.2
	6 bp repeat	2	13.6-13.7
	7 bp repeat	4	16.3-20.4
	8 bp repeat	3	17.0-20.0

Table 9. Limit of detection for copy number alterations and genomic rearrangements other than gene mutations associated with companion diagnostic claims (tumor purity)

Alteration type	N	Range of tumor purity (%)
Copy number amplifications (CN >10)	8	9.6-18.5
Copy number amplifications (CN ≥6 and ≤10)	7	19.5-58.3
Copy number: Homozygous deletions	3	33.4-33.4
Genomic rearrangements	3	9.2-14.9
MSI-High	3	8.3-15.8

- Designation of MSI

  The limit of detection determined on the basis of the tumor purity that provides correct MSI calls with a 95% probability was 7.6%, 11.7%, and 12.4% in 3 high MSI (MSI-H) colorectal cancer specimens.

2.(3).A.4).(f) Interfering substances

The impact of exogenous and endogenous interfering substances on the analytical performance of F1CDx was investigated on the basis of success rate for analysis and concordance between before and after the addition of the interfering substances. The exogenous interfering substances tested were ethanol (2.5% and 5.0%), proteinase K (0.04 and 0.08 mg/mL), and molecular index barcodes (5%, 15%, and 30%); and endogenous interfering substances were melamine (0.025, 0.05, 0.1, and 0.2 μg/mL). FFPE specimens prepared from colorectal, breast, lung, and ovary cancers, and malignant melanoma containing substitutions, indels, copy number alterations, homozygous deletions, and fusion genes were analyzed for this assessment. In a total of 170 runs, the success rate was 100% for each alteration. The concordance with control specimens without addition of interfering substances was 100% in all specimens, except for 1 ethanol-added specimen (3 genes). The discordant specimen was the 2.5% ethanol-added specimen. In the other 3 replicate analyses of the same specimen (1 with 2.5% ethanol added, 2 with 5% ethanol added), the concordance with the control specimen without addition of interfering substances was 100%, suggesting that the discordant result could be explained by the discordance in detection of copy number alterations due to the low tumor purity of the specimen. The non-interfering concentration of ethanol was determined to be 5% for F1CDx. It was also confirmed that the addition of molecular index barcodes did not affect the depth of coverage. Table 10 shows the concentrations of substances that were found to be non-interfering.

[ix] Mutations registered in COSMIC

Table 10. Non-interfering substances and their concentrations

Interfering substances	Concentration
Ethanol	5%
Melanin	0.2 μg/mL
Proteinase K	0.08 mg/mL
Molecular index barcodes	30%

2.(3).A.4).(g) Effect of tissue type

A retrospective analysis was conducted using 80,715 clinical specimens from 43 tissue types that were collected at ≥50 types of biopsy sites, including malignant effusions, and assayed by F1. The following parameters were assessed by tissue type: i) DNA yield after DNA extraction, ii) various post-DNA extraction parameters (the percentage of specimens that passed DNA extraction QC and proceeded with library construction, then resulting in a patient report being issued without quality problems; and DNA yields after the library construction and hybrid capture), iii) median depth of exons coverage, iv) percentage of targeted regions with >100-fold coverage, v) sequencing error rate, and vi) high-noise data during measurement of copy number. The results were as shown below.

i) Of specimens determined, 39 of the 43 tissue types (90.6%) had ≥90% of specimens meeting the requirements for DNA yield after DNA extraction. Tissue types with <90% of specimens meeting the requirements were the lung, pancreas, pelvis, and prostate. Specimens of these tissue types are often collected by aspiration biopsy or needle biopsy, which is likely to contribute to their low DNA yields.
ii) All of the tissue types (100%) had ≥90% of specimens meeting the QC criteria for DNA yields after library construction and hybrid capture.
iii) The average median depth of exon coverage across the tissue types ranged from 702- to 793-fold. All of the tissue types (100%) had ≥90% of specimens meeting the specification.
iv) The mean percentage of targeted regions with >100-fold coverage was 99.0% to 99.8%.
v) The mean sequencing error rate was below the QC criterion of 0.01 for each tissue type.
vi) The effect of noise during measurement of copy number was approximately 6% at maximum. All of the tissue types (100%) had ≥90% of specimens meeting the QC criteria.

2.(3).A.4).(h) Comparability with previous generation panel F1

The performance of F1CDx System and the effect of tumor tissue type on the determination of MSI status are explained on the basis of assessments using F1, the previous generation of F1CDx System. The number of target genes detected and a bait set used for the targeted enrichment of sequences are different between F1 and F1CDx System. Of [redacted] target genes for F1, [redacted] genes are also included in F1CDx System and [redacted] genes are included only in F1. On the other hand, 28 genes are included only in F1CDx System. To justify the extrapolation of the results of the above 2 assessments with F1 to F1CDx System, the following comparability test between F1CDx System and F1 was performed.

The PPA and NPA in analyzing the target genes common to both assay systems were determined using 165 specimens. The PPA between F1CDx System and the F1 system was 98.6% for all variants, 99.4%

for base substitutions, 97.0% for indels, 94.3% for copy number alterations, and 100.0% for fusion genes. The overall concordance in the determination of MSI status was 99.4%. The comparability between the 2 systems in TMB score was assessed on the basis of the logarithmic ratio of TMB score using 21 specimens with a TMB score of ≥10. The 90% CI of the logarithmic ratio of TMB score was −0.246 to −0.047.

