August 19, 2024
Medical Device Evaluation Division
Pharmaceutical Safety 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 cancer genome profiling)
Brand Name	HemeSight Analysis Program
Applicant	Otsuka Pharmaceutical Co., Ltd.
Date of Application	March 29, 2024 (Application for marketing approval)

Results of Deliberation

In its meeting held on August 19, 2024, the Surveillance Committee on Software as a Medical Device, Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs 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 not classified as a biological product or a specified biological product.

Approval Conditions

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 implement appropriate procedures and controls for protecting personal information received and to implement up-to-date data security and privacy measures for preventing unauthorized access to relevant data and information.

Review Report

July 26, 2024

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	Program 01, Diagnostic Program
Term Name	Software for gene variants analysis (for cancer genome profiling)
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Applicant	Otsuka Pharmaceutical Co., Ltd.
Date of Application	March 29, 2024
Items Warranting Special Mention	
	SAKIGAKE designation device (SAKIGAKE Device Designation No. 3 of 2019 [*31 ki*]; PSEHB/MDED Notification No.0619-3 dated June 19, 2020, by the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
	The product for SAKIGAKE comprehensive evaluation consultation for medical devices
Reviewing Office	Office of Software as a Medical Device, Office of *In Vitro* Diagnostics

Review Results

July 26, 2024

Classification	Program 01, Diagnostic Program
Term Name	Software for gene variants analysis (for cancer genome profiling)
Brand Name	HemeSight Analysis Program
Applicant	Otsuka Pharmaceutical Co., Ltd.
Date of Application	March 29, 2024

Results of Review

The HemeSight Analysis Program (hereinafter referred to as the "HemeSight Program") is a gene variant analysis program that provides genomic profiles summarizing information on variants related to hematological malignancies based on the base sequence data as input information obtained by sequence analyses of the deoxyribonucleic acid (DNA) of the tumor and normal specimens and the ribonucleic acid (RNA) of tumor specimens, from patients with hematological malignancies or similar diseases. The data obtained by genomic profiling will be used for diagnosis of hematological malignancies or similar diseases, selection of treatment options, and prediction of prognosis based on the "Guidelines for genomic testing of hematological malignancies," developed by the Japanese Society of Hematology (hereinafter referred to as "Genomic Testing Guidelines") and other guidelines. The HemeSight Program is used in combination with the "HemeSight *In Vitro* Diagnostics" (Receipt No. 5130658000453), for which an application for marketing approval has been filed as a separate product, and a sequencer, "NextSeq 550Dx System" (Notification No. 13B1X10303000001). While comprehensive genomic profiling (CGP) assays for solid tumors have been approved, the HemeSight Program has significant novelty in that it is intended for hematological malignancies and similar diseases.

The current views on the clinical usefulness of CGP in patients with hematological malignancies are described in the Genomic Testing Guidelines and the "Positioning of gene panel testing for hematological malignancies and its use guidelines" formulated by the "Group for the development of a system for providing hematological malignancy gene panel testing and the guidelines" as part of the Comprehensive Research Project for Cancer Control, Disease/Disorder Control Research Areas funded by a Health Labour Sciences Research Grant. Based on these views, it is reasonable to assume that the results should be evaluated by the expert panel at medical institutions specialized in cancer genomic medicine in order to implement testing with the HemeSight Program, equivalent to that implemented for CGP for solid tumors. Accordingly, Approval Condition 1, as discussed later in this section, was included to specify the requirements for medical institutions in which CGP is performed for hematological malignancies as well as the provision for the implementation of an expert panel review.

Conversely, the Genomic Testing Guidelines defines “fast-track” mutations for which expedited reporting of results is preferred without review by the expert panel in order to respond to acute diseases, a point that differs from the CGP for solid tumors. For this reason, the system is designed to return the result for “fast-track” mutations ahead of other results.

In the review of the HemeSight Program, from the viewpoints of whether the system can provide test results that can be used for the diagnosis of hematological malignancies or related diseases, selection of treatment options, and prediction of prognosis based on the Genomic Testing Guidelines and other guidelines, the following were evaluated: (1) the appropriateness of the timing, purpose, and patient population intended for testing with the HemeSight Program; (2) the appropriateness of the preparation process and the content of the analysis result report for “fast-track” mutations and other variants; and (3) the appropriateness of the capability to detect target variants.

As for (1) the timing, purpose, and patient population intended for testing, the Genomic Testing Guidelines state that CGP for the detection of variants related to hematological malignancies and similar diseases is useful for “diagnosis, prediction of prognosis, and selection of treatment options at the first onset of hematological malignancies” and “selection of treatment options for relapsed or refractory hematological malignancies.” The usefulness for each disease by use (diagnosis/prediction of prognosis/selection of treatment option) is summarized as “level of recommendation for panel testing by disease type/stage.” Genes that are regarded as useful for the diagnosis, prediction of prognosis, and selection of treatment options for patients with hematological malignancies are selected as target genes to be analyzed with the HemeSight Program based on the Genomic Testing Guidelines and other guidelines. Based on the above, it was concluded that there are no particular problems with the use of the HemeSight Program within the range specified in the Genomic Testing Guidelines, which were established in accordance with the current consensus. However, there may be cases in which CGP is not necessary, for instance, in cases where conventional tests are sufficient or cases that do not meet the recommended conditions for the indicated intervention measures under consideration. Therefore, whether it is appropriate to perform CGP should be examined thoroughly after comprehensively considering the guidelines of related academic societies and other test options.

As for the appropriateness of the preparation process in (2), the variant detection principle, the details of internal databases that pool information from public databases used in processes such as the annotation process, or the details of in-house databases, operational processes such as updating databases, and the criteria for the output of analysis result reports were assessed for their appropriateness. It was concluded that there were no particular problems. One of the databases referenced in the output of analysis result reports is the “Fast-track mutations database,” which is an in-house database that defines variants which were confirmed to be detectable by the HemeSight Program, among the fast-track mutations listed in the Genomic Testing Guidelines. The database is to be updated when the Genomic Testing Guidelines are revised. When the database is updated, an application for confirmation

of changes to the plan can be submitted based on Article 23-2-10, paragraph 2, Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960). If the capability to detect the fast-track mutations to be added meets the prespecified target criteria, to make changes to the approved matter, a submission of a notification will suffice. The application for confirmation (Receipt No. 5130678004477) was reviewed for the database update procedure and the appropriateness of the target criteria. It was concluded that the results indicated no particular problems.

To support the appropriateness of the capability to detect target variants, the applicant submitted data on accuracy, precision, specificity, the lower limit of detection, and the effect of interfering substances for all target genes to be analyzed, and data on accuracy and the lower limit of detection for fast-track mutations. These endpoints are similar to those for similar approved products intended for CGP of solid tumors except in relation to fast-track mutations. The HemeSight Program is used in combination with the "HemeSight *In Vitro* Diagnostics," which is currently in the application process for marketing approval as a separate product. The endpoints for these products, for which applications were filed separately, do not differ from the endpoints that would be required if an application for the products were to be filed as a combination medical device, indicating that all the required endpoints have been evaluated. After examining the details of evaluation, it was concluded that the results indicate no particular problems.

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

As a result of its review, PMDA has concluded that the HemeSight Program may be approved for the following intended use, with the following conditions, and that the results should be presented to the Surveillance Committee on Software as a Medical Device.

Intended Use

The HemeSight Analysis Program is intended to display and provide the results of analysis conducted based on base sequence data such as those obtained with the HemeSight *In Vitro* Diagnostics, which is used in combination with the HemeSight Analysis Program. The HemeSight Analysis Program provides comprehensive genomic profiling of tumors, etc. in patients with hematological malignancies or similar diseases.

Approval Conditions

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 implement appropriate procedures and controls for protecting personal information received and to implement up-to-date data security and privacy measures for preventing unauthorized access to relevant data and information.

Review Report

July 26, 2024

Product for Review

Classification	Program 01, Diagnostic Program
Term Name	Software for gene variants analysis (for cancer genome profiling)
Brand Name	HemeSight Analysis Program
Applicant	Otsuka Pharmaceutical Co., Ltd.
Date of Application	March 29, 2024
Proposed Intended Use	HemeSight Analysis Program analyzes FASTQ files obtained by base sequencing of DNA libraries to detect genetic abnormalities of hematological malignancies.

Items Warranting Special Mention

SAKIGAKE designation device (SAKIGAKE Device Designation No. 3 of 2019 [*31 ki*]; PSEHB/MDED Notification No.0619-3 dated June 19, 2020, by the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

The product for SAKIGAKE comprehensive evaluation consultation for medical devices

Table of Contents

List of Abbreviations

C-CAT	Center for Cancer Genomics and Advanced Therapeutics
CDx	Companion Diagnostics
CGP	Comprehensive Genomic Profiling
DHL	Double Hit Lymphoma
DNA	Deoxyribonucleic Acid
FFPE	Formalin-Fixed Paraffin-Embedded
FISH	Fluorescent *in situ* Hybridization
GRC	Genome Reference Consortium
ICC	International Consensus Classification
IDATEN	Improvement Design within Approval for Timely Evaluation and Notice
Indel	Insertion/Deletion
IPSS	International Prognostic Scoring System
IPSS-M	Molecular International Prognostic Scoring System
mRNA	messenger RNA
PCR	Polymerase Chain Reaction
RNA	Ribonucleic Acid
SNP	Single Nucleotide Polymorphism
SNV	Single Nucleotide Variant
VAF	Variant Allele Frequency
VUS	Variant of Unknown Significance
WGS	Whole Genome Sequencing
WHO	World Health Organization

I. Product Overview

The HemeSight Analysis Program (hereinafter referred to as the "HemeSight Program") is a gene variant analysis program that generates genomic profiles summarizing information on variants related to hematological malignancies based on the FASTQ files[i] as input information obtained by sequence analyses of the tumor's DNA and of normal specimens and the RNA of tumor specimens, from patients with hematological malignancies or similar diseases. The data generated by genomic profiling will be used for diagnosis of hematological malignancies or similar diseases, selection of treatment options, and prediction of prognosis based on the "Guidelines for genomic testing of hematological malignancies," developed by the Japanese Society of Hematology (hereinafter referred to as "Genomic Testing Guidelines")[1] and other guidelines.

