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	Instrument & Apparatus 17, Blood test instrument
Term Name	Gene variants analysis set (for comprehensive genomic profiling for cancer)
Brand Name	OncoGuide NCC Oncopanel System
Applicant	Sysmex Corporation
Date of Application	June 28, 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 condition. The product is not classified as a biological product or a specified biological product.

Condition of Approval of the Marketing Application

The applicant is required to take necessary measures to ensure that physicians with sufficient knowledge and experience related to 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.

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).

Classification	Instrument & Apparatus 17, Blood test instrument
Term Name	Gene variants analysis set (for comprehensive genomic profiling for cancer)
Brand Name	OncoGuide NCC Oncopanel System
Applicant	Sysmex Corporation
Date of Application	June 28, 2018
Items Warranting Special Mention	SAKIGAKE designation device
Reviewing Office	Office of In Vitro Diagnostics and Office of Medical Devices I

Review Results

November 19, 2018

Classification	Instrument & Apparatus 17, Blood test instrument
Term Name	Gene variants analysis set (for comprehensive genomic profiling for cancer)
Brand Name	OncoGuide NCC Oncopanel System
Applicant	Sysmex Corporation
Date of Application	June 28, 2018
Items Warranting Special Mention	SAKIGAKE designation device

Results of Review

OncoGuide NCC Oncopanel System (hereinafter referred to as "NCC Oncopanel") is a combination medical device comprised of a template deoxyribonucleic acid (DNA) extraction reagent and an analysis software program. NCC Oncopanel is used to provide information on genetic mutations (hereinafter referred to as "mutations") that helps physicians to develop treatment plans on the basis of comprehensive genomic profiling of 114 cancer-related genes collected from patients with solid tumors. NCC Oncopanel is used in combination with a DNA sequencer (NextSeq 550Dx System) to serve as a genetic testing system (hereinafter referred to as "NCC Oncopanel System"). A separate marketing notification has been submitted for the DNA sequencer. By analyzing DNA extracted from tumor tissue specimens (including cytology specimens) and non-tumor tissue specimens (blood) from the same patient, NCC Oncopanel System reads DNA sequences of the target regions, detects mutations such as base substitutions, insertion and deletion alterations (indels), copy number alterations, and gene fusions that may be useful to identify treatment options, calculates the score of tumor mutation burden (TMB), and outputs the results.

The Expert Meeting for Cancer Genomic Medicine Promotion Consortium (hereinafter referred to as "Expert Meeting") is convened to discuss the promotion of precision 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 (i.e., cancer genomic medicine). 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 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 the 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 treatment 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 mutations (comprehensive genomic profiling [CGP]), its clinical utility can be sufficiently promising. On the assumption that the above implementation structure, etc. had already been in place, PMDA reviewed the clinical performance of NCC Oncopanel System as gene panel testing in terms of the appropriateness of the proposed target genes to be analyzed, the sensitivity for detection of the target mutations, and the generation and contents of reports of sequencing test results.

NCC Oncopanel System is designed to analyze 114 target genes chosen to cover genes whose mutations are found in patients with solid tumors. The target genes include those reportedly related to molecular-targeted therapies for which companion diagnostics or biomarkers have been approved or developed, and those reportedly associated with the occurrence, growth, or suppression of cancer. On the basis of the above information, PMDA has concluded that the proposed target genes appropriately cover all genes and their variants that are currently necessary for CGP.

To support the appropriateness of the sensitivity for detection of the target mutations, the applicant submitted the data for accuracy, precision, specificity, and the limit of detection. Representative variant types for detection of base substitutions, indels, copy number alterations, and gene fusions were selected to evaluate the analytical performance of NCC Oncopanel System used for CGP. Comparator assays were chosen to evaluate the accuracy of NCC Oncopanel 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 NCC Oncopanel System has clinical performance that meets requirements for CGP of specimens from patients who have no treatment options.

On the basis of the data submitted, PMDA also concluded that the analysis process through to report output was appropriately controlled according to the mutation detection criteria, data quality criteria, and report output criteria. In the analysis process of NCC Oncopanel System, an in-house database (DB) called Expert Panel DB (EPDB) is consulted to determine whether information on detected mutations is included in the reports. The EPDB is a DB that registers and lists information from external DBs, such as COSMIC, ClinVar, and ExAC, all of which are positioned as clinically known and public DBs. PMDA confirmed that the EPDB will be updated on the basis of publicly available information according to predefined standards. On the above grounds, PMDA concluded that there is no problem with the quality of the variant information presented by NCC Oncopanel System and that changes to the information need not be checked each time they are made after commercialization of NCC Oncopanel System.

The proposed description for the intended use of NCC Oncopanel was modified for the following reasons: (1) The eligible patient population should be decided in accordance with relevant guidelines appropriate for each cancer type and (2) the position 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 NCC Oncopanel were demonstrated by the data submitted.

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

Intended Use

NCC Oncopanel is intended to provide the comprehensive genomic profiling of tumor tissue from patients with solid tumors.

Condition of Approval

The applicant is required to take necessary measures to ensure that physicians with sufficient knowledge and experience related to 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.

Review Report

November 19, 2018

Product Submitted for Approval

Classification	Instrument & Apparatus 17, Blood test instrument
Term Name	Gene variants analysis set (for comprehensive genomic profiling for cancer)
Brand Name	OncoGuide NCC Oncopanel System
Applicant	Sysmex Corporation
Date of Application	June 28, 2018
Proposed Intended Use	NCC Oncopanel is intended to construct libraries for next-generation sequencers using genomic DNA that is extracted from tumor tissue and fragmented, detect somatic mutations (substitutions, amplifications, and rearrangements [fusions]) through mutation analysis, and provide information, including analysis results for these mutations. NCC Oncopanel is used to assist physicians in developing treatment plans based on gene profiling tests for patients with advanced or recurrent solid tumor by providing information to help the physicians to: 1. select treatment taking into consideration participation in clinical studies, including clinical trials, and the use of non-reimbursable combination therapies such as advanced medicine; 2. discuss treatment plans based on prognostic factors and TMB (number of mutations/Mb); and 3. determine cancer type in patients with cancer of unknown primary.