2.(3).A.4).(i) Performance as companion diagnostic system

The clinical performance of F1CDx System as a companion diagnostic system was evaluated on the basis of the analytical comparability with the approved companion diagnostics shown in Table 11. As in the assessment of *ALK* fusion genes and *HER2* genes, all test parameters were assessed by demonstrating the non-inferiority of the concordance between F1CDx System and 2 replicate analyses with the CCDs to the concordance between the 2 replicate analyses with each CCD in accordance with the report by Li.[6]

The non-inferiority margin was determined for each parameter considering the differences in the concordance and test principles between F1CDx System and the approved CCDs. The target sample size was determined to assure a power of approximately 90% at a significance level of one-sided 5% on the basis of the determined non-inferiority margin and an expected concordance.

The comparability between F1CDx System and the CCDs was verified according to the predefined non-inferiority margin. The applicant explained that the comparability and the PPA and NPA between F1CDx System and the CCDs demonstrated the clinical performance of F1CDx System in determining the eligibility of each patient for specific targeted therapies, as presented in the proposed intended use.

Table 11. Comparator companion diagnostics

Mutations	Comparator
(a) *EGFR* gene mutation (exon 19 deletions and L858R)	Cobas EGFR Mutation Test Kit v2.0 (Approval No. 22800EZX00011000)
(b) *EGFR* gene mutation (T790M)	Cobas EGFR Mutation Test kit v2.0 Cobas EGFR Mutation Test kit (Approval No. 22500AMX01790000)
(c) *ALK* fusion genes	Ventana OptiView ALK (D5F3) (Approval No. 22900EZX00041000) Vysis ALK Break Apart FISH Probe Kit (Approval No. 22400AMX00630000)
(d) *BRAF* gene mutation (V600E and V600K)	Cobas BRAF V600 Mutation Test Kit (Approval No. 22600AMX01329000) THxID BRAF kit (Approval No. 22800EZX00005000)
(e) *ERBB2* (*HER2*) copy number alterations	HER2 FISH pharmDx “Dako” (Approval No. 22200AMY00001000)
(f) *KRAS* gene mutation	therascreen KRAS RGQ PCR kit (Comparability with TheraScreen K-RAS mutation detection kit [Approval No. 22200AMX00341000] have been confirmed.)

2.(3).B Outline of the review conducted by PMDA

2.(3).B.1) Data for review

Prior to review of F1CDx System, PMDA clarified the requirements for gene mutation analysis systems used in cancer genomic profiling from the following points of view.

2.(3).B.1).(a) Positioning of gene panel testing in cancer genomic medicine

The Expert Meeting for Cancer Genomic Medicine Promotion Consortium ("Expert Meeting") is convene to realize "precision medicine that helps physicians to optimize treatment, predict prognosis, and prevent occurrence of cancer based on genomic information from tumor and normal tissues of patients with cancer." The Expert Meeting members discussed what functions and resources are necessary to establish a system that provides the Japanese people with access to the latest cancer genomic medicine.

The Expert Meeting Report[8] compiled in June 2017 defines gene panel testing as "a test that simultaneously analyzes multiple genes related to cancer, etc." According to this report, the implementation of cancer genomic medicine requires that healthcare professionals be provided with not only gene mutation information for selection of approved molecular-targeted drugs (based on testing with companion diagnostics) but also genomic information that is helpful in making various medical decisions for treatment. The report also states that gene panel testing should be approved promptly and provided as a medical service reimbursable by health insurance at medical institutions that meet certain requirements to ensure the efficacy and safety of the testing while taking cost-effectiveness into consideration.

The position of related academic societies on gene panel testing is described in the Clinical Practice Guidance for Next-Generation Sequencing in Cancer Diagnosis and Treatment (Edition 1.0),[9] jointly issued by the Japanese Society of Medical Oncology, the Japan Society of Clinical Oncology, and the Japanese Cancer Association ("Trilateral Academic Society Guidance") and it is shown below.

- Gene panel testing is primarily intended to predict the therapeutic effect of pharmacotherapies in patients for whom pharmacotherapy is indicated and who are not responsive to standard of care.

- The optimal timing of gene panel testing depends on cancer type. Patients with solid tumors who are not responsive to standard of care but are eligible for pharmacotherapy should undergo the testing prior to the start of pharmacotherapy in principle. Patients for whom standard of care is indicated should receive the testing if new therapy needs to be explored for treatment of recurrent or advanced disease after the completion of standard of care. The testing should be performed in pediatric cancer patients or patients with orphan cancers as part of the diagnostic process to support physicians in making a diagnosis, predicting prognosis, and developing treatment plans based on genomic mutation findings or prior to pharmacotherapy. The testing in patients with cancers of unknown primary is intended to assist physicians in making a diagnosis and selecting therapy that

has promising efficacy in such patients. For the treatment of other cancers, physicians should refer to guidelines or guidance documents developed by related academic societies.

- Specimens for gene panel testing should be managed appropriately in accordance with the "Guidelines on the handling of pathological tissue samples for genomic research[10]" developed by the Japanese Society of Pathology and other guidelines.

- Medical institutions, etc. where gene panel testing is performed must be capable of assuring the quality of the test process, etc., generating test data that allow for objective and reasonable interpretation, and providing treatment based on test results while taking into consideration the use of appropriate approaches, such as clinical studies including clinical trials and non-reimbursable combination therapies (e.g., advanced medicine).

- Patients or their legally acceptable representatives should be informed by the treating physician about the benefits and limitations of the test, and restrictions in reflecting test results in treatment plans, before giving consent to gene panel testing. The physician should also explain the possible detection of accidental or secondary findings, such as germline mutations, in cooperation with specialists in hereditary cancers, as necessary, during the informed consent process.

- Test results obtained must be handled with care in accordance with the Act for Partial Revision to the Act on the Protection of Personal Information and the Act on the Use of Numbers to Identify a Specific Individual in Administrative Procedures.