As shown in Figure 1, the HemeSight Program consists of a DNA analysis pipeline, which analyzes DNA for single nucleotide variants (SNVs) and short insertions and deletions (Indels), or SNVs/Indels, as well as structural variants, and an RNA analysis pipeline, which analyzes RNA for fusion genes and structural variants. Genes that are useful for the diagnosis, prediction of prognosis, and selection of treatment options for patients with hematological malignancies are selected as target genes to be analyzed with the HemeSight Program. The number of genes for each variant type was as follows: SNVs/Indels by DNA analysis pipeline, 319 genes; structural variants by the DNA analysis pipeline, 329 genes; and fusion genes and structural variants by the RNA analysis pipeline, 197 genes. The DNA analysis pipeline is composed of an analysis system to call SNVs/Indels (hereinafter referred to as "Genomon mutation call" and an analysis system to call structural variants (hereinafter referred to as "Genomon SV." The RNA analysis pipeline is composed of "Genomon RNA," an analysis system which detects overall fusion genes and structural variants, "Proximal RNA," an analysis system which detects fusion genes and structural variants present in intergenic or intragenic proximal regions that are difficult to detect with Genomon RNA, and "Genomon SV RNA," an analysis system which detects fusion genes and structural variants related to the *DUX4* gene.

[i] A text file that contains the base sequence of each read and its quality

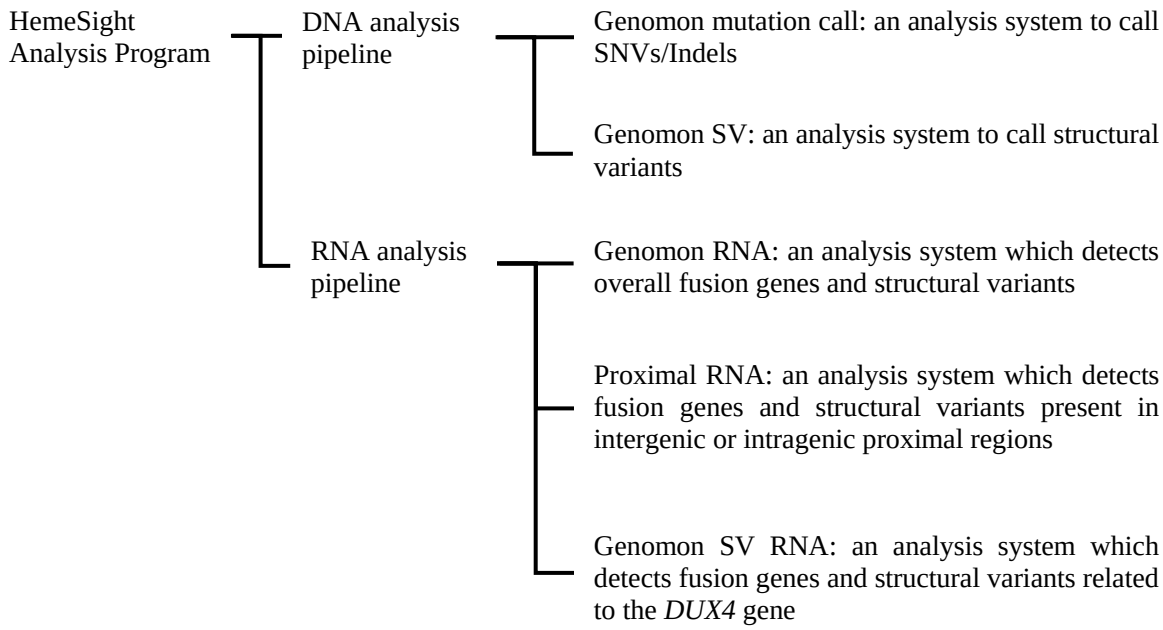

Figure 1. Outline of analysis pipelines

Figure 2 shows the flowchart of an analysis procedure with the HemeSight Program. First, DNA and RNA of tumors from fresh specimens (peripheral blood, bone marrow fluid, tissue, or celomic fluid) are obtained from patients or from formalin-fixed paraffin-embedded (FFPE) specimens. As matched control samples, DNA was extracted from the normal tissue of oral mucosa or nail of patients. After library preparation, polymerase chain reaction (PCR) amplification, and target enrichment by hybrid capture, a FASTQ file is generated by sequencing. The process uses the "HemeSight *In Vitro* Diagnostics" (Receipt No. 5130658000453), for which an application for marketing approval has been filed as a separate product, and a sequencer, "NextSeq 550Dx System" (Notification No. 13B1X10303000001). The FASTQ file generated in this process is input to the HemeSight Program. The analysis steps with the HemeSight Program are summarized as follows. When an FASTQ file generated in the process described above is uploaded to a prescribed cloud computing system by the user, the FASTQ file is input to the HemeSight Program, and after alignment with the reference sequence, variants are called. In the DNA analysis pipeline, after comparing the tumor and normal data, a sequence found only in tumor is called as a variant. Each called variant is annotated with information on clinical significance based on multiple databases, and filtering of variants is performed based on quality information and output requirements. Variants that meet the filtering condition are output into an analysis result report. The analysis report also provides variant calling results, which are reference information not within the scope of this approval, such as variants classified as multi-base substitution and germline variants. In addition, the following types of information listed in the Genomic Testing Guidelines is also provided: the evidence levels[ii] for clinical usefulness, diagnosis, the selection of treatment option and the prediction of prognosis, as well as drug information. These are also regarded

[ii] The result is presented on a 4-point scale (A-D), with A being the highest evidence level.

as information not within the scope of the approval. The analysis report can be obtained through access to the prescribed cloud computing system by the user.

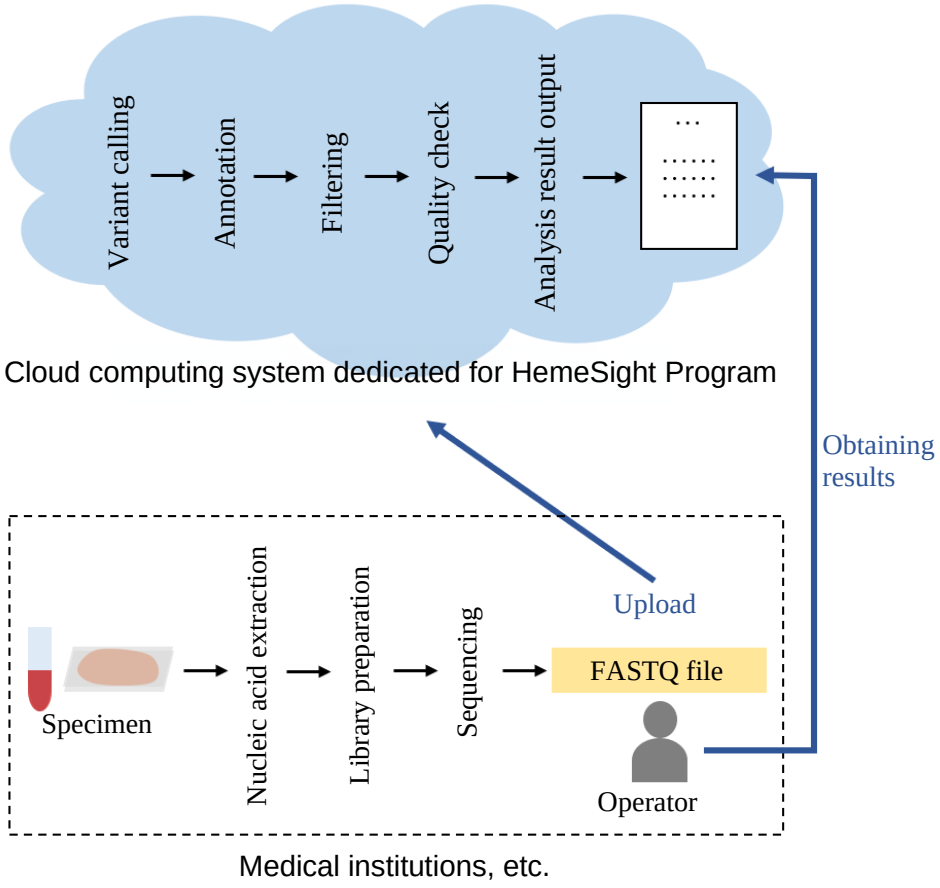

Figure 2. Flowchart of overall testing

The method of reporting results for the HemeSight Program was evaluated based on the current clinical practice regarding hematological malignancies and the details of the Genomic Testing Guidelines. Some hematological malignancy diseases are acute diseases, which advance rapidly, such as acute myeloid leukemia. In the Genomic Testing Guidelines, these diseases are included among the targets of comprehensive genomic profiling (CGP). In acute diseases and other specific diseases, it is desirable to report the results promptly to allow appropriate treatment for the disease type to be initiated without delay. Conversely, variants that need more meticulous interpretation should be evaluated by the expert panel. To address these issues, the Genomic Testing Guidelines were partially revised in 2022, and the revised guidelines define “fast-track” mutations for which expedited reporting of results is desirable without review by the expert panel. The guidelines recommend that the rest of the variants should be evaluated in detail by the expert panel.

Based on the situation above, the results obtained with the HemeSight Program are reported as shown in Figure 3. To identify the fast-track mutations, the HemeSight Program references the “Fast-track

mutation database," which is an internal database. This database is an in-house database that defines variants which were confirmed to be detectable by the HemeSight Program, among the fast-track mutations listed in the Genomic Testing Guidelines. Currently, the variants defined in the database are either SNVs/Indels or structural variants called in the DNA analysis pipeline. To meet the requirements for reporting of results recommended by the Genomic Testing Guidelines above, in the HemeSight Program, first, FASTQ files derived from DNA specimens are analyzed in the DNA analysis pipeline, and the results for fast-track mutations are generated as an interim report. The analysis for the rest of the variants is performed with the HemeSight Program when FASTQ files derived from RNA specimens are obtained, together with FASTQ files derived from DNA specimens, and an analysis result report (final report) will be generated.