Items Warranting Special Mention

SAKIGAKE designation device

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List of Abbreviations

ACMG	American College of Medical Genetics and Genomics
ALK	Anaplastic Lymphoma Kinase
BRAF	v-raf murine sarcoma viral oncogene homolog B1
C-CAT	Center for Cancer Genomics and Advanced Therapeutics
CGP	Comprehensive Genomic Profiling
CI	confidence interval
CLIA	The clinical laboratory improvement amendment
DNA	Deoxyribonucleic Acid
EGFR	Epidermal Growth Factor Receptor
FFPE	Formalin Fixed Paraffin Embedded
FISH	Fluorescence in situ hybridization
HER2	Human Epidermal Growth Factor Receptor 2
NCCN	The National Comprehensive Cancer Network
PCR	Polymerase Chain Reaction
SNP	Single Nucleotide Polymorphism
TMB	Tumor Mutation Burden

I. Product Overview

OncoGuide NCC Oncopanel System (hereinafter referred to as "NCC Oncopanel") is a combination medical device comprised of a template DNA extraction reagent (OncoGuide NCC Oncopanel Kit) and an analysis software program (OncoGuide NCC Oncopanel Analysis Program). NCC Oncopanel is used to provide information on genetic mutations ("mutations") that helps physicians to develop treatment plans on the basis of comprehensive genomic profiling of 114 cancer-related genes collected from patients with solid tumors. NCC Oncopanel is used in combination with a DNA sequencer (NextSeq 550Dx System) to serve as a genetic testing system (hereinafter referred to as "NCC Oncopanel System"). Marketing notification for NextSeq 550Dx System has been submitted by Illumina Inc.

Figure 1 shows the flowchart of the analysis process by NCC Oncopanel System.

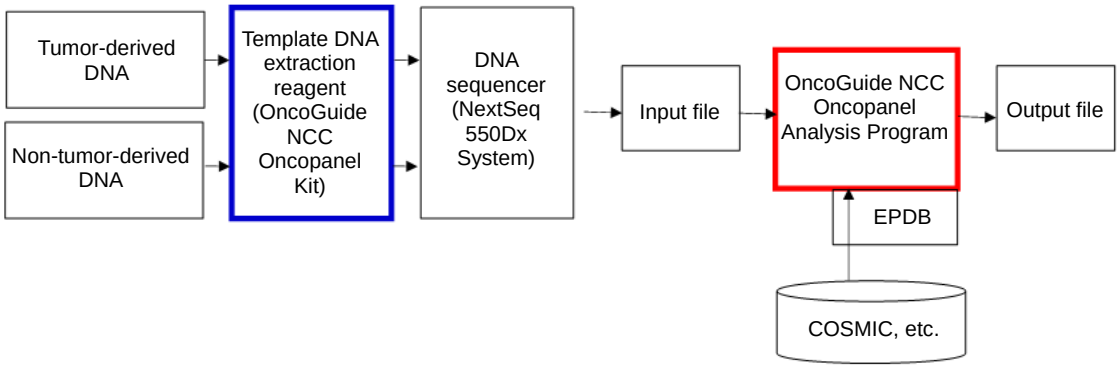

Figure 1. Flowchart of the analysis process by NCC Oncopanel System

The analysis process by NCC Oncopanel System includes the following steps: fragmentation of DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens (including cytology specimens) and non-tumor tissue specimens (blood) prepared at medical institutions; polymerase chain reaction (PCR) amplification of DNA fragments; DNA hybrid capture-based target enrichment; and sequencing of the target region by a DNA sequencer. Subsequently, the analysis software program allows the sequencing reads of DNA derived from tumor and non-tumor tissues to be mapped to the reference sequence and detects any difference in the DNA sequencing reads between tumor tissues and non-tumor tissues. Differences detected in the sequencing reads are identified as variants when they meet the predefined requirements for base substitutions, insertion and deletion alterations (indels), copy number alterations, or gene fusions. The annotation function of the analysis software program checks the variants identified against the external DBs (e.g., COSMIC and ClinVar) and the in-house DB (Expert Panel DB [EPDB]), and annotates a clinical significance status, position, type (synonymous or non-synonymous), and allele frequency for each mutation. Subsequently, data quality is evaluated. The results of the above analysis are output as the following 5 reports: i) a summary report, ii) a sequencing report, iii) a QC report, iv) the detailed analysis of detected variants, and v) detailed mapping.

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 present 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 the product 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

NCC Oncopanel System was developed on the basis of a gene panel testing system used in clinical research at the National Cancer Center. This clinical research (Trial of Onco-Panel for Gene-profiling to Estimate both Adverse events and Response [TOP-GEAR] project) was conducted in patients with solid tumors who had completed standard of care. Treatment plans were to be developed on the basis of the results of DNA sequencing performed in compliance with the Clinical Laboratory Improvement Amendments (CLIA). Analysis results were available in 131 of 183 patients who were enrolled in the clinical research between July 2013 and October 2014. Of the 131 patients, 51 patients (45%) with mutations detected were found to be possibly eligible for treatment with approved molecular-targeted therapies, and 11 patients (8%) were treated with molecular-targeted therapies based on the treatment plans determined according to their mutations.[1]

The applicant was involved in the quality control and operation of the testing system in the above clinical research. The necessity of cancer genomic medicine is being more widely recognized in and outside Japan. Given these circumstances, the applicant has submitted the marketing application for NCC Oncopanel so that the information on mutations is used for physicians to select drugs expected to be effective in patients, obtain information concerning prognosis predication, and identify cancer type in patients with cancer of unknown primary.

NCC Oncopanel System was designated as a device for SAKIGAKE designation system (SAKIGAKE Device Designation No. 1 of 2016 [*28 Shin*]) as of February 28, 2017.

1.A.(2) Use in foreign countries

NCC Oncopanel is not approved or certified overseas.

2. Data Relating to Design and Development

2.(1) Performance and safety specifications

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

The release specifications for the template DNA extraction reagent, specifications for the analytical performance of NCC Oncopanel System, process control criteria for the analysis process, and acceptance criteria for system suitability have been established.