- Each report of gene panel testing is prepared by a panel of experts who are capable of making medical interpretations of test results. Preferably, the reports contain the quality of the specimen and data, the biological significance and the level of evidence of each genomic mutation detected, secondary findings if any and their levels of evidence, availability of therapeutic drugs, and knowledge/information on relevant therapeutic drugs.

2.(3).B.1).(b) System required for utilization of gene panel testing

The Expert Meeting Report recommends the establishment of new functions necessary to provide cancer genomic medicine, including core hospitals for cancer genomic medicine and the Center for Cancer Genomics and Advanced Therapeutics (C-CAT).

The "Guidance related to facilities such as core hospitals for cancer genomic medicine" (Attachment to HSB Notification No. 1225-3 dated December 25, 2017, issued by the Health Service Bureau, Ministry of Health, Labour and Welfare) defines core hospitals for cancer genomic medicine (hereinafter referred to as "core hospitals") as leading medical institutions with advanced functions in cancer genomic medicine in Japan. On April 1, 2018, eleven medical institutions were designated as core hospitals. These core hospitals must meet at least the following requirements to provide cancer genomic medicine: having a structure for performing gene panel testing (including outsourcing to

external laboratories); having a panel of experts who are capable of making medical interpretations of the results of gene panel testing; being capable of providing professional genetic counselling to patients with hereditary tumor, etc.; having a certain number of candidate patients for gene panel testing; and being capable of collecting and managing the results of gene panel testing and clinical information in a secure manner, and registering necessary information in the C-CAT. The core hospitals are also required to hold discussions at least once a month in the presence of the above panel of experts consisting of specialists in cancer pharmacotherapy, genetic medicine, pathology, molecular genetics, cancer genomic medicine, and bioinformatics necessary for genetic analysis using next-generation sequencers, and genetic counselors (expert panel). The panel discussion is intended to make medical interpretations of the results of the gene panel testing and determine personalized medicine for individual patients. In addition, the core hospitals must ensure that appropriate cancer genomic medicine is provided to patients in cooperation with 135 cooperative hospitals for cancer genomic medicine (hereinafter referred to as “cooperative hospitals”) (as of October 1, 2018) around Japan.

Genomic information obtained after introduction of the gene panel testing into Japan will be accumulated in the Cancer Knowledge Database to register and link it with clinical information, relevant clinical study information, etc. The C-CAT established in June 2018 is responsible for constructing and managing the database. The Cancer Knowledge Database, which will be constructed in Japan in the future, will enable patients to receive optimal treatment that is selected according to the condition of each patient and on the basis of the genomic information from the Japanese population. The database will also be useful for development of new drugs and other medical products.

2.(3).B.1).(c) Comprehensive genome profiling

As aforementioned, the gene panel is expected to be used in tests that provide comprehensive information on cancer-related gene mutations (comprehensive genomic profiling [CGP]) using the patient’s tumor tissue.

The expected process flow of gene panel testing is as follows: i) explanation to the patient about the testing, ii) preparation of specimens, iii) DNA sequencing, iv) generation of test reports containing information on mutations found in tumor tissue from the patient, v) discussion by the expert panel to make medical interpretations of the results based on the test reports and to develop a treatment plan, vi) explanation to the patient about the test results, and vii) treatment selected based on the test results.

The results of gene panel testing outsourced by a core hospital to an external laboratory are reviewed by the expert panel of the core hospital before selection of treatment. For this purpose, all clinically significant mutations detected in the cancer-related genes must be appropriately indicated as such in the test reports. The expert panel will review the test reports, investigate and discuss clinical evidence on treatment options and the mutations reported, check currently available treatment options, and determine an optimal treatment plan. The expert panel will also issue reports with appropriate

modifications and additions based on the results of discussion. The expert panel reports will be used by the treating physician to explain the test results to the patient.

2.(3).B.1).(d) Data for review

On the basis of the above, PMDA reviewed this gene mutation analysis system used for CGP according to the following policy.

The Expert Meeting recommended that gene panel testing with assured quality and performance should be approved as a system which provides the Japanese people with access to the latest cancer genomic medicine and be promptly introduced to medical institutions that meet certain requirements, and that treatment should be selected based on CGP results and taking into consideration the use of an appropriate treatment approaches, such as clinical studies including clinical trials and non-reimbursable combination therapies (e.g., advanced medicine). The implementation structure and therapies for cancer genomic medicine recommended by the Expert Meeting currently represent the optimal treatment approaches determined by specialists in cancer genomic medicine considering needs for personalized medicine in clinical settings in Japan. In this framework, the clinical utility of gene panel testing can be sufficiently promising. Not all therapies to be selected based on CGP results have established efficacy or safety. For the following reasons, however, PMDA currently considers that this gene mutation analysis system used for CGP can be approved and introduced into clinical settings in Japan:

- The core hospitals, the C-CAT, and other structures have been established to ensure the efficacy and safety of cancer genomic medicine, and to collect and accumulate genomic and clinical information required for cancer genomic medicine. The clinical utility of CGP will be well established as more information is accumulated in the future.

- The Trilateral Academic Society Guidance states the relevant academic societies' current position on precision cancer medicine that enables cancer patients to have access to optimal cancer treatment tailored to their individual characteristics on the basis of CGP results. The guidance document serves as a clear guide for healthcare professionals as to the clinical positioning of gene panel testing, eligible patients, and how to handle test results.