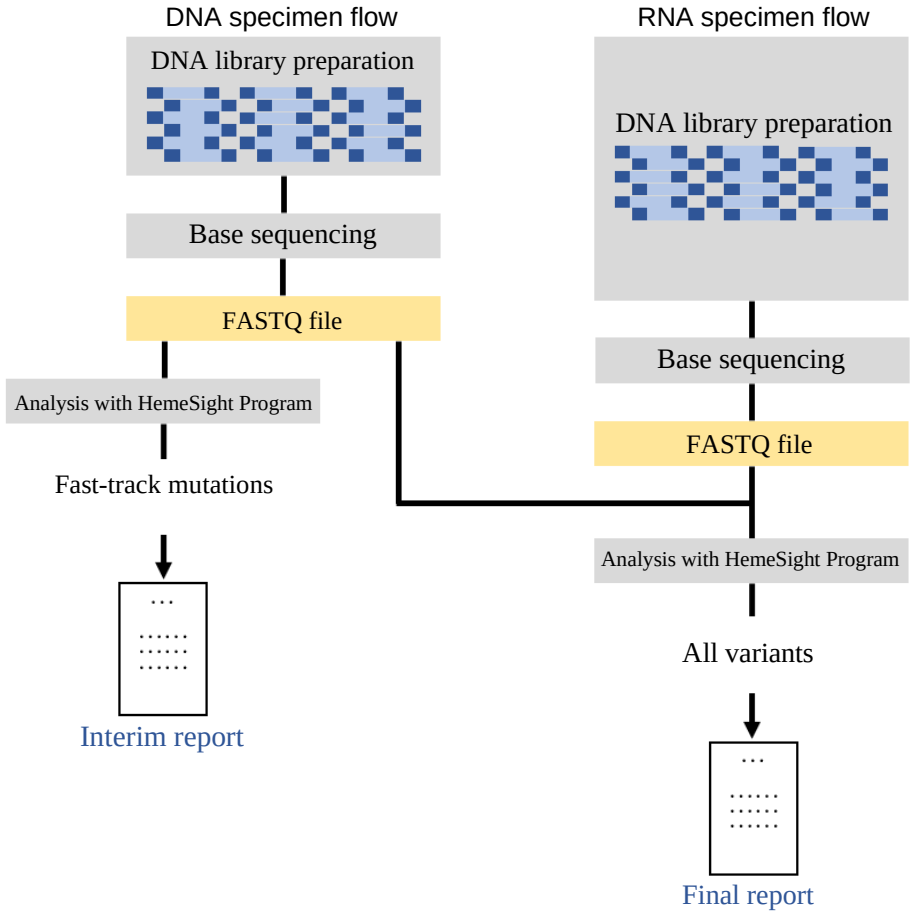

Figure 3. Flowchart for reporting the results of the HemeSight Program

The database is generated according to the Genomic Testing Guidelines. When the Genomic Testing Guidelines are revised to add new fast-track mutations, the database is to be updated to reflect the changes. Normally, filing of a partial change application is required because it is necessary to confirm the capability to detect newly added variants by conducting a review. The applicant considers that it is appropriate to promptly implement changes introduced by the revised Genomic Testing Guidelines. Accordingly, separately from the present application, the applicant filed an application for confirmation

of changes to the plan concerning updating of the database (Receipt No. 5130678004477; hereinafter referred to as "Improvement Design within Approval for Timely Evaluation and Notice [IDATEN] application") in accordance with Article 23-2-10, paragraph 2, Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960).

II. Summary of the Data Submitted and Outline of the 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 relevant expert advisors present during the Expert Discussion on the HemeSight Program have declared that they do not fall under the Chapter 3, Section 5 of the "Rules for Convening Expert Discussions, etc. by the Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

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

1.A Summary of the data submitted

1.A.(1) History of development

In Japan, multiple products intended to be used for CGP of solid tumors have been approved and included in public healthcare insurance coverage, and these products are mainly used for the purpose of selecting treatment options. In the area of hematological malignancies, many pathogenic variants specific to hematological malignancies have been discovered. There is a need for CGP of hematological malignancy-associated genes to be covered by public healthcare insurance. Accordingly, based on the currently available evidence, the following guidelines were formulated: the "Guidelines for genomic testing of hematological malignancies" ("Genomic Testing Guidelines") in 2018; and the "Positioning of gene panel testing for hematological malignancies and its use guidelines" (hereinafter referred to as the "Use Guidelines")[2] by the "Group for the development of a system for providing hematological malignancy gene panel testing and the guidelines" as part of Comprehensive Research Project for Cancer Control, Disease/Disorder Control Research Areas funded by a Health Labour Sciences Research Grant in 2022. In addition, World Health Organization (WHO) disease classifications[3-5] were revised, and International Consensus Classification (ICC)[6,7] was published in 2022; therefore, accurate diagnosis on the basis of variants is now required. As for the prediction of prognosis, the Molecular International Prognostic Scoring System (IPSS-M) was released in 2022 after adding variants for myelodysplastic syndromes to the International Prognostic Scoring System (IPSS). Based on the above, in the treatment of hematological malignancies in clinical practice, genomic testing is regarded as useful not only for treatment selection but also for diagnosis and prediction of prognosis.

There is a need for CGP of hematological malignancies, and the Genomic Testing Guidelines and other guidelines have been established. In response to these circumstances, the applicant submitted

applications for marketing approval of the HemeSight Program and "HemeSight *In Vitro* Diagnostics," which is to be used in combination with the HemeSight Program.

The HemeSight Program was designated as a device for the SAKIGAKE designation system (SAKIGAKE Device Designation No. 3 of 2019 [*31 ki*] dated June 19, 2020).

1.A.(2) Use in foreign countries

The HemeSight Program is not approved or certified in other countries.

2. Design and Development

2.(1) Performance and safety specifications

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

The specifications for the analytical performance of the HemeSight Program, the process control criteria for the DNA library preparation step and analysis process have been established. The specifications for the qualification of the DNA library preparation step, and the qualification, accuracy, and repeatability of DNA libraries were specified as the quality control methods of the "HemeSight *In Vitro* Diagnostics," which is to be used in combination with the HemeSight Program. The following 4 types of control materials have been established: DNA (DNA 1 control sample) containing representative SNVs/Indels for hematological malignancies shown in Table 1; DNA (DNA 3 control sample) containing the structural variants (IGH::*MYC* rearrangement) shown in Table 2; RNA (RNA control sample) containing representative abnormal fusion genes for hematological malignancies shown in Table 3; and as matched-control samples, DNA (DNA 2 control sample) that does not contain specified abnormal genes.

Table 1. Variants to be evaluated contained in DNA 1 control sample

Gene	Mutation	Refseq number	Reference sequence	Substitution sequence	Variant type	VAF
ASXL1	G646fs*12	NM_015338	A	AG	Insertion	40.00%
BCOR	Q1174fs*8	NM_001123383	G	GT	Insertion	70.00%
GATA1	Q119*	NM_002049	C	T	SNV	10.00%
GATA2	G200fs*18	NM_001145662	AC	A	Deletion	35.00%
KRAS	G13D	NM_033360	C	T	SNV	40.00%
NRAS	Q61L	NM_002524	T	A	SNV	10.00%
RUNX1	M267I	NM_001754	C	T	SNV	35.00%

Table 2. Variants to be evaluated contained in DNA 3 control sample

Gene	Position	Mutation
IGH	Chromosome 14	Rearrangement
MYC	Chromosome 8	Rearrangement

Table 3. Variants to be evaluated contained in RNA control sample

Fusion gene	HGVS nomenclature
BCR::ABL1	BCR{NM_004327.3}:r.1_3378_ABL1{NM_005157.3}:r.83_5384
ETV6::ABL1	ETV6{NM_001987.4}:r.1_737_ABL1{NM_007313.2}:r.576-5881
FIP1L1::PDGFRA	FIP1L1{NM_030917.3}:r.1_1109_PDGFRA{NM_006206.5}:r.2037_6590
MYST3::CREBBP	MYST3{NM_006766.4}:r.1_3803_CREBBP{NM_004380.2}:r.290_10197
PCM1::JAK2	PCM1{NM_006197.3}:r1_4365_JAK2{NM_004972.3}:r.2008_5285
RUNX1::RUNX1T1	RUNX1{NM_001754.4}:r.1_803_RUNX1T1{NM_004349.3}r.419-7420
TCF3::PBX1	TCF3{NM_003200.3}:r.1_1519_PBX1{NM_002585.3}:r.729_6918

The safety of the HemeSight Program was confirmed in the assessment of conformity to 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 Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as "the Essential Principles") (MHLW Ministerial Announcement No. 122, 2005). No new specifications have been established. The applicant submitted data evaluated for the conformity of the software lifecycle process and usability engineering of the HemeSight Program to JIS T 2304:2017 and JIS T 62366-1:2022, respectively, separately from the declaration of conformity presented in Section II.3.

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

PMDA reviewed the submitted data on the proposed specifications for performance and safety and concluded that there was no particular problem with safety.

2.(2) Performance

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

The applicant submitted data relating to the performance of the HemeSight Program presented in Sections 2.(2).A.1), 2), and 3), and data relating to the quality of the "HemeSight *In Vitro* Diagnostics" to be used in combination, presented in Section 2.(2).A.4).

2.(2).A.1) Selection of target genes to be analyzed

Genes that were regarded as useful for diagnosis of hematological malignancies, prediction of prognosis, and selection of treatment options were chosen in accordance with the Genomic Testing Guidelines, WHO disease classifications, and other guidelines, published at the time of developing the HemeSight Program. The number of analysis target genes was as follows: 319 genes for SNVs/Indels using Genomon mutation call; 329 genes for structural variants using the Genomon SV; and 197 genes for fusion genes and structural variants using the overall RNA analysis pipelines. Currently, 115 variants for SNVs/Indels and 1 structural variant (2 patterns with different breakpoint positions) are defined as fast-track mutations reportable with the HemeSight Program.

2.(2).A.2) Sequencing

The FASTQ files generated by the DNA sequencer are used as input in the HemeSight Program. The data are processed by variant calling, annotation, filtering, and quality check using the DNA analysis pipeline and RNA analysis pipeline.

2.(2).A.2).(a) DNA analysis pipeline

In the variant calling function, FASTQ files generated by sequencing of DNA from tumor and normal samples are aligned to the reference sequence GRCh38 to call candidates for SNVs/Indels and structural variants that are characteristic of tumors using Genomon mutation call and Genomon SV. The Genomon SV extracts candidate structural variants derived from a reference sequence with 2 read locations and characteristic of tumor samples by tests such as the Fisher's exact test. Structural variant candidates are filtered based on breakpoint position, read direction, the number of reads, and other factors, followed by annotation. Among SNVs/Indels and structural variants, variants meeting the condition in Table 4 are excluded.