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 NCC Oncopanel System was confirmed in the assessment of conformity to the Essential Principles. There is no newly established safety specification. For assessment of conformity to the Essential Principles, the applicant submitted data supporting the conformity of the software lifecycle process of NCC Oncopanel to IEC62304:2006, separately from the declaration of conformity presented in Section II.3.

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

PMDA reviewed the data submitted and concluded that there was no particular problem with safety.

2.(3) Performance

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

The applicant submitted the following data relating to the quality and performance of NCC Oncopanel presented in Section 2.(3).A.1) to 2.(3).A.4).

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

Target genes selected for analysis by NCC Oncopanel System consist of 114 cancer-related genes whose mutations have been reported to activate or inactivate the function of their gene products. On the basis of the sequencing reads of genomic DNA, including that of non-tumor tissues, gathering of information on hereditary cancer genes for clinical reference was also chosen as one of the concepts for the development of NCC Oncopanel. Accordingly, 13 hereditary cancer genes listed in the American College of Medical Genetics and Genomics (ACMG) Statement are also included in these 114 target genes. In accordance with publications, the target genes are classified as follows: i) 66 genes that may be useful to develop treatment plans when their activating mutations are detected, ii) 48 genes that may be useful to develop treatment plans when their loss-of-function mutations are detected, or iii) 12 genes that may be useful to develop treatment plans when gene fusions are detected.

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

The sequencing reads provided by a DNA sequencer are input in the analysis software program and subjected to various processing steps (mutation detection, annotation, quality assessment, and data output), and then a summary report, a sequencing report, a quality control (QC) report, the detailed analysis of detected mutations, and detailed mapping are output.

The gene alteration detection function performs mapping of the sequencing reads of DNA derived from tumor and non-tumor tissues to the reference sequence “hg19, GRCh37 Genome Reference Consortium Human Reference37” and detects variants by comparing the sequencing read for the tumor tissue with the sequencing read for the non-tumor tissue and the reference genome sequence. The annotation function adds the following information when mutations detected meet any of the criteria presented in Table 1:

i) Clinical significance of the mutation and its effect on the function of gene products (activation or loss of function), and the number of registered mutations (in reference to the clinical variant DBs [EPDB, COSMIC, and ClinVar])
ii) Information on whether the mutation affects the functional domain and the type of mutation (e.g., missense, nonsense, frame shift, and silent mutations) (in reference to the gene definition DBs [RefSeq and Ensembl])
iii) Allele frequency in the target population (in reference to the Single Nucleotide Polymorphism [SNP] DBs [1000 Genome Project, ESP6500, ExAC, and HGVD])

The quality assessment function reports out false-positive mutations by consulting the in-house DB, then calculates the number of mutations detected and tumor mutation burden (TMB), and flags a comment as low reliability data on each alteration that does not meet the quality control criteria presented in Table 2. The data output function determines mutations that should be reported according to the mutation calling threshold and on the basis of relevant information added through the above processing steps.

A summary of the 5 different types of reports generated in the data output process is presented below:

- Summary report: A summary of analysis results. This report describes mutations detected and their allele frequency and clinical significance, the version No. of each reference genome DB, and other information. The clinical significance of each mutation detected is determined in accordance with the “Gene mutation wording determination procedures” and based on relevant information registered in the reference genome DBs and the number of registered mutations. It is explained by clarifying whether the mutation can be an activating mutation, loss-of-function mutation, gain-of-function mutation, or drug-resistance mutation.
- Sequencing report: This report describes more detailed information on individual mutations listed in the summary report. This report is expected to be used for quality control at the institution’s laboratory testing department, etc. and discussion by the expert panel.
- QC report: This report describes the quality and statistics of sequencing results. As with the sequencing report, this report is also expected to be used for quality control at the institution’s testing department, etc. and discussion by the expert panel.
- Detailed results of detected mutations and detailed mapping: These files are necessary for data visualization by the Integrative Genomics Viewer. These are expected to be used for quality control at the institution’s laboratory testing department, etc.

Table 1. Mutation detection criteria

Type of mutation	Acceptance criteria
Substitution and indels	(a) Depth ≥100 at the mutation site and allele frequency ≥5% (b) Mutations that are not screened out as a false-positive mutation during the following filtering processes: Primary filtering: Strand-bias filter, read-end-call filter, within-long homopolymer filter, mapping quality zero filter, surrounded-by-dust filter, and misalignment filter Secondary filtering: Second fisher filter Tertiary filtering: VAF lees filter
Copy number alteration	(a) Median depth ≥200 and the number of copies ≥8 (depth), ratio ≥4, and log (depth ratio) ≥2 in the region of gene amplification
Gene fusion	(a) One of the sequencing reads detected is derived from the following 12 genes: • *AKT2, ALK, BRAF, ERBB4, FGFR2, FGFR3, NRG1, NTRK1, NTRK2, PDGFRA, RET, ROS1* (b) The sequencing read fused with the sequencing read in (a) is derived from the following 12 genes; • *AHCYL1, BICC1, CCDC6, CD74, EML4, EZR, KIAA1549, KIF5B, SDC4, SLC34A2, TACC3, TPM3* (c) Allele frequency ≥3% (d) The percentage of gene fusion reads to the total number of reads ≥2.0e-6

Table 2. Mutation detection method and quality control

Type of mutation	Reference base sequence	Quality control standard
Substitution and indels	[redacted]	[redacted]
Copy number alteration	[redacted]	[redacted]
Gene fusion	[redacted]	[redacted]

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

To support the analytical performance of NCC Oncopanel System, the applicant submitted the data for accuracy, precision, specificity, limit of detection, and comparability with its prototype. A summary of evaluation is shown below.

(a) Accuracy

The following results of accuracy evaluation were submitted:

- Concordance with approved *in vitro* diagnostics

  Positive percent agreement and negative percent agreement between NCC Oncopanel System and approved *in vitro* diagnostics as comparators were determined using 34 clinical specimens for *human epidermal growth factor receptor 2 (HER2)* gene, *anaplastic lymphoma kinase (ALK)* fusion gene, and *ROS1* fusion gene (Table 3). Because the 34 specimens did not include those negative for *ALK* fusion gene or those positive for *ROS1* fusion gene, concordance for these variants was not assessed in this test.