PMDA reviewed the clinical performance of F1CDx System for CGP from the standpoint on whether it provides appropriate information that helps the expert panel to make treatment plans in accordance with the Expert Meeting Report and the Trilateral Academic Society Guidance. In addition, the review focused on the following issues that are important for the expert panel to make medical interpretations, diagnosis, and treatment plans:

- Appropriateness of proposed target genes
- Appropriateness of the sensitivity for detection of the target mutations
- Appropriateness of the generation and contents of result reports

2.(3).B.2) Appropriateness of the proposed intended use

The applicant's explanation about the identification of patients eligible for the use of F1CDx System and patients defined in the proposed intended use:

According to publications on clinical research of F1 (the previous generation panel of F1CDx System) in patients with different cancer types, variants that might inform treatment options were detected in 83% to 95% of patients, of whom 11% to 34% were found to have mutations and had individual treatment plans developed based on their analysis results. Of the 324 genes included in F1CDx System, [redacted] genes are also included in F1. The above outcomes are reasonably applicable to F1CDx System. The clinical utility of F1CDx System is promising as an aid for physicians to develop treatment plans regardless of cancer types.

The timing of use of F1CDx System by cancer type is as follows:

- F1CDx System is intended to be used as a companion diagnostic system. Patients with cancers who may benefit from treatment with therapies available for cancer types identified by F1CDx will undergo gene panel testing prior to starting their initial pharmacotherapy.

- F1CDx System is intended to be used for the diagnosis of cancers of unknown primary and orphan cancers prior to starting the initial pharmacotherapy. Patients with cancers of unknown primary will undergo testing with F1CDx System to identify a primary lesion while patients with orphan cancers will have the testing because of no standard of care established.

- F1CDx System will be used to develop treatment plans for patients with other solid tumors who have completed standard of care.

For the proposed intended use of F1CDx, the intended patient population that covers those described above was defined as "patients with solid tumor."

PMDA's view:

The intended patient population and timing of CGP that are currently agreed by specialists in cancer genomic medicine in Japan are included in the Trilateral Academic Society Guidance. The Trilateral Academic Society Guidance recommends that CGP be used primarily in patients with solid tumors for whom no standard of care is available and patients whose disease has progressed after standard of care, and cancer types selected for GCP according to the disease characteristics include pediatric cancers, orphan cancers, and cancers of unknown primary. Given these facts, there is no problem with the proposed patient population and timing of use of F1CDx System. The intended patient population of CGP recommended currently by the Trilateral Academic Society Guidance is patients who have completed standard of care. However, F1CDx System is expected to be used to determine treatment options for patients who were found to have mutations, etc. shown in Table 11. PMDA has no objection to patients undergoing CGP testing for detection of these mutations, etc. prior to the initial pharmacotherapy. However, F1CDx should be used at medical institutions that have an established cooperative system with medical institutions that are capable of developing treatment plans based on

CGP results, for the following reasons: (i) The output of test results by F1CDx System is inseparable from the output of CGP results; and (ii) the results output by F1CDx System will be used for the purpose of CGP in patients for whom no available therapy was identified as a result of companion diagnostics.

With the increased use of gene panel testing approved, and accumulation of clinical experience based on test results obtained in routine clinical settings and evidence of advanced medicine based on CGP results, the intended patient population of CGP will be discussed and reviewed in the future by related academic societies and the Cancer Genomic Medicine Promotion Consortium steering committee. Accordingly, the idea of a more eligible population will be communicated to healthcare professionals through revisions of the guidance or by other means.

The proposed intended use of F1CDx was modified as shown below because (1) the intended patient population for the use of F1CDx System should be decided in accordance with relevant guidelines appropriate for each cancer type and (2) the positioning of CGP for each cancer type may be subject to change as more findings accumulate in the future. It is appropriate to specify separately that the Trilateral Academic Society Guidance, etc. should be consulted to determine the intended population of GCP. The proposed intended use includes the development of plans for treatment with cancer immunotherapy based on MSI status and TMB score, which is covered by the intended use of F1CDx as a CGP test.

Intended Use

- F1CDx is intended to provide comprehensive genomic profiling of tumor tissues from patients with solid tumors.
- F1CDx is intended to serve as a companion diagnostic to identify patients who may benefit from treatment with therapeutic drugs listed in the table below. (Table not shown)

When F1CDx System is used for CGP, its use will be limited to the core hospitals and cooperative hospitals for the time being in accordance with the Expert Meeting Report. When F1CDx System is used for companion diagnostic purposes, similar limitations need to be imposed on its use. Although the requirements for medical institutions that are allowed to perform CGP will be changed with the increased use of CGP, the use of F1CDx System should be limited to medical institutions that meet certain requirements, such as having an expert panel and being capable of providing genetic counselling. As aforementioned, it should be separately specified that the Trilateral Academic Society Guidance, etc. should be consulted to determine the intended population for CGP. Based on the above review, PMDA concluded that the following condition of approval should be imposed.

Condition of Approval

The applicant is required to take necessary measures to ensure that physicians with sufficient knowledge and experience in cancer genomic medicine determine the patient’s eligibility for and timing of genetic testing in accordance with the latest guidelines developed by related academic

societies and that the physicians use the product at medical institutions capable of providing diagnosis and treatment based on cancer genomic profiling in a manner that fulfills the requirements of the guidance on designation of core hospitals for cancer genomic medicine.

Development of treatment plans based on the test results with F1CDx System requires medical interpretations of the results by the expert panel. In this process, the expert panel needs to make reference to the latest Cancer Knowledge Database, literature, etc. to select therapies. Thus, the following precautions should be included in the instructions for use.

Precautions for intended use or indications

Physicians specialized in cancer genomic medicine should make a comprehensive decision on diagnosis and treatment plans on the basis of the output results of comprehensive genomic profiling with F1CDx, after consulting the latest medical knowledge and considering the patient's history, other diagnostic test results, and clinical symptoms.