The annotation function references the annotation databases in Table 5 and adds basic information on genes to variants detected by variant calling. Single nucleotide polymorphism (SNP) databases shown in Table 5 are referenced for SNVs/Indels, and information to exclude SNP is added using the filtering function, which will be discussed later. The Catalogue of Somatic Mutations in Cancer (COSMIC) database and the Database of human genomic variations classified for diseases are then referenced, while adding information on variants relating to hematological malignancies.

The filtering function performs filtering of variants annotated based on the annotation result, breakpoint location, number of reads, whether included in a blacklist, and other information to extract variants requiring reporting. The quality check function determines whether the process control criteria relating to the analysis process are met.

The analysis result output function references the databases for abnormal gene targets shown in Table 5 for variants requiring reporting, and adds information on whether the criteria for fast-track mutations or important gain-of-function mutation are met.

Table 4. Exclusion criteria in variant calling function in the DNA analysis pipeline

Variant type	Exclusion criteria
SNVs/Indels	[redacted]
Structural variants	[redacted]

Table 5. Reference databases

Database outline	Specific database name	Public/in-house
Annotation database	RefSeq	Public
	Ensembl	Public
	Cytoband information	Public
	IG/TCR gene region list	In-house
	IG/TCR region list	In-house
	List of definition of upstream/downstream of specified genes	In-house
SNP database	ToMMo	Public
	HGVD	Public
	gnomAD	Public
	1000 Genomes Project	Public
	dbSNP	Public
Catalogue of Somatic Mutations in Cancer database	COSMIC	Public
Database of human genomic variations classified for diseases	ClinVar	Public
Database used to determine mutations	Fast-track mutation database	In-house
	Mitelman database	Public

2.(2).A.2).(b) RNA analysis pipeline

The variant calling function is generally similar to structural variant calling in the DNA analysis pipeline, while for reads containing soft-clipped bases, the area is realigned to search for the breakpoint. In the Genomon RNA, reads that meet all the following conditions are generated as candidates for fusion genes and structural variants.

[redacted]

In the Proximal RNA, in order to also detect variants with a short distance between the coordinates that would otherwise be removed as introns by Genomon RNA, a modified Genomon RNA, in which the threshold to classify a variant as an intron has been modified, is used. [redacted]

The annotation function references the annotation databases in Table 5 and adds basic information on genes to the candidates for fusion genes and structural variants detected.

The filtering function performs filtering of variants annotated based on the annotation result, the number of reads, or other information to extract variants requiring reporting, equivalent to the steps performed in the DNA analysis pipeline. The quality check function determines whether the process control criteria relating to the analysis process are met.

The analysis result output function references the databases used to determine mutations shown in Table 5 for variants requiring reporting, and adds information on whether the criteria for important gain-of-function mutation are met.

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

To support the analytical performance of overall testing using the HemeSight Program, the applicant submitted the data on accuracy, precision, specificity, the lower limit of detection, and the effect of interfering substances for all target genes to be analyzed, and data on accuracy and the lower limit of detection for fast-track mutations. The tests are summarized in the following sections.

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

- DNA analysis pipelines (Genomon mutation call and Genomon SV) and Genomon RNA among RNA analysis pipelines

For each variant type, clinical specimens were analyzed using the comparator shown in Table 6 to determine the concordance between the assay methods. Table 6 shows the results.

Among the specimen types that can be used with the HemeSight Program, peripheral blood, bone marrow fluid, tissue from fresh specimens, and FFPE specimens were used as tumor samples, while oral mucosa was used as matched control samples. It was confirmed by other test methods that celomic fluid and nail can be used as tumor and normal samples, respectively, without affecting the test performance. The specimens used were classified into the types of hematological malignancies shown in Table 7. No effects of disease type on test performance were noted. Rare variants not contained in clinical specimens were evaluated using artificially constructed specimens as discussed in Subsections “Structural variants with deletions among target variants for the Genomon SV DNA analysis pipeline” and “Proximal RNA and Genomon SV RNA among the RNA analysis pipelines.”

Table 6. Concordance between the HemeSight Program and comparator methods

Variant type	Comparator	Endpoint	Number of variants	Percent agreement [95% CI]
SNVs/Indels	Amplicon Sequencing	Positive % agreement	246	93.9% [90.1%, 96.8%]
		Negative % agreement	2003	99.9% [99.6%, 100%]
	LeukoStrat CDx *FLT3* mutation assay (ITD)	Positive % agreement	8	100% [63.1%, 100%]
		Negative % agreement	27	100% [87.2%, 100%]
	LeukoStrat CDx *FLT3* mutation assay (TKD)	Positive % agreement	4	100% [39.9%, 100%]
		Negative % agreement	31	100% [88.8%, 100%]
	ipsogen JAK2 DX reagent (*JAK2* V617 mutation)	Positive % agreement	8	100% [63.1%, 100%]
		Negative % agreement	1	100% [2.5%, 100%]
	Total of above assays	Positive % agreement	266	94.4% [90.9%, 96.8%]
		Negative % agreement	2062	99.9% [99.6%, 100%]
Structural variant	WGS (fresh specimens)	Positive % agreement	34	94.1% [80.3%, 99.3%]
		Negative % agreement	161	98.1% [94.7%, 99.6%]
	FISH (FFPE specimens)	Positive % agreement	4	100% [39.8%, 100%]
		Negative % agreement	1	0.0% [0.0%, 97.5%]
	Total of above assays	Positive % agreement	38	94.7% [82.3%, 99.4%]
		Negative % agreement	162	97.5% [93.8%, 99.3%]
Fusion gene	Leukemia chimera gene screening	Positive % agreement	52	100% [93.2%, 100%]
		Negative % agreement	1508	100% [99.8%, 100%]

Table 7. Classification of disease type

Disease classification (WHO)	Number of patients
Malignant lymphoma	56
Acute myeloid leukaemia	45
Acute lymphocytic leukaemia/lymphoblastic lymphoma	40
Multiple myeloma	22
Myeloproliferative neoplasm	18
Myelodysplastic syndrome	6
Immunodeficiency-associated lymphoproliferative disorder	1

- Structural variants with deletions among target variants for the Genomon SV DNA analysis pipeline

Among target variants for Genomon SV, structural variants with deletions are not included in the specimens for accuracy testing; therefore, detection capability was evaluated using multiple artificially constructed specimens containing *CALR* p.L367fs*46. Measurements were performed by adjusting the variant allele frequency (VAF) at 5%, and the detection rate for the variants was 100%.

- Proximal RNA and Genomon SV RNA among the RNA analysis pipelines

Since the target variants for Proximal RNA and Genomon SV RNA, among the RNA pipelines, are rare variants, the detection capability was assessed using artificially constructed specimens that contain such variants. The detection capability of Proximal RNA and Genomon SV RNA was assessed using multiple artificially constructed specimens that contain [redacted] (Proximal RNA), and those that contain [redacted] (Genomon SV RNA). Measurements were performed at a dilution series varying within [redacted]% of RNA containing the variants to be evaluated. The target variants were detected at all measurements.

- Fast-track mutations

In addition to the evaluation using clinical specimens described in "DNA analysis pipeline (SNVs/Indels and structural variants) and among RNA analysis pipelines, Genomon RNA (fusion genes and structural variants)" above, all fast-track mutations reportable with the HemeSight Program were evaluated using multiple artificially constructed specimens that contain these variants. Measurements were performed at a VAF varying between 5% to 10%. The detection rate for all fast-track mutations was 100%.

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

- **Intermediate precision**

The intermediate precision of the HemeSight Program was assessed with measurement day, laboratory technician, and reagent lot, as variation factors, using DNA 1, DNA 3, and RNA control samples as evaluation samples and DNA 2 control samples as matched-control samples. Multiple runs were performed for each variation factor. The results met the process control criteria for DNA library preparation and analysis process in all runs, and detection rate for variants requiring evaluation contained in each control sample was 100% for all variation factors.

- **Reproducibility**

The reproducibility of the HemeSight Program was assessed with between-device difference (same DNA sequencer model) as a variation factor using DNA 1, DNA 3, and RNA control samples as evaluation samples and DNA 2 control samples as matched-control samples. In this evaluation, DNA libraries prepared at one site were analyzed on a total of 3 DNA sequencers placed at 2 different sites. Multiple runs were performed, and at all runs the results met the process control criteria for DNA library preparation, with the exception of the *ETV6*::*ABL1* fusion gene for the RNA control sample, which was not detected by one of the DNA sequencers.

The reproducibility of the HemeSight Program was assessed based on library preparation and measurement data at 2 different laboratories. This evaluation used identical reagent lots with measurement day, laboratory technician, and between-device difference as variation factors. Multiple runs were performed at each laboratory. The results met the process control criteria for DNA library

preparation and analysis process at all measurements, and detection rate for variants requiring evaluation contained in each control sample was 100% at both laboratories.

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

As for the specificity of baits when preparing DNA libraries from DNA, the percentage of bases with a coverage of ≥100-fold, the percentage aligned to the target region, and the uniformity of coverage were assessed using BAM files generated by sequencing of the control samples DNA 1, DNA 2, and DNA 3. The results showed that 93% to 94% of bases had a coverage of ≥100-fold, [redacted]% aligned to the target region, and [redacted]% uniformity of coverage. To provide a rationale for a coverage of 100-fold being sufficient, the applicant explained that based on the evaluation of the lower limit of detection in 2.(2).A.3).(d), a coverage of ≥100-fold allows detection of variants with a VAF of 5%. In addition, the applicant explained that clinically important variants, such as hotspots of driver genes, are not contained in the region with a coverage of <100-fold.

As for the specificity of baits when preparing DNA libraries from RNA, in order to confirm if the bait sequence is designed in an appropriate manner, a homology search was performed on the reference sequence for each sequence ([redacted] base) and the percentage of alignments that do not meet any of the following requirements was evaluated:

i) All the [redacted] bases match the reference sequence.
ii) When alignments are added together, all [redacted] bases match the reference sequence.
iii) Of [redacted] bases, [redacted] bases match the reference sequence.

The applicant provided the following rationales for the establishment of the requirements:

i) If all the [redacted] bases consecutively match the reference sequence, it is considered possible to capture human cell-derived RNA.
ii) An RNA bait targeting fusion messenger RNA (mRNA) targets an mRNA sequence derived from 2 genes present at different positions on the reference sequence, and there are cases in which a bait is aligned to a reference genome sequence at different positions.
iii) If similarity for bait-target hybridization is ≥[redacted]%, it is considered to have adequate similarity. Cases such as the following are regarded as a mismatch with the reference sequence.