  The accuracy of NCC Oncopanel System in detection of *epidermal growth factor receptor (EGFR)* gene mutation, *KRAS* gene mutation, *v-raf murine sarcoma viral oncogene homolog B1 (BRAF)* gene mutation, *HER2* gene, and *ALK* or *ROS1* fusion gene was assessed using specimens from 187 patients

enrolled in the TOP-GEAR research, on the basis of the positive percent agreement and negative percent agreement between the prototype[i] of NCC Oncopanel System and approved comparators (Table 4).

To confirm that the analytical performance does not substantially differ between NCC Oncopanel and the approved *in vitro* diagnostics, the applicant determined a necessary sample size. A total of [redacted] specimens were needed to be positive for each mutation in order to detect a difference in performance between NCC Oncopanel and a comparator based on the upper bound of 95% confidence interval (CI) assuming a positive percent agreement of [redacted]%. Considering a low detection frequency of fusion gene-positive specimens, at least [redacted] positive specimens were needed for assessment.

Table 3. Concordance between NCC Oncopanel System and approved *in vitro* diagnostics

Mutation	Comparator	Positive percent agreement [95% CI]	Negative percent agreement [95% CI]
ALK fusion gene	Histofine ALK iAEP kit (Approval No. 22600AMX00667000) Ventana OptiView ALK (D5F3) (Approval No. 22900EZX00041000)	80.0% (4/5) [37.6%, 96.4%]	Not assessed.
ROS1 fusion gene	OncoGuide AmoyDx ROS1 Gene Fusions Detection Kit (Approval No. 22900EZX00002000)	Not assessed.	100% (5/5) [56.6%, 100%]
HER2 gene amplification	Dako HercepTest (Approval No. 21200AMY00257000)	55.6% (5/9) [26.7%, 81.1%]	100% (9/9) [70.1%, 100%]

Table 4. Concordance between prototype and approved *in vitro* diagnostics

Mutation	Comparator	Positive percent agreement [95% CI]	Negative percent agreement [95% CI]
EGFR gene mutation	Therascreen EGFR Mutation Detection Kit RGQ [Qiagen] (Approval No. 22300AMX01256000) Cobas EGFR Mutation Test Kit v2.0 (Approval No. 22800EZX00011000) Cobas EGFR Mutation Test Kit (Approval No. 22500AMX01790000)	100% (15/15) [78%, 100%]	82% (18/22) [60%, 95%]
ALK fusion gene	Vysis ALK Break Apart FISH Probe Kit (Approval No. 22400AMX00630000)	86% (6/7) [42%, 100%]	100% (16/16) [79%, 100%]
ROS1 fusion gene	OncoGuide AmoyDx ROS1 Gene Fusions Detection Kit (Approval No. 22900EZX00002000)	100% (3/3) [29%, 100%]	100% (8/8) [64%, 100%]
KRAS gene mutation	MEBGEN RASKET Kit (Approval No. 22700AMX00094000)	100% (13/13) [75%, 100%]	100% (13/13) [75%, 100%]
BRAF gene mutation	Cobas BRAF V600 Mutation Test Kit (Approval No. 22600AMX01329000) THxID BRAF Kit (Approval No. 22800EZX00005000)	100% (9/9) [66%, 100%]	100% (8/8) [64%, 100%]
HER2 gene amplification	Dako HercepTest (Approval No. 21200AMY00257000)	55.6% (5/9) [21%, 86%]	100% (9/9) [66%, 100%]

- Concordance with Sanger sequencing

  To assess the accuracy of NCC Oncopanel System for detection of substitutions and indels, [redacted] mutation-positive clinical specimens, including those with [redacted] substitutions and [redacted] indels, were

[i] The prototype differs from NCC Oncopanel System in that the prototype uses [redacted].

analyzed to determine concordance between the prototype[ii] of NCC Oncopanel System and Sanger sequencing. The positive percent agreement was 95.8% (95% CI [79.7%, 99.3%]).

- Concordance with MassARRAY system
  To assess the accuracy of NCC Oncopanel System in detection of substitutions and indels, [redacted] clinical specimens, including those with [redacted] substitutions and [redacted] indels, were analyzed to determine concordance between the prototype[iii] of NCC Oncopanel System and MassARRAY system. The positive percent agreement was 100% (95% CI [97.1%, 100%]) for substitutions and 100% (95% CI [75.8%, 100%]) for indels.

- Concordance with quantitative PCR
  To assess the accuracy of NCC Oncopanel System in detection of copy number alterations, [redacted] clinical specimens were analyzed to determine concordance between NCC Oncopanel System and quantitative PCR. The positive percent agreement was 100% (95% CI [64.6%, 100%]).

- Correlation with whole exon sequencing
  To assess the accuracy of NCC Oncopanel System in detection of TMB, [redacted] clinical specimens ([redacted] lung cancer specimens, [redacted] breast cancer specimens, and [redacted] ovarian cancer specimens) were analyzed to assess correlation between TMB with whole exon sequencing and that with NCC Oncopanel System. The correlation coefficient (R^2) was 0.98.

(b) Precision

The intermediate precision of NCC Oncopanel System was assessed based on the allele frequency of positive and negative specimens. The positive specimen used was [redacted] having any of the following alterations: substitutions, indels, copy number alterations, and gene fusions. The negative specimen used was NA18507 (National Human Genome Research Institute). Test date and inter-batch variation were used as variation factors. The coefficient of variation relative to the expected allele frequency of 5% was 8.8% to 20.7%. The repeatability determined by 4 replicate analyses of the above specimens was 8.5% to 19.4%.

(c) Specificity

The specificity of the probe used to enrich the target gene region was assessed based on the number of reads using 3 commercially available specimens, i.e., [redacted], HapMap blood-derived genomic DNA specimen (NA18507), and [redacted], as well as [redacted] clinical specimens. The number of reads was ≥100 for 99.13% to 99.60% of bases for the commercial specimens and 97.02% to 98.68% of bases for the clinical specimens.