2.(3).B.3) Appropriateness of proposed target genes

The applicant's explanation about the appropriateness of the proposed target genes of F1CDx System for CGP:

F1CDx System is designed to analyze 324 target genes, found in patients with solid tumors, which are associated with molecular-targeted drugs with corresponding companion diagnostics or biomarkers that are approved or under development, or whose mutations are reportedly associated with tumor development, growth, or suppression.

The 324 genes include i) 102 genes whose variants are associated with approved drugs for at least 1 type of cancer and ii) 36 genes whose variants or associated signaling pathways are targeted by drugs that are currently being evaluated in clinical studies. This information is based on the current availability of approved drugs and the current status of drug development in Japan. For reference purposes, the proposed target genes were classified on the basis of the information available as of October 29 to November 12, 2018 according to the levels of evidence shown in Attached Table 1 of the Trilateral Academic Society Guidance. The proposed target genes include ≥120 genes that have been reported to have mutations with a level of evidence of ≥3A, which is reliable enough to be discussed by the expert panel to decide whether the results, including information on available treatment options, should be returned. The proposed target genes also include ≥100 and ≥50 genes with a level of evidence of ≥3 whose usefulness in making diagnosis and prognosis, respectively, is suggested by the results of the clinical studies.

On the basis of the above, the proposed target genes and their mutations to be analyzed with F1CDx System are reasonable.

PMDA's view:
Since CGP is performed to identify patients who may benefit from pharmacotherapies, F1CDx must adequately cover genes with a level of evidence of ≥3A according to the Trilateral Academic Society Guidance. The applicant's explanation and the results of the clinical research using the previous generation of F1CDx indicate that F1CDx System appropriately covers genes with a level of evidence of ≥3A on the basis of the latest medical knowledge. At present, the proposed target genes are adequate. The proposed target genes with a level of evidence of ≤3B are included rather for exploratory purposes. However, considering that gene information registered in the C-CAT, together with clinical information, will be utilized in the development of world-leading, novel, innovative therapies and diagnostic methods, there will be no particular problem with including these genes in the target genes.

Prior to the use of F1CDx System, Patients or their legally acceptable representatives should be informed by the treating physician about the possibility that CGP with F1CDx System does not always lead to the identification of optimal treatment options including enrollment in clinical trials or treatment with unapproved drugs, before giving consent to testing with F1CDx System. This advice must be included in the instructions for use.

2.(3).B.4) Appropriateness of the sensitivity for detection of the target mutations

The applicant's explanation about the analytical performance of F1CDx System to detect mutations:
The applicant's position on the set of variants and the number of specimens for the variants used for evaluation of each validation characteristic are presented below:

- To evaluate the accuracy of F1CDx, specimens were selected taking into consideration the feasibility of adequate DNA yield, presence of driver mutations, and whether specimens represent 46 different types of cancers. Then, 188 specimens from 46 cancer types were analyzed. In selection of the specimens, no particular consideration was given to the size of indel, GC content, or presence of homopolymer. However, F1CDx demonstrated the sensitivity for detection of indels with different sizes and homopolymers. The specimens included those having short variants at homopolymer and tandem repeat contexts that are technically difficult to detect. The sensitivity for detection of these short variants was also confirmed.

- The precision of F1CDx was evaluated using ≥40 specimens. A total of 717 alterations were assessed, including 443 substitutions, 188 indels, 55 copy number amplifications, 13 copy number losses, and 18 fusion genes. This evaluation also involved specimens containing short variants at dinucleotide repeat and homopolymer repeat contexts, which are difficult to detect. Table 12 presents the breakdown of the specimens analyzed.

Table 12. Breakdown of specimens used in precision evaluation

Number of specimens	Alteration type	Size of inserted or deleted sequences	Genomic context
3	Substitution	-	-
2	Insertion	1-2bp	Homopolymer repeats
2	Insertion	1-2bp	Dinucleotide repeats
2	Insertion	3-5bp	-
2	Insertion	>5bp	-
2	Deletion	1-2bp	Homopolymer repeats
2	Deletion	1-2bp	Dinucleotide repeats
2	Deletion	3-5bp	-
2	Deletion	>5bp	-
3	Copy number alteration	-	-
3	Homozygous deletion	-	-
3	Genomic rearrangement	-	-

- Various specimens representing all variants detectable by F1CDx were selected for evaluation of the limit of detection, and the variants included those with homopolymer repeats, and inserted and deleted sequences of various types and sizes. Then, 19 specimens having ≥200 variants were analyzed.

- To assess the robustness and stability of F1CDx assay, specimens were selected to include [redacted].

The analytical performance of F1CDx System for detecting the target mutations was assessed as the accuracy of F1CDx System for detecting substitutions and indels. A representative set of mutations (156 genes) for analysis were selected taking into consideration the size of indels, homopolymer, and repeats. The test results by F1CDx System were compared with those by an externally validated gene panel (University of Washington [UW] OncoPlex Cancer Gene Panel).

The accuracy of F1CDx System for detecting copy number alterations was evaluated on the basis of the concordance with a product approved for detection of copy number alterations in *HER2* gene. This type of alterations is detected on the basis of the depth of coverage and MAF in approximately 3500 SNPs across the entire genome, independent of the base sequence of the gene. The accuracy of F1CDx System for detecting copy number alterations in other genes can be, therefore, supported by the results of analysis of copy number alterations in representative genes. F1, the previous generation of F1CDx having the same next-generation sequence platform as F1CDx is confirmed to be comparable with F1CDx System in detection of copy number alterations. F1 was assessed for concordance with [redacted] by fluorescence *in situ* hybridization (FISH) or immunostaining assay as a comparator. The concordance was 95% to 100%, suggesting that the accuracy of F1CDx System is appropriate for detecting copy number alterations.