[redacted]

Consequently, bait sequences that do not meet any of the requirements are [redacted]. The applicant explained that the results indicate that the sequence of each bait is sufficiently homologous to the reference sequence and that it is possible to specifically hybridize the target region. The applicant

explained that these bait sequences do not meet requirements i), ii), or iii), because they have characteristics such as the following: "alignment is [redacted]," "[redacted]," and "[redacted]."

2.(2).A.3).(d) Lower limit of detection

- DNA analysis pipelines (Genomon mutation call and Genomon SV) and Genomon RNA among RNA analysis pipelines

The limit of detection at the lower limit of the DNA content required by the HemeSight Program was evaluated based on the actual percentage of detection when the analysis was repeated 22 times using DNA 1, DNA 2, and RNA control samples. The results are shown in Tables 8 and 9.

Table 8. Lower limit of detection for SNVs/Indels

Variant type	Variant	VAF	% Detection
SNVs/Indels	*ABL*:T315I	4.9%	100% (22/22)
	ASXL:W796C	4.9%	100% (22/22)
	CBL:S403F	5.3%	100% (22/22)
	DNMT3A:R882C	4.9%	100% (22/22)
	EZH2:R418Q	4.4%	95.5% (21/22)
	FLT3:D835Y	5.1%	100% (22/22)
	IDH1:R132C	5.1%	100% (22/22)
	IDH2:R172K	5.0%	100% (22/22)
	JAK2:V617F	7.5%	100% (22/22)
	SF3B1:G740E	4.8%	100% (22/22)
	TET2:R1261H	4.6%	100% (22/22)
	TP53:S241F	5.2%	100% (22/22)
	JAK2:F537-K539>L	7.5%	100% (22/22)
	NPM1:W288fs*12	10%	100% (22/22)
Structural variant	IGH::*MYC*	5.0%	100% (22/22)

Table 9. Lower limit of detection for fusion genes

Variant type	Variant	Copy number	% Detection
Fusion genes	*BCR*::*ABL1*	1742 copies/µL	100% (22/22)
	ETV6::*ABL1*	2533 copies/µL	100% (22/22)
	FIP1L1::*PDGFRA*	1645 copies/µL	100% (22/22)
	MYST3(KAT6A)::*CREBBP*	1507 copies/µL	100% (22/22)
	PCM1::*JAK2*	1960 copies/µL	100% (22/22)
	RUNX1::*RUNX1T1*	2373 copies/µL	100% (22/22)
	TCF3::*PBX1*	1329 copies/µL	100% (22/22)

- Proximal RNA and Genomon SV RNA among RNA analysis pipelines

The limit of detection for Genomon SV RNA at the lower limit of the DNA content required by the HemeSight Program was evaluated based on the actual percentage of detection when the analysis was repeated 22 times using artificially constructed specimens that were confirmed to contain the IGH::*DUX4* translocation. The detection rate was 100% for a tumor purity of 20%. The applicant explained that the lower limit of detection for proximal RNA is similar to that for Genomon RNA because the only difference is the range of removal as introns, and the tests were not performed.

- Fast-track mutations

Tests were performed together with the evaluation of accuracy, and the limit of detection for fast-track mutations at the lower limit of the DNA content required by the HemeSight Program was evaluated based on the actual percentage of detection when the analysis was repeated 22 times. Table 10 shows the results.

Table 10. Lower limit of detection for fast-track mutations

Gene	Amino acid change	VAF	% Detection
ABL1	T315I, G250E, Y253H, E255K, V299L, F317L, F359V	5%	100% (22/22)
BRAF	V600E	5%	100% (22/22)
CALR	L367TfsTer46, K385NfsTer47	5%	100% (22/22)
CD79B	Y196H	5%	100% (22/22)
CSF3R	T618I	5%	100% (22/22)
EZH2	Y646C	7.5%	100% (22/22)
FLT3	D835Y, N676K	5%	100% (22/22)
IDH1	R132C, R132H	5%	100% (22/22)
IDH2	R140Q, R172K	5%	100% (22/22)
JAK2	V617F	7.5%	100% (22/22)
KIT	D816V	7.5%	100% (22/22)
KRAS	G12C, G12D, G12V, G13D, Q61H, Q61L, Q61R	5%	100% (22/22)
KRAS	G12A, G12R, G12S, G13C	5%	95.5% (21/22)
MPL	W515L	5%	100% (22/22)
MYD88	L252P	5%	100% (22/22)
NPM1	W288CfsTer12	10%	100% (22/22)
NPM1	W288LfsTer12	7.5%	95.5% (21/22)
NRAS	G12D, G12V, G13D, Q61H, Q61K, Q61L, Q61R	5%	100% (22/22)
SF3B1	K700E, N626Y	5%	100% (22/22)
SF3B1	K666N, R625C	7.5%	100% (22/22)
STAT3	D661Y, Y640F	5%	100% (22/22)
RHOA	G17V	5%	100% (22/22)

2.(2).A.3).(e) Effect of interfering substances

The impact of exogenous and endogenous interfering substances on test performance was evaluated using artificially constructed specimens that were confirmed to contain the IGH::*MYC* rearrangement and the *PML*::*RARA* fusion gene based on the criteria for the quality of DNA library construction and sequencing, and the percentage of detection of target variants when each interfering substance in Table 11 was added. The concentration of each exogenous interfering substance added was set at higher than the maximum concentration expected for a general nucleic acid extraction method, while the concentration of each endogenous interfering substance added was set at higher than the contamination concentration expected in the actual assay. The results showed that all specimens met the evaluation criteria for quality with a detection rate of 100%. In addition, concerning the impact of the endogenous substance albumin on the test performance, the applicant explained that the substance is removed by the nucleic acid isolation kit used in the DNA extraction step.

Table 11. Interfering substances to be evaluated

Interfering substance		Concentration added
Exogenous	Proteinase K	80 μg/mL
	Ethanol	10%
Endogenous	Unbound bilirubin	199 μg/mL
	Conjugated bilirubin	201 μg/mL
	Hemoglobin	4.7 mg/mL
	Chyle	1630 FTU
	Heparin sodium	30 U/mL

2.(2).A.4) Quality of template DNA preparation reagents

The applicant submitted the test results on the quality control method as data relating to the quality control method for "HemeSight *In Vitro* Diagnostics," which is to be used in combination with the HemeSight Program. The details of the test are summarized in the following sections.

2.(2).A.4).(a) Qualification of DNA library preparation step

The qualification of the DNA library preparation step was evaluated based on the evaluation criteria for the case in which DNA libraries were prepared from each control sample. The results showed that all control samples met the quality evaluation criteria. When DNA libraries were prepared from DNA 1, DNA 2, and DNA 3 control samples, the amplified DNA library after pre-capture PCR was ≥500 ng, and the peak of the fragments in the DNA library was in the range between 200 and 400 bp. When DNA libraries are prepared with RNA control samples, the amplified DNA library after pre-capture PCR was ≥200 ng, and the peak of the fragments in the DNA library was in the range between 200 and 350 bp.

2.(2).A.4).(b) Qualification of DNA libraries

The qualification of the DNA library preparation step was evaluated based on the evaluation criteria for the case in which sequencing and analysis were performed using the DNA libraries obtained in (a). The results showed that all control samples met the quality evaluation criteria. The number of mapped reads for DNA 1, DNA 2, and DNA 3 control samples was 15 million or more, average coverage of ≥400, 100-fold coverage proportion ≥0.85, and a PCR duplication rate of ≤60%. The number of mapped reads was 3 million or higher for RNA control samples.

2.(2).A.4).(c) Accuracy

The accuracy was evaluated based on the evaluation criteria for the case in which DNA library preparation, sequencing, and analysis were performed using each control sample. The results showed that all control samples met the quality evaluation criteria. When DNA libraries prepared from DNA 1 and DNA 3 control samples were analyzed using DNA libraries prepared using DNA 2 control samples as matched-control samples, all prespecified variants were detected. When DNA libraries prepared from RNA control samples, 6 out of 7 or 7 out of 7 prespecified variants were detected.

2.(2).A.4).(d) Repeatability

The repeatability was evaluated based on the evaluation criteria for the case in which DNA library preparation, sequencing, and analysis were performed using each control sample. The results showed that all control samples met the quality evaluation criteria. When DNA libraries were prepared from DNA 1, DNA 2, and DNA 3 control samples simultaneously 4 times, the results met all the criteria. When DNA libraries were prepared from RNA control samples simultaneously 4 times, each of the prespecified 7 variants was detected ≥3 times, and ≥90% of all evaluation points showed detection of the prespecified variants.

To support the stability of "HemeSight *In Vitro* Diagnostics," the applicant submitted the data on the selection of the storage conditions and shelf life. The reagents were stored at the temperatures listed in Tables 12 and 13. At the start of the study, and at Months 3, 6, 12, 18, and 24, tests for the quality control method were performed using each control sample, and the results were evaluated based on the evaluation criteria for the quality control method.

Table 12. Storage method for the DNA detection reagents in stability study

Inner box label	Temperature setting
DNA Capture Library	−70°C
Library Prep Kit (Pre PCR)	−20°C
Index Primers 1-32 (Pre PCR)	−20°C
Hyb Module Box 1 (Post PCR)	30°C
Hyb Module Box 2 (Post PCR)	−20°C

Table 13. Storage method for the RNA detection reagents in stability study

Inner box label	Temperature setting
RNA Capture Library	−70°C
RNA Library Prep Box1	−20°C
Target Enrichment Box 1 for RNA	30°C
Target Enrichment Box 2 for RNA	−20°C

The results met the quality evaluation criteria for all control samples at all timepoints, demonstrating that the storage method and shelf life for the reagents in Tables 14 and 15 are appropriate.