(d) Limit of detection

The limit of detection was determined based on the percent detection of mutations between the lower limit (10 ng) and upper limit (200 ng) of the DNA content that can be analyzed by NCC Oncopanel

[ii] The prototype differs from NCC Oncopanel System in that the prototype uses [redacted].
[iii] The prototype differs from NCC Oncopanel System in terms of [redacted] and [redacted].

System when the analysis was repeated [redacted] times. Specimens which has multiple allele frequencies or copy numbers, [redacted], were used, while a blood-derived genomic DNA specimen (NA18507) was used as a non-tumor tissue specimen. NCC Oncopanel System is designed to use cutoff values of [redacted] for detection of substitutions and indels, and [redacted] for gene fusions. To assess the detection sensitivity, including the range of allele frequency not more than these cutoff values, however, the limit of detection was determined based on the percent detection of mutations without using the above cutoff values. The limit of detection was [redacted]% for substitutions, [redacted]% for indels, [redacted] copies for copy number alterations, and [redacted]% to [redacted]% for gene fusions.

(e) Interfering substances

The effect of interfering substances has not been assessed for the following reasons:

- The recommended DNA extraction kit (QIAamp DNA FFPE Tissue Kit, Qiagen) for NCC Oncopanel is designed to appropriately remove impurities so that they are not carried over to the subsequent steps of processing.
- The previous clinical research has shown no particular problems.
- Intrinsic melanin is a known interfering substance and therefore its effect on the testing is clear.

(f) Effect of tissue type

The effect of tissue type on the detection sensitivity has not been assessed for the following reasons:

- Foreign substances that inhibit enzyme reactions appear to be eliminated during preparation of FFPE blocks and DNA extraction.
- When used in clinical research using specimens of ≥40 different types of cancers, including orphan cancers, NCC Oncopanel detected mutations in all tissue specimens used.

(g) Comparability with prototype

The prototype of NCC Oncopanel System was used in the accuracy evaluation using the MassARRAY system as a comparator. A template DNA extraction reagent for the prototype was different from that for NCC Oncopanel System. To justify the accuracy of NCC Oncopanel System demonstrated by the results of this test, the comparability between NCC Oncopanel System and its prototype was assessed using [redacted] clinical specimens on the basis of the positive percent agreement in detecting 53 substitutions, 16 indels, 22 copy number alterations, and 2 gene fusions. (Table 5)

Table 5. Positive percent agreement between prototype and NCC Oncopanel System

Result with prototype		Result with NCC Oncopanel System	
Type of mutation	Number of mutations	Number of positive calls	Positive percent agreement [95% CI]
Substitution	53	53	100% [93.2%,100%]
Indels	16	16	100% [80.6%, 100%]
Copy number alteration	22	22	100% [85.1%, 100%]
Gene fusion	2	2	100% [34.2%, 100%]
Total	93	93	100% [96.0%, 100%]

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

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

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

(a) Positioning of gene panel testing in cancer genomic medicine

The Expert Meeting for Cancer Genomic Medicine Promotion Consortium ("Expert Meeting") is convened 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[2] 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)[3] 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[4]" 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 to 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.

(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 cancer, 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 expert panel 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.

(c) Comprehensive genomic profiling

As aforementioned, the gene panel is intended 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) 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 made based on the results of discussion. The expert panel reports will be used by the patient's treating physician to explain the test results to the patient.

(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 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 functions have been established to ensure the efficacy and safety of cancer genomic medicine, and to collect and accumulate genomic and clinical information required for advancement of 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 NCC Oncopanel 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 determination of the eligibility of patients for the use of NCC Oncopanel System and patients defined in the proposed intended use:

The TOP-GEAR clinical research project using the prototype of NCC Oncopanel System was conducted from 2013 to 2014 in patients with solid tumors who had completed standard of care. In this clinical research, mutations that were useful in developing treatment plans were detected in 59 of 131 patients for whom analysis results were available. The results suggested the possibility of offering new treatment options. The results of the clinical research conducted in patients with advanced or recurrent solid tumor from 2016 to 2018 suggested the clinical utility of NCC Oncopanel System in obtaining information on the diagnosis and prognosis of patients with solid cancers, including orphan cancer for which no standard of care is available and cancer of unknown primary, as well as diagnosing hereditary cancers. The Trilateral Academic Society Guidance also recommends the use of CGP in these patient populations. For these reasons, the above mentioned patient populations should be included in the intended use population for NCC Oncopanel System. Since the main intended population for NCC Oncopanel System will be patients who have completed standard of care or patients for whom no standard of care is available, companion diagnostic claims are not included in the intended use of NCC Oncopanel System.

The patient population for the proposed intended use of NCC Oncopanel was defined as “patients with advanced or recurrent solid tumors.”

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 that 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 for the use of NCC Oncopanel System. In addition, considering that the intended patient population of CGP recommended currently by the Trilateral Academic Society Guidance is patients who have completed standard of care, NCC Oncopanel System can be introduced to clinical settings without including companion diagnostic claims in the intended use.

With the increased use of gene panel testing approved, accumulation of clinical experience based on test results obtained in routine clinical settings, and increased 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 target population will be communicated to healthcare professionals through revisions of the guidance or by other means.

The proposed intended use of NCC Oncopanel is modified as shown below because (1) the candidate patient population for the use of NCC Oncopanel 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 target population.

Intended Use
NCC Oncopanel is used to obtain the comprehensive genomic profile of tumor tissue of patients with solid tumors.

NCC Oncopanel System will be 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. Although the requirements for medical institutions that are allowed to perform CGP will be changed with the increased use of CGP, the use of NCC Oncopanel 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 patient 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 related to 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 NCC Oncopanel 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 NCC Oncopanel, 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 NCC Oncopanel System:

The 114 proposed target genes to be analyzed with NCC Oncopanel System were selected based on publications, etc. The target genes include genes that are considered relevant for cancer genomic medicine and those that are likely to lead to the development of new therapies. NCC Oncopanel is designed to detect ≥100 genes because (i) it is clinically useful to present the results of TMB obtained in gene panel testing used for CGP and (ii) information on sequencing of genes within a region of approximately 500 kB is necessary for precise measurement of TMB. For reference purposes, the proposed target genes were classified based on the information available as of August 21, 2017 and according to the levels of evidence shown in Attached Table 1 of the Trilateral Academic Society Guidance. The proposed target genes include ≥50 genes that have been reported to have mutations with a level of evidence of ≥3A where test results, together with information on available treatment options, can be assessed by the expert panel and then explained to the relevant patient. The proposed target genes also include 19 and 10 genes with a level of evidence of ≥3 which is useful in making diagnosis and prognosis, respectively. This finding is based on the results of the clinical studies.