There is no assay method with an established analytical performance available for accuracy evaluation in detecting fusion genes, other than those for *ALK* fusion genes. In evaluation of the accuracy of

F1CDx System for detecting substitutions and indels, UW-OncoPlex Cancer Gene Panel was used as a comparator. Its accuracy in detecting fusion genes was evaluated only using 11 specimens in companion with the FISH assay. The performance of UW-OncoPlex Cancer Gene Panel for detecting this type of alterations has not been fully validated. For this reason, approved companion diagnostic kits for testing *ALK* fusion genes and *ALK* fusion proteins were used as comparators in evaluation of the accuracy of F1CDx System for detecting fusion genes. A total of 10,559 fusion genes have been registered in COSMIC as of May 2017. F1CDx System is designed to detect 93.0% of the fusion genes.

In addition to the above evaluations, F1CDx System has been shown to have a satisfactory concordance of TMB score and MSI status with the respective comparators. These test results can support the analytical performance of F1CDx System for the target mutations detectable by this system.

PMDA's view:
The rationale for selection of the set of representative mutations used in evaluation of the analytical performance of F1CDx System for detecting substitutions and indels is acceptable. Although the positioning of the external gene panel test selected for comparison in Japan remains unclear, PMDA has no objection to the concept of assessing the accuracy of F1CDx System by comparing with an externally validated comparator. Given that this comparator assay has been used in the US to a certain extent and that currently there is no gene panel with a publicly established analytical performance in Japan, the applicant's decision to use the external assay method is acceptable.

The applicant's justification for assessing the performance of F1CDx System for detecting copy number alterations by comparing with a *HER2* companion diagnostic is acceptable.

The performance of F1CDx System for detecting fusion genes was assessed only by comparing with an approved *ALK* companion diagnostic. This is understandable because currently there is no established assay available to assess the accuracy of gene panels for detecting fusion genes. F1CDx System, which uses a DNA sequencer, potentially increases the number of false-negative calls compared with immunostaining and FISH methods because of a difference in the test principle. The results of these performance tests and appropriate precautions about the limited performance of F1CDx System for detecting fusion genes should be included in the instructions for use to communicate appropriate information to healthcare professionals.

The data submitted show no particular problem in the other analytical performance of F1CDx System.

PMDA concluded that F1CDx System has performance that meets clinical requirements for CGP.

2.(3).B.5) Appropriateness of the generation and contents of result reports

The applicant's explanation about the appropriateness of the generation and contents of the result reports of F1CDx System:

In the analysis provided by FMI, mutations are classified into any of the following 3 categories (see Table 1): Known, Likely, and Unknown. FMI's rules specify that known and likely alterations, which are output as cancer-related genes by F1CDx System, should be identified according to information included in external DBs such as COSMIC and criteria predetermined by the FMI's CBO on the basis of such information, and reported to ordering physicians.

To change the category of each variant in the reference file of Analysis Pipeline, FMI's relevant teams collect clinical or nonclinical evidence data from public information, such as [redacted] and perform [redacted] on the basis of the public information and [redacted]. When a variant meets the definition of another variant category as a result of the above data collection and discussions, the category of the variant is upgraded or downgraded according to the scheme predefined in the written standard operating procedure. The result is [redacted] of Analysis Pipeline. Review of variant category according to the above procedure will be performed [redacted]. For each review, [redacted] verifies that the system appropriately reflects each change without any unintended change being added.

In summary, the output of mutation information by F1CDx System can be objective and valid information based on the latest medical knowledge available at the time of an assay, for the following reasons: (i) mutation information is appropriately output in the reports according to the category definition predetermined based on clinically relevant information included in the external DBs and (ii) there is an established system that ensures that the category of each alteration is updated after confirming that the collected relevant information meets the predefined levels of evidence.

Although F1CDx System searches DBs that are commonly used in clinical practice, including the dbSNP, there are limitations to registration of Japanese-specific SNP data. PMDA therefore asked the applicant to explain the possibility of SNPs being reported as VUS in Japanese patients.

The applicant's explanation:

The DBs used in F1CDx System to exclude SNPs do not necessarily well reflect SNPs found in races other than Caucasians. The dbSNP used for VUS filtering does not reflect Japanese-specific SNPs either. Japanese-specific SNPs not registered in international DBs are potentially reported as VUS. However, VUS is a variant whose scientific and clinical significance are currently unknown, and a VUS call does not provide any information useful for identifying molecular-targeted drugs and clinical studies. Even if such a rare SNP is reported as VUS, it does not affect the selection of therapy. As aforementioned, FMI has established a system that ensures that the category of VUS is regularly reviewed on the basis of external DBs and published literature to reflect the latest information in the

system. When appropriate evidence-based Japanese genomic information is reported, it can be reflected in the system.

PMDA's view:
On the basis of the data submitted, PMDA concluded that the analysis process through to report output was appropriately managed on the basis of the established mutation detection criteria, data quality criteria, report output criteria, and the standard operating procedure for data review. Japanese-specific SNPs, if any, are unlikely to cause substantial problems in clinical practice in Japan because a system has been established to ensure that the latest information based on external DBs and literature information is reflected in the system.

The DBs referenced by F1CDx System to determine the category of each variant (COSMIC, dbSNP, and ExAC) can be positioned as clinically known and public DBs because i) all of these DBs are publicly available and their transparency is assured, ii) they are already widely used as an important tool by specialists in cancer genomic medicine in and outside Japan, and iii) they are operated for non-commercial purposes. The validation of data registered in these DBs does not need for the regulatory review of F1CDx. Variants reported by F1CDx System include those identified according to the definitions predetermined by the CBO. They represent indels that may affect the function of products of tumor-suppressor genes, alterations at known activation contexts, and fusion genes involving newly-reported partners. These are appropriate as variants that suggest an association with cancer. PMDA concluded that there was no particular problem with mutation information reported by F1CDx System because such information is ultimately evaluated and reviewed by the expert panel in Japan before use.