Table 14. Storage method and shelf life of DNA detection reagents

Inner box label	Storage temperature	Shelf life
DNA Capture Library	≤−70°C	24 months
Library Prep Kit (Pre PCR)	≤−20°C	
Index Primers 1-32 (Pre PCR)	≤−20°C	
Hyb Module Box 1 (Post PCR)	15°C-30°C	
Hyb Module Box 2 (Post PCR)	≤−20°C	

Table 15. Storage method and shelf life of RNA detection reagents

Inner box label	Storage temperature	Shelf life
RNA Capture Library	≤−70°C	24 months
RNA Library Prep Box1	≤−20°C	
Target Enrichment Box 1 for RNA	15°C-30°C	
Target Enrichment Box 2 for RNA	≤−20°C	

2.(3) Reference database updating procedure

Regarding the analysis process for the HemeSight Program, in the annotation and analysis result report output steps, each variant is annotated by referencing internal databases, which pool public database information following specified rules, or in-house internal databases. The internal databases based on public database information specified the criteria for data to be pooled, while the in-house internal databases explained how to create a database. For internal databases that require updating, the interval and method have been established.

As discussed in Section "I. Product Overview," regarding the "fast-track mutation database," which is to be referenced in the analysis result output step, updating of the database via the IDATEN application has been planned separately from the present application. The applicant explained that it has planned to update the database by the IDATEN application based on the following procedure:

- Confirm whether the new fast-track mutations that have been added in association with the revision of the Genomic Testing Guidelines are within the range of the target genes to be analyzed with the HemeSight Program.
- Evaluate the capability to detect variants within the range of analysis.
- Add variants to the database that meet the prespecified target criteria based on the results of the detection capability evaluation.

Regarding the evaluation for detection capability, the applicant explained that it has planned to conduct tests similar to those implemented for the evaluation of the lower limit of detection for the fast-track mutations described in Section "2.(2).A.3) Analytical performance" to evaluate the new fast-track

mutations to be added. The target criteria for determining whether additional variants need to be included were established as follows: the minimum VAF detectable ≥95% of the time when measured repeatedly by varying VAF using 22 specimens should be ≤[redacted]%. After approval of an IDATEN application, the issues described above will be assessed in line with updating of the Genomic Testing Guidelines. If the results meet the prespecified target criteria, the fast-track mutation database is to be updated by submitting a notification regarding changes in line with the plan.

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

2.(2).B.1) Evaluation of HemeSight Program

The HemeSight Program is used to obtain comprehensive genomic profiles of patients with hematological malignancies, an objective similar to that of similar already approved products intended for CGP of solid tumors. In contrast, although CGP of solid tumors is currently performed for the purpose of choosing treatment options after standard therapy, tests with the HemeSight Program are performed for diagnosis, prediction of prognosis, and selection of treatment options; therefore, the HemeSight Program differs from other approved products in that it is intended to be used at the initial onset of the disease for certain conditions. In addition, its operation differs in terms of prompt reporting on the presence or absence of variants classified as the fast-track mutations. Accordingly, in addition to the review strategy for CGP of solid tumors, PMDA conducted a review of the HemeSight Program focusing primarily on the following three points, taking into account the difference described above.

- The appropriateness of the timing, purpose, and patient population targeted for testing with the HemeSight Program
- The appropriateness of the preparation process and the content of the analysis result report for fast-track mutations and other variants
- The appropriateness of the capability to detect target variants

2.(2).B.1).(a) The appropriateness of the timing, purpose, and patient population targeted for testing with the HemeSight Program

In the Genomic Testing Guidelines, the level of recommendation is summarized by use (diagnosis/prediction of prognosis/selection of treatment option) for each disease type. The applicant explained that the HemeSight Program should be used based on the level of recommendation in the Genomic Testing Guidelines in patients with hematological malignancies or similar diseases.

PMDA's discussion:

Genes that are considered useful for the diagnosis, prediction of prognosis, and selection of treatment options for hematological malignancies are selected as the target genes to be analyzed with the HemeSight Program based on the Genomic Testing Guidelines and other guidelines. In the Genomic Testing Guidelines, the level of recommendation for panel testing by disease type/stage (hereinafter

referred to as "test recommendation level")[iii] has been published. Given the circumstances, there are no problems with the use of the HemeSight Program within the range of the Genomic Testing Guidelines, which were established in accordance with the current consensus. Conversely, based on current clinical practice regarding hematological malignancies, there would be cases where CGP is not needed even where the test recommendation level in the Genomic Testing Guidelines is "strong recommendation (SR)" or "recommendation (R)." For instance, it is considered that genomic testing is necessary to identify double hit lymphoma (DHL)[iv] for the diagnosis of aggressive B-cell non-Hodgkin lymphomas and the test recommendation level is "strong recommendation (SR)." However, the detailed explanation for the test recommendation level states that CGP is strongly recommended where conventional testing is not possible. The identification of DHL is possible by fluorescent *in situ* hybridization (FISH), a conventional method, and therefore CGP is not necessarily required, as it is stated in the detailed explanation. Furthermore, when determining the appropriateness of interventions such as hematopoietic stem cell transplantation, publications such as the "Guidelines on Hematopoietic Stem Cell Transplantation: Myelodysplastic Syndrome/Myeloproliferative Neoplasm (adult) third edition"[8] by the Japan Society for Hematopoietic Cell Transplantation, also recommended conditions for eligibility based on age, disease stage, prognosis class, chromosomal aberration, presence of pathogenic variants, and other factors. Therefore, before considering whether CGP should be performed, the Genomic Testing Guidelines, as well as the guidelines of related academic societies should also be taken into consideration. Based on the above, it was decided that the package insert should include cautionary statements to the effect that the appropriateness of CGP should be comprehensively evaluated by taking all aspects into consideration, including the guidelines of related academic societies and other testing options.

2.(2).B.1).(b) The appropriateness of the preparation process and the content of the analysis result report for fast-track mutations and other variants

The appropriateness of the preparation process discussed in the review of the HemeSight Program includes the following areas: the principle of variant detection, public or in-house databases referenced in the annotation step, updating of the database and other operational aspects, the criteria for output to the analysis report. Output data of the analysis result report for the HemeSight Program includes variants of unknown significance (VUS) whose relationship with hematological malignancies is unclear. PMDA asked the applicant to explain the appropriateness.

The applicant's explanation:
It is appropriate for the HemeSight Program to generate an analysis result report that includes VUS, which is to be discussed by the expert panel for the following 3 reasons:

[iii] The level is presented on a 4-point scale: strong recommendation (SR), recommendation (R), clinical option (CO), and no recommendation (NR).
[iv] B-cell lymphoma with concurrent *MYC* and *BCL2* or *BCL6* rearrangements, known to be associated with poorer prognosis than B-cell lymphoma without these variants.

- Only a few variants have been reviewed for pathogenicity by academic societies. The pathogenicity of many other variants has not been clarified.
- For variants that have been registered in both the SNP databases and the COSMIC database, the pathogenic relevance should be determined in a comprehensive manner based on the number registered in each database, information on pathogenicity from the Database of human genomic variations classified for diseases, and other data. For instance, *JAK2* V617F is a pathogenic variant causing myeloproliferative neoplasms and is registered multiple times in the COSMIC database. Conversely, it is also registered frequently in the SNP databases because it is detected in clonal hematopoiesis in healthy individuals.
- It is known that variants that lead to loss of function are distributed across genes instead of forming hotspots. For this reason, even pathogenic loss-of-function variants are registered less frequently in the COSMIC database, which sometimes makes it difficult to determine pathogenicity.

In addition, because the burden on the expert panel is expected to increase, a pairwise analysis using normal tissue is adopted to reduce this burden. If a variant of interest is detected at a high frequency in patient specimens in post-marketing settings, this variant will be added to the blacklist after discussion with experts specialized in hematological malignancies, and removal from the analysis result report is considered.

PMDA's discussion:
The interpretation of the analysis result generated by the HemeSight Program requires examination by the expert panel. Given that currently available measures to reduce the burden on the expert panel have already been put in place, it is considered acceptable that an analysis result report with some VUS is generated.

The Genomic Testing Guidelines recommends that the results on the fast-track mutations should be reported promptly without review by the expert panel, while the entire analysis results should be examined in detail by the expert panel. The HemeSight Program, as recommended by the Genomic Testing Guidelines, reports the results on the fast-track mutations as the first step and reports the results on other variants as the second step. For patients with acute diseases, prompt reporting of the results for fast-track mutations will allow an early decision on an intervention policy to be made. Variants for which interpretation has been established are selected by the academic societies for the fast-track mutations. Accordingly, when an intervention policy is considered based only on the results, it is extremely unlikely that an erroneous decision will be made on the intervention policy, and therefore, PMDA concluded that there are no particular problems with reporting the results in a step-by-step manner.

2.(2).B.1).(c) The appropriateness of the capability to detect target variants

It is considered that endpoints required to evaluate the capability to detect pathogenic variants do not depend on the type of tumors such as solid tumors or hematological tumors. However, unlike combination products consisting of a medical device and *in vitro* diagnostics, such as "OncoGuide NCC Oncopanel System" (Approval No. 23000BZX00398000), applications for HemeSight were filed separately, for the analysis program (medical device) and the template DNA extraction reagent (*in vitro* diagnostics). Therefore, it is necessary to verify that the endpoints for the overall testing using the HemeSight Program are sufficiently met.

The endpoints for the overall testing using the HemeSight Program, described earlier, were examined together with the endpoints submitted for the application for the HemeSight *In Vitro* Diagnostics. The endpoints were similar to those for similar approved products intended for CGP of solid tumors; therefore, PMDA concluded that there are no particular problems with the endpoints.

The results for each test were examined for the following 4 points.

- The evaluation results by analysis pipeline and by specimen type in the accuracy test
- The evaluation results of between-device difference in DNA sequencers in the reproducibility test
- The evaluation results of the specificity test
- Measures for albumin contamination, which is not included as a target in the interfering substance testing

Considering the product design of the HemeSight Program, detection capability should be evaluated for each of the 5 analysis pipelines as shown in Figure 1. In the accuracy test, single or multiple control comparator methods are established for each variant type, and positive percent agreement and negative percent agreement of the HemeSight Program against each comparator method were evaluated. The SNVs/Indels included in the specimens for the test were detected only in the Genomon mutation call and fusion genes were detected only in the Genomon RNA, while structural variants are detectable by the Genomon SV and Genomon RNA. Because the detection capability of every analysis pipeline should be evaluated in an appropriate manner, PMDA asked the applicant to explain which analysis pipeline produced the detection results based on which the positive and negative percent agreement for structural variants in Table 6 were calculated.