In the clinical research using the prototype of NCC Oncopanel System, conducted in patients with advanced or recurrent solid tumor from 2016 to 2018, 212 patients underwent CGP. Of those, 187 patients had the results of CGP. Of the 187 patients, 156 patients (83%) had ≥1 mutation with any level of evidence defined in the Trilateral Academic Society Guidance. Among them, 25 patients (13%) received approved drugs, medications for off label use, or study drugs on the basis of the analysis results. MSK-IMPACT approved in the US in 2017 is a gene panel platform that is capable of detecting 468 genes. Clinical research using this gene panel testing was conducted to analyze specimens from ≥10,000

patients with advanced solid cancer, of whom 5009 were followed up for 1 year prior to the analysis, and of the 5009 patients, 527 (approximately 11%) were enrolled in clinical studies.[5] Although there are limitations in comparing the US data with the Japanese data because of differences in the status of approved drugs and clinical trials, the proposed target genes and mutations to be analyzed with NCC Oncopanel System are reasonable, considering that the percentage of patients who received pharmacotherapies based on the results with NCC Oncopanel System is similar to that of patients who received pharmacotherapies based on the results with MSK-IMPACT.

PMDA asked the applicant to explain how information on mutations in hereditary cancer genes presented as reference information were expected to be used in cancer genomic medicine.

The applicant's explanation:

- NCC Oncopanel System is not primarily intended to detect germline mutations, but expected to help physicians to address accidental or secondary findings.

- If any mutation in germ cells is detected, its result is presented as "germline mutation" on the sequencing report. Since the sequencing report is submitted to the expert panel as reference information, whether information on a germline mutation is returned to the patient will be decided in accordance with rules formulated for the institutional expert panel and the medical institution.

- As this information is positioned as reference information, whether a mutation is a germline mutation will be reported to the ordering physician upon request.

Patients or their legally acceptable representatives should be informed by the treating physician about the possible detection of germline mutations as accidental or secondary findings, before giving written consent to testing with NCC Oncopanel System. This advice is included in the instructions for use. For these reasons, even when information on hereditary cancer is obtained through gene panel testing with NCC Oncopanel System, the current structure of cancer genomic medicine can address appropriately such information.

PMDA's view:

Since CGP is performed to identify patients who may be subjected to pharmacotherapies, NCC Oncopanel must adequately cover genes with a level of evidence of ≥3A determined according to the Trilateral Academic Society Guidance. The applicant's explanation and the results of the clinical research using the prototype indicate that NCC Oncopanel 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.

If NCC Oncopanel System detects any mutation in 13 hereditary cancer genes, whether the mutation detected is a germline mutation will be reported to the ordering physician upon request. CGP will be performed only at the core hospitals and cooperative hospitals. Since these hospitals must meet the requirements for genetic counselling, etc., there will be no problem with the inclusion of germline mutations in the output report. As explained by the applicant, however, these analysis results are regarded as secondary findings to be used for reference purposes because NCC Oncopanel System is intended to help develop treatment plans for patients with solid tumors. Detection of germline mutations should not be included in the intended use.

Patients or their legally acceptable representatives should be informed by the treating physician about not only the possible detection of germline mutations as accidental or secondary findings but also the possibility that CGP with NCC Oncopanel System does not always lead to the identification of optimal treatment options including enrollment in clinical trials and treatment with unapproved drugs, before giving consent to testing with NCC Oncopanel 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 NCC Oncopanel System to detect mutations:

Because the main patient population for NCC Oncopanel System consists of patients who have completed standard of care and patients for whom no standard of care is available, the applicant decided not to include companion diagnostic claims in the intended use of NCC Oncopanel System. NCC Oncopanel System was designed with a focus on assurance of its analytical performance for collectively measuring multiple target genes. A comparison of the analytical performance for genes with mutations related to approved molecular-targeted drugs between NCC Oncopanel System and companion diagnostics demonstrated no marked difference. A verification test of their analytical comparability was not performed. The analytical performance of NCC Oncopanel was assessed according to the concept shown below.

A set of representative mutations selected for assessment of the analytical performance for detecting base substitutions and indels meet the following requirements: (i) covering all types of mutations (substitutions and indels associated with activating or loss-of-function mutations), (ii) containing guanine-cytosine (GC)-rich sequences, and (iii) including mutations in the homopolymer regions. In addition, the size of an inserted or deleted region of the selected indels had to range from [redacted] to [redacted] bp. The analytical performance for detection of these mutations was considered to allow for detection of mutations with the size of an inserted or deleted region within the above range. The number of mutations required for accuracy evaluation was estimated to be ≥[redacted] from the results of the clinical research, etc., assuming an expected concordance of [redacted] and an acceptable range of concordance of [redacted]%. The accuracy evaluation of NCC Oncopanel using [redacted] substitutions and [redacted] indels was, therefore, considered appropriate.

For assessment of the performance for detection of copy number alterations and gene fusions, *HER2* and *ALK*, respectively, were selected as representative gene mutations because of the limited number of

companion diagnostics with verified performance that can serve as a comparator. Considering the difference in the test principle, the number of mutations required for accuracy evaluation was estimated to be [redacted], assuming an expected concordance of [redacted] and an acceptable range of concordance of [redacted]%. The accuracy evaluation of NCC Oncopanel using [redacted] copy number alterations and [redacted] gene fusions was, therefore, considered appropriate. NCC Oncopanel System is designed to detect [redacted]% of [redacted] target gene fusions registered in COSMIC.

In summary, the evaluation results submitted support the appropriate analytical performance of NCC Oncopanel.

PMDA asked the applicant to explain the rationale for the comparators selected to evaluate accuracy in detecting base substitutions and indels.