There is also no particular problem with change of the category of each variant by FMI because the category is updated in accordance with the predefined rules. To change the category of each variant, [redacted] is used. As [redacted], it appears to have no substantial impact on the development of treatment plans.

Based on the above, PMDA concluded that there was no particular problem with the quality of the mutation information presented by F1CDx System and that changes to the information need not be checked each time they are made after commercialization of F1CDx System.

On the basis of the discussions in Sections 2.(3).B.2) to 2.(3).B.5) above, PMDA has concluded that F1CDx System for CGP can provide appropriate information that supports the expert panel in developing treatment plans in accordance with the Trilateral Academic Society Guidance.

2.(3).B.6) Performance as companion diagnostic system

The data submitted demonstrated the analytical comparability between F1CDx System and companion diagnostics approved in Japan. PMDA has therefore concluded that F1CDx System is capable of identifying patients who can benefit from treatment with the specific targeted therapies. In *HER2* gene testing, however, positive calls were made by the comparator while the copy number of 4 was indicated by F1CDx System. The instructions for use should advise healthcare professionals to be aware of false-negative calls potentially made by F1CDx System when.

3. Conformity to the Requirements Specified in Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics

3.A Summary of the submitted data

The applicant submitted a declaration of conformity declaring that the product meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (hereinafter referred to as "the Essential Principles") (MHLW Ministerial Announcement No. 122, 2005). Data supporting the conformity of the software lifecycle processes of the product to JIS T 2304: 2012 were also submitted.

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of F1CDx to the Essential Principles.

PMDA's conclusion on the conformity of F1CDx to Article 1, which defines preconditions, etc. for designing medical devices:

As described in Section "2.(3).B.2) Appropriateness of the proposed intended use," physicians and medical institutions qualified to use F1CDx should use the product in compliance with the guidance for proper use in order to promote the proper use of F1CDx. In line with this, PMDA added a condition of approval to ensure that the applicant takes necessary measures regarding this issue.

PMDA's conclusion on the conformity of F1CDx to Article 3, which specifies that medical devices should achieve their intended performance and purpose:

As described later in Section "IV.(3) Quality assurance of input data," the quality of sequence data, which serve as input data for F1CDx, and their analysis results need to be controlled in order to ensure the efficacy and safety of the intended performance and purpose of F1CDx System. In line with this, PMDA added a condition of approval to ensure that the applicant takes necessary measures regarding this issue.

PMDA's conclusion on the conformity to Article 12, which defines requirements for development lifecycle of software incorporated in medical devices:

As described later in Section “IV.(2) Handling of personal information and cybersecurity,” information security needs to be continuously managed. PMDA added a condition of approval to ensure that the applicant takes necessary measures regarding this issue

Based on the above, PMDA has comprehensively reviewed the conformity of F1CDx to the Essential Principles and concluded that there is no particular problem.

4. Risk Management

4.A Summary of the submitted data

The applicant submitted a summary of risk management, the risk management system, and its implementation status in reference to ISO 14971 “Medical devices—Application of risk management to medical devices.”

4.B Outline of the review conducted by PMDA

PMDA comprehensively reviewed the document on risk management taking into account the discussion presented in Section “3.B Outline of the review conducted by PMDA” and concluded that there was no particular problem.

5. Manufacturing Process

5.A Summary of the submitted data

Relevant data were not submitted in accordance with the notification entitled “Handling of Medical Device Software” (MS Notification No. 1121-33 issued by Counsellor [for Medical Devices and Regenerative Medical Products], Minister’s Secretariat, MHLW, PFSB/SD Notification No. 1121-1 issued by Direction of the Safety Division, Pharmaceutical and Food Safety Bureau, MHLW, PFSB/CND Notification No. 1121-29 issued by Director of the Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, MHLW; dated November 21, 2014).

5.B Outline of the review conducted by PMDA

PMDA concluded that there was no particular problem with submitting no manufacturing process data for F1CDx on the basis of the above notification.

6. Clinical Data or Alternative Data Accepted by Minister of Health, Labour and Welfare

6.A Summary of the submitted data

The applicant submitted no clinical data. The clinical performance of F1CDx System was evaluated as part of the performance tests described in Section 2.(3).

6.B Outline of the review conducted by PMDA

PMDA concluded that there was no particular problem with using the data from the clinical performance tests instead of data from clinical studies.

7. Plan for Post-marketing Surveillance etc. Stipulated by Paragraph 1 of Article 2 of Ministerial Ordinance on Good Post-marketing Study Practice for Medical Devices

7.A Summary of the submitted data

The applicant explained that no post-marketing use-results survey, etc. was necessary because F1CDx and its previous generation have been widely used in the US and no particular consideration needs to be given to ethnic difference to use the system.

7.B Outline of the review conducted by PMDA

PMDA concluded that no post-marketing use-results survey of F1CDx was necessary for the following reasons:

- F1CDx System and its previous generation have been used overseas to a certain extent.

- The performance of F1CDx has been evaluated on the basis of its analytical performance and the appropriateness of the analytical process through to report output. The efficacy or safety of F1CDx will not vary according to a patient population in the post-marketing setting.

- Clinical and genomic information based on gene panel testing is planned to be accumulated and evaluated mainly by the C-CAT. The applicant needs to appropriately coordinate and cooperate with the C-CAT taking into consideration the use of F1CDx System in cancer genomic medicine. However, separate use-results surveys are of no importance.