The applicant's explanation:

Of the 38 structural variants contained in the specimens used for the accuracy test, 36 structural variants were detected in the HemeSight Program, with 36 variants detected by Genomon SV and 10 variants detected by Genomon RNA. Therefore, the detection capability of both analysis pipelines was evaluated by the test. The 10 structural variants detected by the Genomon RNA were detected also by the Genomon SV. In general, structural variants with no structural changes at the RNA level are difficult to detect by a test using an RNA specimen. In contrast, baits used in the preparation of DNA libraries from DNA in

the HemeSight *In Vitro* Diagnostics include introns that may be breakpoints as the capture target, allowing detection of the structural variants by the Genomon SV.

PMDA's discussion:
Of the structural variants detected by the HemeSight Program in the accuracy test, the number of variants per pipeline was provided and the role of each pipeline was explained. Therefore, as explained by the applicant, PMDA concluded that the detection capability of each of the analysis pipelines was evaluated in an appropriate manner by the test. In the evaluation of the capability of the HemeSight Program as a whole, Genomon SV and Genomon RNA combined, to detect structural variants, whole genome sequencing (WGS) and fluorescent *in situ* hybridization (FISH) were selected as comparator methods for fresh specimens and FFPE specimens, respectively. When both results were added together, the positive agreement and negative agreement were 94.7% and 97.5%, respectively, which indicate no issues with the detection capability. However, given that the number of FFPE specimens evaluated was small and it is well known that nucleic acids in FFPE specimens are susceptible to fragmentation, PMDA asked the applicant to explain why FFPE specimens are considered to be useable for testing in clinical settings.

The applicant's explanation:
An additional evaluation was performed using 1 variant with a structural variation-positive result and 99 variants with a structural variation-negative result assigned by the medical institutions that provided the specimens, in addition to the data from the accuracy test submitted when the application was filed. The variant with a structural variation-positive result tested negative in the comparator assay method, indicating that it is the same as that used as a negative specimen in the accuracy test. For the 99 variants with a structural variation-negative result, no assessment results by comparator methods are available; therefore, the assessment result assigned to the specimen by the medical institution that provided the specimen was assumed to be the true result. The results showed a positive agreement of 100% (1 of 1 variant) and a negative agreement of 97.0% (96 of 99 variants). The results met the process control criteria for DNA library preparation and analysis process. Therefore, the results demonstrated that FFPE specimens can be used for testing.

PMDA's discussion:
In principle, when evaluating accuracy based on concordance, the assessment result obtained by the comparator assay method specified should be regarded as the true result. However, the evaluation with additional specimens did not use the result of the comparator assay method as the true value; therefore, it is not appropriate as an accuracy evaluation. Nonetheless, it was demonstrated that the process control criteria for DNA library preparation and analysis process were met. Accordingly, it is considered that FFPE specimens can be used for testing. Given the applicant's explanation on the basis of the additional data, evaluation results with FFPE specimens also met the process control criteria for DNA library preparation and analysis process, demonstrating no impacts on the detection capability. Therefore, it

was concluded that there are no particular problems with using FFPE specimens for testing in clinical settings.

In the reproducibility test, between-device difference in the DNA sequencers (same model) was evaluated, while the effects of measurement day, laboratory technician, and between-device difference at 2 different laboratories were evaluated. In the former evaluation, the *ETV6*::*ABL1* fusion gene in the RNA control sample was not detected by one of the devices. Conversely, in the latter evaluation, which was performed under more complex variation factors, the detection rate for variants requiring evaluation contained in each control sample was 100% at both laboratories. Therefore, it was concluded that between-device difference had no effect on the detection capability.

In the evaluation of specificity of baits when preparing DNA libraries from RNA, a homology search was performed on each bait sequence of [redacted] bases to the reference sequence, and the percentage of alignments that do not meet the requirements for being sufficiently homologous was evaluated. The test results showed that 2,514 (8.61%) bait sequences did not meet any of the requirements. Based on the established requirements and the rationale for selection of the requirements, PMDA concluded that there are no problems with the evaluation method. However, given the results, which indicate that approximately 10% of bait sequences did not meet the requirements, PMDA asked the applicant to explain why these baits failed to meet the requirements and how the results are to be interpreted.

The applicant's explanation:
Bait sequences that did not meet any of the requirements were characterized by "alignment is [redacted]," "[redacted]," and "[redacted]." It was difficult to identify targets by the techniques adopted in the test for the following reasons.

- Alignment is [redacted].
  In the specificity test, if alignment was [redacted], evaluation was acceptable by adding completely matched sequences. However, if [redacted], each alignment length would be [redacted], which hinders accurate evaluation in homology search; therefore, it was excluded from the targets of evaluation.
- Because the length of target region at the time of design was <[redacted] bases, [redacted] contains repetitive sequences.
  When preparing DNA libraries from RNA, baits are designed in a manner such that the total base length is [redacted] bases, [redacted] designed. As a result, mismatches occurred in the repetitive parts of the sequences in the test.

[redacted]

[redacted]

Despite these discordant cases, sequences were identified in 91.39% of baits overall, indicating that the bait has sufficient homology.

PMDA's discussion:
No evaluation methods have been established for baits for RNA, and the evaluable range is limited; therefore, it is understandable that alignments that do not meet the requirements exist to some extent. Therefore, it was concluded that there are no particular problems with the applicant's analysis.

In the evaluation of interfering substances, regarding the effects of albumin, as an endogenous interfering substance, on the detection capability, the applicant explained that the substance is effectively removed by the nucleic acid isolation kit used in the DNA extraction step. However, the nucleic acid isolation kit is not a product the removable capability of which has been demonstrated; therefore, it was considered that other methods to evaluate the effect on albumin is necessary. PMDA asked the applicant to explain how albumin contamination would be addressed during actual testing in clinical settings.

The applicant's explanation:
The effects of albumin contamination can be excluded by following the instructions on use of the HemeSight Program as follows: when performing actual tests in clinical settings, operators are to follow instructions for the nucleic acid extraction kit being used in accordance with the instruction manual. After nucleic acid extraction, the chemical purity of extracted nucleic acid should be confirmed by measurement of absorbance or other parameters.

The instructions on use specified by the applicant ensure that the user checks for albumin contamination before the test is performed; therefore, it was concluded that there are no problems with the applicant's approach.

2.(2).B.2) System to implement testing with the HemeSight Program

Currently, CGP of solid tumors requires interpretation of results by the expert panel, and therefore, testing is performed at core hospitals for cancer genomic medicine in accordance with "The Clinical Practice Guidance for Next-Generation Sequencing in Cancer Diagnosis and Treatment" jointly issued by the Japanese Society of Medical Oncology, the Japan Society of Clinical Oncology, and the Japanese Cancer Association. Similarly, for CGP targeting hematological malignancies, it is deemed appropriate to conduct tests using the HemeSight Program within a similar framework, namely, a medical care system centered around core hospitals for cancer genomic medicine. This is to ensure that results are interpreted appropriately in a manner equivalent to that for CGP of solid tumors. The Use Guidelines state that if medical institutions conducting these tests are limited to the core hospitals for cancer genomic medicine, only approximately 50% to 70% of the primary treatment facilities for hematological

malignancies may be covered. According to the explanation by the Ministry of Health, Labour and Welfare, the medical care system will be expanded depending on the need. The expert advisors, deliberating under this premise, supported the plan that testing with the HemeSight Program will be initiated at the core hospitals for cancer genomic medicine.

Based on the discussions in Sections 2.(2).B.1) and 2) above, PMDA concluded that the HemeSight Program can be used appropriately by imposing the following approval conditions, similar to those applied to similar already approved products intended for CGP targeting solid tumors.

Approval Conditions

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.

PMDA concluded that the following cautionary statement should be included in the package insert for the HemeSight Program.

Precautions Concerning Intended Use or Indication

When determining intervention policies based on the output results of comprehensive genomic profiling with the HemeSight Analysis Program, decisions should be made by physicians specialized in cancer genomic medicine in a comprehensive manner based on the latest medical knowledge, taking various aspects into account including prior therapy, other diagnostic test results, and clinical symptoms.

2.(2).B.3) Appropriateness of IDATEN application

As discussed in Section "I. Product Overview," regarding the "fast-track mutations database," which is to be referenced in the analysis result output step, updating of the database via the IDATEN application has been planned separately from the present application. Given that a specific draft for approval that incorporates planned changes can be prepared, and that the change is the type of change in which acceptable target criteria can be set in advance as a change plan, PMDA concluded that the use of IDATEN application is appropriate. In addition, the planned change is founded on the Genomic Testing Guidelines; the procedure to determine the necessity of change is appropriate; and the test for the lower limit of detection can be used for evaluation of accuracy, indicating it is sufficient as an evaluation package. PMDA therefore concluded that there are no particular problems with the change plan.

The target criteria (minimum VAF detectable ≥95% of the time should be [redacted]%) to submit a notification were reviewed as follows. The recommendation for the condition of tissue specimens used

for genomic testing is provided in the "Guidelines on the handling of pathological tissue samples for genomic research"[9] developed by the Japanese Society of Pathology. A tumor purity of 30% to 50% or more is considered to be desirable, therefore, there are no problems with the target. As for specimens such as blood and bone marrow fluid, there are no established recommended conditions such as tumor purity, or a rough standard for VAF values for which consensus has been reached. Given the current clinical practice regarding hematological malignancies and the status of testing of similar already approved products, PMDA concluded that there are no problems with the clinical use of the HemeSight Program provided that it is used with the target criteria presented by the applicant.

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

3.A Summary of the data submitted

The applicant submitted a declaration of conformity declaring that HemeSight Program meets the Essential Principles.

3.B Outline of the review conducted by PMDA

PMDA's conclusion on the conformity of the HemeSight Program to Article 1, which defines preconditions, etc. for designing medical devices:
As described in Sections "2.(2).B.1) Evaluation of HemeSight Program," and "2.(2).B.2) System to implement testing with the HemeSight Program," in order to ensure proper use of the HemeSight Program, compliance with guidelines developed by the related academic societies, selection of appropriate users/medical facilities are important. Therefore, an approval condition was added to ensure that necessary measures are taken.

PMDA's view on the conformity of the HemeSight Program to Article 10, which stipulates requirements that ensure accuracy, precision, and stability sufficient for the intended use of the medical device:
It was decided to include information on the evaluation results for analytical performance in the package insert, in a manner equivalent to the approved products.