The applicant's explanation:
There was no approved gene panel test in Japan during the development of NCC Oncopanel System. Sanger sequencing and the MassARRAY assay were selected as comparators, although both have a different test principle from that of NCC Oncopanel System. The accuracy of NCC Oncopanel in detecting base substitutions and indels was evaluated by comparing the results with these comparators methods. Indels can be detected by EGFR mutation tests. The accuracy of NCC Oncopanel in detecting these mutations was also evaluated using an EGFR mutation test kit approved as a companion diagnostic. The results of analysis of [redacted] frozen tissue or FFPE specimens by an external gene panel test [redacted] in compliance with CLIA were used to determine concordance between NCC Oncopanel and this comparator method in detecting mutations in a certain gene region common to both methods. The positive percent agreement was 96.4% (95% CI [82.3%, 99.4%]) and the positive predictive rate was 93.1% (95% CI [78.0%, 98.1%)]. Of [redacted] specimens that were called positive by the comparator method but negative by NCC Oncopanel System, [redacted] specimens were considered negative eventually because the mutations were not reported as clinically significant mutations by NCC Oncopanel System. The remaining [redacted] specimens were also considered negative after high-background filtering. Despite the performance tests conducted only to a limited extent, the results of detection of base substitutions and indels by NCC Oncopanel System were consistent with those by other DNA sequencers. The GC content may affect the depth and percentage of coverage. The GC content did not affect the mean depth of coverage in the tested region with a GC content of 40% to 60%.

PMDA asked the applicant to explain the reason why some specimens were called positive for a copy number alteration or gene fusion by the approved diagnostics but negative by NCC Oncopanel System.

The applicant's explanation:
All of the 4 discordant specimens called negative for the amplification of *HER2* gene by NCC Oncopanel System had intratumoral heterogeneity of *HER2* gene amplification or *HER2* protein expression and a tumor cell content of <50%. The DNA derived from tumor cells accounting for ≥50% of the tissue specimens that were negative for gene amplification or the DNA derived from normal cells appeared to have contributed to the negative result of these specimens. NCC Oncopanel System needs to use DNA probes to identify the target genes involved in gene fusions. Research by the National Cancer Center

revealed fusions with repetitive sequences in [redacted] of *ALK* fusion-positive [redacted] specimens. As it is difficult to design probes that can detect these fusion genes, this assay is less sensitive to detect the fusion genes than fluorescence *in situ* hybridization (FISH) using NCC Oncopanel System. On the basis of these findings, the applicant will provide the following advice: NCC Oncopanel System has no sufficient established performance for detecting gene fusions and copy number alterations compared with the comparator methods; and specimens should be re-analyzed using an available approved companion diagnostics if information on those mutations not presented in the summary report is required.

PMDA asked the applicant to explain the rationale for the accuracy of NCC Oncopanel System verified on the basis of the evaluation results with the prototype, which uses a different analysis software program, library construction reagents, or panel reagents from those of NCC Oncopanel System.

The applicant's explanation:
The concordance between NCC Oncopanel System and the approved *in vitro* diagnostics or Sanger sequencing method was evaluated using the analysis software program [redacted], which is a different version from that of NCC Oncopanel System. However, the update from [redacted] to the analysis software program [redacted] used in NCC Oncopanel System was intended to strengthen error handling with a change to the access authority of output files, address file naming conventions after returning DNA sequence data, and add a title to the QC report. The change did not involve the detection of mutations or calling performance. For this reason, the accuracy of NCC Oncopanel System can be assured based on the results of evaluation using the previous version of the analysis software program.

PMDA's view:
The applicant explained the rationale for the selection of a set of representative mutations used in evaluation of the analytical performance for detection of base substitutions and indels, as well as the rationale for the accuracy of NCC Oncopanel System verified on the basis of the evaluation results with the previous generation of NCC Oncopanel System. The applicant's explanations are acceptable. Gene panels with publicly established analytical performance, which can serve as a comparator, are not currently available in Japan. The applicant therefore had no choice but to use the assay methods having a different test principle as comparators and perform assay with the suboptimal number of specimens to allow a certain level of discordance because of a difference in the test principle. The applicant's situation is understandable. In the context of cancer genomic medicine, external precision control with the use of an appropriate comparator method and a mutation set is essential when gene panel test systems, including NCC Oncopanel System, are used in core hospitals and other related institutions. Collection of further information on the accuracy of NCC Oncopanel System and provision of such information to healthcare professionals should be continuously discussed, based on the results of external precision controls performed in the post-marketing clinical setting.

The performance of NCC Oncopanel System for detection of copy number alterations and gene fusions was assessed only by comparing it with approved companion diagnostics for *ALK* and *HER2*. Considering that only a limited number of comparators are available, this approach is acceptable. The study results presented in this regulatory submission support the applicant's position that NCC

Oncopanel System to be used in a DNA sequencer cannot achieve a detection sensitivity comparable to that of immunostaining or FISH because of a difference in the test principle. Since the approved test kits for detection of gene amplifications or gene fusions target only a limited number of genes or cancer types, the introduction of NCC Oncopanel System into clinical practice will be of some significance. Although the performance test was evaluated only to a limited extent, NCC Oncopanel System achieved 100% specificity and 100% positive percent agreement in detecting *ALK* fusion genes and *HER2* gene amplifications. The likelihood of calling false positive by NCC Oncopanel System appears to be at least low. Nevertheless, the results of these performance tests should be included in the instructions for use and communicated to healthcare professionals. In addition, appropriate advice on limitations to the performance of NCC Oncopanel System in detecting copy number alterations and gene fusions should also be included in the instructions for use.

The data submitted show no particular problem in other analytical performances of NCC Oncopanel.

PMDA concluded that NCC Oncopanel System has a certain level of performance that meets requirements for CGP in clinical practice.

The applicant did not investigate the effect of interfering substances and tissue type in the performance assessment of NCC Oncopanel System. This is considered acceptable because the quality of gene panel testing will be assured on the basis of the basic concept developed by laboratory test-related academic societies, etc. in Japan.