III. Results of Compliance Assessment Concerning the New Medical Device Application Data and Conclusion Reached by PMDA

The new medical device application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (Law No. 145 of 1960). On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

IV. Overall Evaluation

F1CDx is an analysis software program that provides information on mutations on the basis of comprehensive profiling of 324 cancer-related genes isolated from tissue from patients with solid tumors. Such information may help physicians to develop treatment plans and to determine the eligibility of each patient for treatment with targeted therapies. There were 3 key issues to be addressed in the review of F1CDx. On the basis of comments from the Expert Discussion, PMDA reached the following conclusions.

(1) Clinical performance

The review of F1CDx System was conducted on the assumption that the medical system for cancer genomic medicine centered on the core hospitals is in place and the diagnosis and treatment of cancer

are provided based on CGP according to the Trilateral Academic Society Guidance. The appropriateness of the proposed target genes to be analyzed, the sensitivity for detection of the target mutations, and the generation and contents of result reports were evaluated. The data submitted has demonstrated the clinical performance of F1CDx System. Conditions of approval should be imposed regarding the requirements for medical institutions that are permitted to perform CGP using F1CDx and rules for identifying eligible patients.

(2) Handling of personal information and cybersecurity

(2).1) Protection of personal information

F1CDx System handles personal information, including personal identification codes. PMDA therefore asked the applicant to explain what measures are planned to be in place to protect personal information.

The applicant's response:

The applicant plans to take the following measures in accordance with the Act on the Protection of Personal Information (Act No. 57 of 2003). F1CDx System is designed to handle the minimum amount of information to prevent misidentification of specimens, mutation information, and analysis results, as well as to maintain the assay precision. The information is anonymized at medical institutions. However, it includes personal information and special care-required personal information, and may be used for improvement of the assay precision of F1CDx System, research, etc. For this reason, testing with F1CDx System requires patient informed consent. Healthcare professionals must obtain consent to testing from individual patients after explaining that their personal information is provided to an overseas third party and used for specific purposes. In addition, before an F1CDx assay is ordered, healthcare professionals must check whether informed consent has been obtained from the patient. The applicant, as a business operator handling personal information, is required to identify the purpose of use, obtain personal data in a proper manner, and take security measures, etc. Therefore, the applicant has signed with FMI a Memorandum of Understanding on compliance with relevant laws, including those on disposal of specimens and data, in order to supervise FMI, which is the laboratory that actually conducts F1CDx assays.

PMDA accepted the applicant's explanation.

(2).2) Cybersecurity

F1CDx assays involve transmission of genetic information through a telecommunication line. PMDA therefore asked the applicant to explain the cybersecurity preparedness in place.

The applicant's response:

[redacted]

[redacted]. This measure will be administered in compliance with the "Guidelines for the Security Management of the Medical Information System" (5th edition),[11] published by the MHLW, etc.

FMI has developed plans for software maintenance and cybersecurity, and conducted risk assessment according to these plans. In addition, the information to implement effective cybersecurity management meets the "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices,[12]" issued by the FDA.

PMDA concluded that there is no particular problem with the applicant's explanation. However, given that data including analysis results are communicated between Japanese medical institutions and the overseas laboratory in the course of the F1CDx assay, further consideration should be given for protecting personal information and preventing unauthorized access. To clarify the responsibilities of the marketing authorization holder in Japan, PMDA concluded that a relevant condition of approval should be imposed.

(3) Quality assurance of input data

To enable F1CDx System to output appropriate mutation information, it is important to assure the quality of data in the acquisition of DNA sequence data from tumor tissue and the analysis of such data. The applicant should specify requirements to assure data quality and take appropriate actions when the requirements need to be changed. Accordingly, PMDA concluded that a relevant condition of approval should be imposed.

Based on the above discussion, PMDA has concluded that the product may be approved after modifying the intended use as shown below, with the following conditions of approval.

Intended Use

- F1CDx is intended to provide comprehensive genomic profiling of tumor tissues from patients with solid tumors.
- F1CDx is intended to serve as a companion diagnostic to identify patients who may benefit from treatment with therapeutic drugs listed in the table below. (Table not shown)

Conditions of Approval

1. The applicant is required to take necessary measures to ensure that physicians with adequate knowledge and experience in cancer genomic medicine determine the patient's eligibility for and timing of genetic testing in accordance with the latest guidelines developed by related academic societies and that the physicians use the product at medical institutions capable of providing diagnosis and treatment based on cancer genomic profiling in a manner that fulfills the requirements of the guidance on designation of core hospitals for cancer genomic medicine.

2. The applicant is required to perform appropriate procedures and controls for protecting personal information concerning tumor tissue specimens sent to the laboratory and associated information and to implement up-to-date data security and privacy measures for preventing unauthorized access to relevant data and information.

3. The applicant is required to perform quality control of input data as described in the Remarks column of the Application Form. Any changes to the quality control of input data as described in the Remarks column of the Application Form (excluding minor changes defined by the Ordinance of the Ministry of Health, Welfare and Labour, as specified under Article 23-2-5, Paragraph 11 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics [PMD Act]) must be approved by the Minister of Health, Welfare and Labour pursuant to Article 23-2-5, Paragraph 11 of the PMD Act. Note that the provisions of Article 23-2-5, Paragraph 13; Article 23-2-6; and Article 23-2-7 of the PMD Act are applicable mutatis mutandis to the approval of said changes.

The product is not classified as a biological product or a specified biological product. No post-marketing use-results survey of the product is required.

PMDA has concluded that this application should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics

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