PMDA's view on the conformity of the HemeSight Program to Article 12, which stipulates requirements that must be considered in relation to the development life cycle of program-driven medical devices:
As described later in Section "IV.(3) Cybersecurity," cybersecurity needs to be maintained without interruption; therefore, it was decided to add an approval condition to ensure that necessary measures are taken.

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

4. Risk Management

4.A Summary of the data submitted

The applicant submitted a summary of risk management, the risk management system, and its progress in accordance with 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 Sections "II.2. (1) Performance and safety specifications" and "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 data submitted

Data relating to the manufacturing process were not submitted in accordance with the notification "Handling of Medical Device Software" (MS Notification No. 1121-33 issued by Counsellor of Minister's Secretariat [for Medical Devices and Regenerative Medicine Product Evaluation], MHLW, PFSB/SD Notification No. 1121-1, issued by Director of the Safety Division, Pharmaceutical and Food Safety Bureau, MHLW, and 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 are no particular problems with not submitting manufacturing process data on the basis of the above notification.

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

6.A Summary of the data submitted

Data relating to clinical studies were not submitted, and the clinical performance of the HemeSight Program was evaluated as part of the performance test described in Section "2.(2) Performance."

6.B Outline of the review conducted by PMDA

PMDA concluded that there are no particular problems with using the data from clinical performance tests instead of data relating to clinical studies.

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

7.A Summary of the data submitted

The applicant explained that no post-marketing surveillance such as a use-results survey was necessary due to the establishment usage record of the previous model of the HemeSight Program. Clinical and

genomic data obtained in the testing with the HemeSight Program are to be accrued at the Center for Cancer Genomics and Advanced Therapeutics (C-CAT), and required actions have been completed.

7.B Outline of the review conducted by PMDA

PMDA's conclusion:

Clinical and genomic data based on gene panel testing should be accrued and evaluated mainly through the C-CAT, in a manner equivalent to similar already approved products intended for CGP of solid tumors. The applicant needs to coordinate and cooperate with the C-CAT in an effective manner; however, PMDA determined that conducting a separate use-results survey is not meaningful.

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

The medical device application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (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

The HemeSight Program is a gene variant analysis program that detects hematological malignancy-related gene variants in DNA and RNA extracted from tumor tissue or other specimens obtained from patients with hematological malignancies, and generates information for the diagnosis, selection of treatment options, and prediction of prognosis for hematological malignancies. There are 3 key issues to be addressed in the review of the HemeSight Program. Taking account of comments raised at the Expert Discussion, PMDA reached the following conclusions:

(1) Timing of testing with the HemeSight Program and targeted patients

As discussed in Section "II.2.(2).B.1).(a) The appropriateness of the timing, purpose, and the patient population targeted for testing with the HemeSight Program," the HemeSight Program is used for the diagnosis, selection of treatment options, and prediction of prognosis for hematological malignancies based on the level of recommendation in the Genomic Testing Guidelines. In particular, for diseases such as myelodysplastic syndrome, a heterogeneous disease, an accurate diagnosis at the initial onset is important, and therefore genomic testing is essential. In a clinical study[10] conducted at the National Cancer Center Japan, 176 patients with hematological malignancies were analyzed using the previous model of the HemeSight Program. At least one variant was detected in 171 of 176 patients (97%). The detected variants include not only common variants but also rare structural variants and fusion genes. In the assessment of usefulness of detected variants in terms of diagnosis, selection of treatment options, and prediction of prognosis, variants with evidence level A were detected in 76%, 12%, and 44% of patients, respectively, for the corresponding uses. In the joint clinical research conducted at 4 medical

institutions including the National Cancer Center Japan, 68 patients with hematological malignancies were analyzed using the previous model of the HemeSight Program. At least one variant was detected in 63 of 68 patients (93%). In the assessment of usefulness of detected variants in terms of diagnosis, selection of treatment options, and prediction of prognosis, variants with evidence level A were detected in 66%, 26%, and 57% of patients, respectively, for the corresponding uses. Given these results, it is likely that CGP can make a useful contribution, especially to diagnosis. Therefore, for diseases for which there is a high need for a test, it is appropriate to use the test at the first visit according to the test recommendation level in the Genomic Testing Guidelines. In the event of relapse, the genetic background for main tumor cells may differ from that at the first visit. For this reason, it is recommended to evaluate the genetic background by CGP at the time of relapse so that an appropriate intervention policy can be considered depending on the disease. For instance, when a drug indicated for the treatment of relapsed or refractory and *ALK* fusion gene-positive T/NK cell non-Hodgkin's lymphoma is available and conventional testing cannot be used, CGP is strongly recommended. In another case, where a variant known to be an indicator for acquired drug resistance is present, switching to another drug is recommended. Based on the above, PMDA concluded that there are no problems with performing a test with the HemeSight Program at the time of follow-up visit according to the test recommendation level in the Genomic Testing Guidelines.

As for patients eligible for testing, there may be cases where the test is used in patients with a disease that causes cytopenia, such as aplastic anemia and inherited bone marrow failure syndrome, which are difficult to distinguish from hematological malignancies. For this reason, it is concluded that similar diseases should be included in the targeted patient population for the HemeSight Program in accordance with the Genomic Testing Guidelines, instead of limiting to hematological malignancies.

Conversely, as described in Section "II.2.(2).B.1).(a) The appropriateness of the timing, purpose, and patient population targeted for testing with the HemeSight Program," there may be cases where CGP is not needed even when the test recommendation level in the Genomic Testing Guidelines is "strong recommendation (SR)" or "recommendation (R)." Therefore, it was decided to include a cautionary statement in the package insert to the effect that whether to perform CGP should be thoroughly considered by referencing the guidelines of the related academic societies.

(2) Clinical positioning

The HemeSight Program has advantages of the ability to test for the presence/absence of variants related to diagnosis, prediction of prognosis, and selection of treatment options over a wide range. Conversely, compared with already-approved companion diagnostics (CDx) and *in vitro* diagnostics, which analyze a single gene, a longer time is required to report the result. Even if the results for the fast-track mutations are reported promptly, this may not be suitable for acute conditions. Accordingly, it is expected that in cases of acute diseases, already approved CDx or *in vitro* diagnostics is used to determine the initial intervention policy based on the test result of the conventional product, and a more precise intervention

policy can be considered later based on the test result of the HemeSight Program. In addition, due to the principle of the DNA sequencer to be used in combination with the HemeSight Program, it is difficult to detect abnormalities such as chromosomal aberrations using the HemeSight Program. Therefore, even after implementing the HemeSight Program, genomic testing of hematological malignancies will not be fully covered by the HemeSight Program. It is important to use the HemeSight Program and conventional testing depending on the situation. Moreover, the HemeSight Program, which is used before the start of treatment, may detect a pathogenic variant that is the target of CDx. For solid tumors, when a pathogenic variant that is the target of CDx is confirmed by CGP, physicians are allowed to administer drugs following the review by the expert panel.[11] For hematological malignancies, similar to the case of solid tumors, when a pathogenic variant that is the target of CDx is confirmed by testing with the HemeSight Program, the current plan is to allow administration of drugs following the review by the expert panel without requiring re-examination with CDx. Therefore, it is considered that drugs can be used without the need to conduct unnecessary tests.

(3) Cybersecurity

The use of the HemeSight Program involves transmission of genomic information through a telecommunication line to external servers, PMDA asked the applicant to explain the cybersecurity preparedness in place.

The applicant's explanation:

At the time of filing the application, cybersecurity was put in place based on the "Guidance on Ensuring Cybersecurity of Medical Devices" (PSEHB/MDED Notification No. 0724-1 and PSEHB/PSD Notification No. 0724-1, dated July 24, 2018). Cybersecurity will be in place by the product launch in accordance with the "Revision of Guidance on Introducing Cybersecurity to Medical Devices" (PSEHB/MDED Notification No. 0331-11 and PSEHB/PSD Notification No. 0331-4, dated March 31, 2023). It is considered that by implementing the best cybersecurity risk control measures available today, the risk level will be reduced to an acceptable level.

Based on the "Handling of Software as Medical Device for Which Inclusion in Public Healthcare Insurance Coverage is Requested" (Administrative Notice: Policy Planning Division for Pharmaceutical Industry Promotion and Medical Information Management, Health Policy Bureau, and the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated July 19, 2022) (hereinafter referred to as the "Administrative Notice"), to confirm if the product that is up-to-date with the latest cybersecurity is on schedule to be finalized before the start of marketing covered by the public healthcare insurance, PMDA asked the applicant to submit a revision plan. PMDA reviewed the revision plan concerning cybersecurity, and concluded that there was no particular problem with the proposed revision plan concerning cybersecurity. After approval, whether revision has been completed will be confirmed in accordance with the Administrative Notice. In addition, to clarify the responsibilities of the marketing authorization holder for the protection of personal information and

prevention of unauthorized access, PMDA concluded that an approval condition should be added to address the issues.

Approval Conditions

The applicant is required to implement appropriate procedures and controls for protecting personal information received and to implement up-to-date data security and privacy measures for preventing unauthorized access to relevant data and information.

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

The HemeSight Analysis Program is intended to display and provide the results of analysis conducted based on base sequence data such as those obtained with the HemeSight *In Vitro* Diagnostics, which is used in combination with the HemeSight Analysis Program. The HemeSight Analysis Program provides comprehensive genomic profiling of tumors, etc. in patients with hematological malignancies or similar diseases.

Approval Conditions

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 implement appropriate procedures and controls for protecting personal information received and to implement up-to-date data security and privacy measures for preventing unauthorized access to relevant data and information.

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

PMDA has concluded that this application should be deliberated at the Surveillance Committee on Software as a Medical Device.

References

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8. “Guidelines on Hematopoietic Stem Cell Transplantation” (Japanese Society for Transplantation and Cellular Therapy or the Japan Society for Hematopoietic Cell Transplantation)

9. “Guidelines on the handling of pathological tissue samples for genomic research” (Japanese Society of Pathology, dated March 1, 2018)

10. Fukuhara S, Kumade Y, et al. Feasibility and clinical utility of comprehensive genomic profiling of hematological malignancies. Cancer Sci. 2022: 113(8): 2763–2777.

11. “Points to Consider Concerning Health Insurance Coverage of Gene Panel Testing” (Administrative Notice issued by the Cancer and Disease Control Division, Health Services Bureau, MHLW, the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, and the Medical Economics Division, Health Insurance Bureau, MHLW, dated May 31, 2019)