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 NCC Oncopanel System:

NCC Oncopanel System employs the following 5 types of DBs: clinical variant DBs, gene definition DBs, SNP DBs, a known mutation DB, and a false positive mutation DB, of which the latter two are in-house DBs (Table 6). The DBs already known by specialists in cancer genomic medicine in Japan, except for the in-house EPDB, are used as clinical variant DBs, gene definition DBs, and SNP DB. The EPDB, developed by the National Cancer Center, includes the availability of approved companion diagnostics and a list of variants selected according to the National Comprehensive Cancer Network (NCCN) guidelines, treatment guidelines, and publications in PubMed. The known mutation DB used in the mutation detection process and the false-positive mutation DB used in the quality evaluation process are both in-house DBs and are managed as unique DBs different from the EPDB. The EPDB, known mutation DB, and false-positive mutation DB are planned to be regularly updated [redacted] times. These DBs will be updated and managed according to the written in-house procedures.

Prior to update of the DBs, a knowledge management team will collect information to be registered in the DBs according to the written procedures. The written procedures specify the items to be used and procedures for collecting information, including guidelines to be followed, for each DB. A judging committee will judge whether the information collected by the knowledge management team is registered in the DBs. The knowledge management team and the judging committee consist of specialists in cancer genomic medicine, who meet the respective qualifications.

Table 6. DBs used by NCC Oncopanel System

Positioning	DB	Applicable process
Clinical variant DB	EPDB (in-house DB), COSMIC, ClinVar	Annotation process
Gene definition DB	RefSeq, Ensembl	Annotation process
SNP DB	1000 Genome Project, ESP6500, ExAC, HGVD	Annotation process
Known mutation DB	In-house DB	[redacted]
False-positive mutation DB	In-house DB	[redacted]

PMDA's view:
On the basis of the data submitted, PMDA concluded that the analysis process through to report output was appropriately managed based on the predefined mutation detection criteria, data quality criteria, and report outputting criteria.

The DBs used by NCC Oncopanel System for detection of mutations, except for the in-house DBs, can be positioned as clinically known and public DBs because i) all of these DBs are opened to the public and their transparency is assured, ii) they are already widely used as main search tools by healthcare professionals and researchers specialized 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 was considered unnecessary for regulatory review of NCC Oncopanel System. The use of the in-house DBs is unlikely to cause any bias in interpretations of mutations for the following reasons:

- EPDB: This DB lists representative mutations or gene fusions in 114 genes, extracted by the National Cancer Center. These mutations have been reported multiple times in publications and their significance has been determined as a result of analysis using systems other than next-generation sequencers.

- Known mutation DB: This DB lists mutations with a level of evidence of [redacted] according to the therapeutic efficacy criteria, developed by the Trilateral Academic Society Guidance on the basis of information on genetic mutations identified by approved companion diagnostic tests and literature reports in and outside Japan and indels spanning ≥[redacted] bases that have been registered ≥[redacted] times in COMIC.

- False-positive mutation DB: This DB lists mutations called false-positive after filtering based on a predefined threshold.

The external DBs used by NCC Oncopanel System will be updated as scientific and clinical findings are accumulated in the future. The applicant intends to update the in-house DBs every [redacted]. The clinical significance of variants identified on the basis of well-known public DBs will be determined in accordance with the criteria and procedures evaluated in the review, and the in-house DBs will be updated on the basis of information on genetic mutations identified by approved companion diagnostic tests and publications in and outside Japan according to the procedures evaluated in the review. The quality of mutation information presented by NCC Oncopanel System can be assured, provided that the analysis process is appropriately controlled. The use of the updated DBs is unlikely to cause any bias in interpretations of mutations as far as the information registered in the DBs is appropriately managed as

described above. Changes in the DBs need not be checked each time they are made after commercialization of NCC Oncopanel System.

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

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 of 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of NCC Oncopanel to the Essential Principles.

PMDA’s conclusion on the conformity of NCC Oncopanel 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,” appropriate physicians and medical institutions selected for the use of NCC Oncopanel should use the product in compliance with the guidance for proper use in order to promote the proper use of NCC Oncopanel. In line with this, PMDA added condition of approval to ensure that the applicant takes necessary measures.

Based on the above, PMDA has comprehensively reviewed the conformity of NCC Oncopanel System 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 conclusion presented in Section “3.B Outline of the review by conducted PMDA” and concluded that there was no particular problem.

5. Manufacturing Process

5.A Summary of the submitted data

The applicant submitted data on the manufacturing process and site as well as quality control data for the evaluation of the manufacturing process of NCC Oncopanel System.

5.B Outline of the review conducted by PMDA

PMDA reviewed the data on the manufacturing process and concluded that there was no particular problem.

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 NCC Oncopanel 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 NCC Oncopanel has been widely used as part of advanced medicine at the National Cancer Center.

7.B Outline of the review conducted by PMDA

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

- NCC Oncopanel has been used as part of advanced medicine in Japan to a certain extent.

- The performance of NCC Oncopanel has been evaluated on the basis of its analytical performance and the appropriateness of the analytical process through to report output. The efficacy and safety of NCC Oncopanel 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 NCC Oncopanel 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 (Act 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

NCC Oncopanel is a combination medical device comprised of a template DNA extraction reagent and an analysis software program. NCC Oncopanel is used to provide information on genetic mutations that helps physicians to develop treatment plans based on comprehensive profiling of 114 cancer-related genes isolated from tissue from patients with solid tumors. There was only 1 key issue to be addressed in the review of NCC Oncopanel. On the basis of comments from the Expert Discussion, PMDA reached the following conclusions.

(1) Clinical performance

The review of NCC Oncopanel 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 NCC Oncopanel System. A condition of approval should be imposed regarding the requirements for medical institutions that are permitted to perform CGP using NCC Oncopanel and the rules for identifying eligible patients.

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 condition of approval.

Intended Use

NCC Oncopanel is intended to provide the comprehensive genomic profiling of tumor tissue from patients with solid tumor.

Condition of Approval

The applicant is required to take necessary measures to ensure that physicians with sufficient knowledge and experience related to 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.

The product is not classified as a biological product or a specified biological product. No post-marketing use-results survey for NCC Oncopanel is required.

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

References

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