Quality Control of Software as a Medical Device for Genomic Testing

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Disclaimer

Since a part of this talk goes beyond the duties of the PMDA, it contains many personal views and is not the official views of the PMDA.

Changes in the scope of applications for approval

Simple threshold characterization

e. g. PCR, FISH

Complex analytic algorithms

e. g. Genomic panel test

- A program that only performs threshold characterization has been considered as an accessory for in vitro diagnostics, and no application for approval of software is required as a software as a medical device (SaMD).
- On the other hand, bioinformatic analysis programs such as genomic panel tests are the main source of variant detection, and the basis of variant classification may change based on the latest evidence. Therefore, an application for approval is requested as SaMD to be used in combination with in vitro diagnostics, and its performance is confirmed in the review.

New attempts in SaMD for genomic/genetic testing

＜Issues to be addressed＞

① Development of companion diagnostics (CDx) are required to approve the targeted drug, whereas this CDx, which was developed at that time, was not a product distributed but was performed at a specific laboratory in US. However, approval of this CDx was likely to be required for insured use of the drug.

② The evidence for CDx-positive variants is currently accumulating, and it was considered appropriate for patients to determine the variant classification on the basis of current evidence.

③ Testing by using the next-generation DNA sequencer can yield many results at the same time, but some of them could explain the clinical significance.

＜Proposal＞

① Considering a test performed at a specific laboratory to provide the right to use SaMD

② Approval of classification method and procedure, not variant classification results

③ Acceptance of Out-of-Range Output

Distribution form of SaMD

Marketing authorization holder (MAH)

e. g. reagents, DNA sequencer, SaMD

Manufacture and sale

Medical institution

Perform the test

Distribution regulations similar to those for drugs and medical devices

SaMD have to be manufactured and sold as distributed products (electronic media, downloads).

Medical institution

Data analysis

Data entry

Output of the results

MAH

Server on which the SaMD is installed

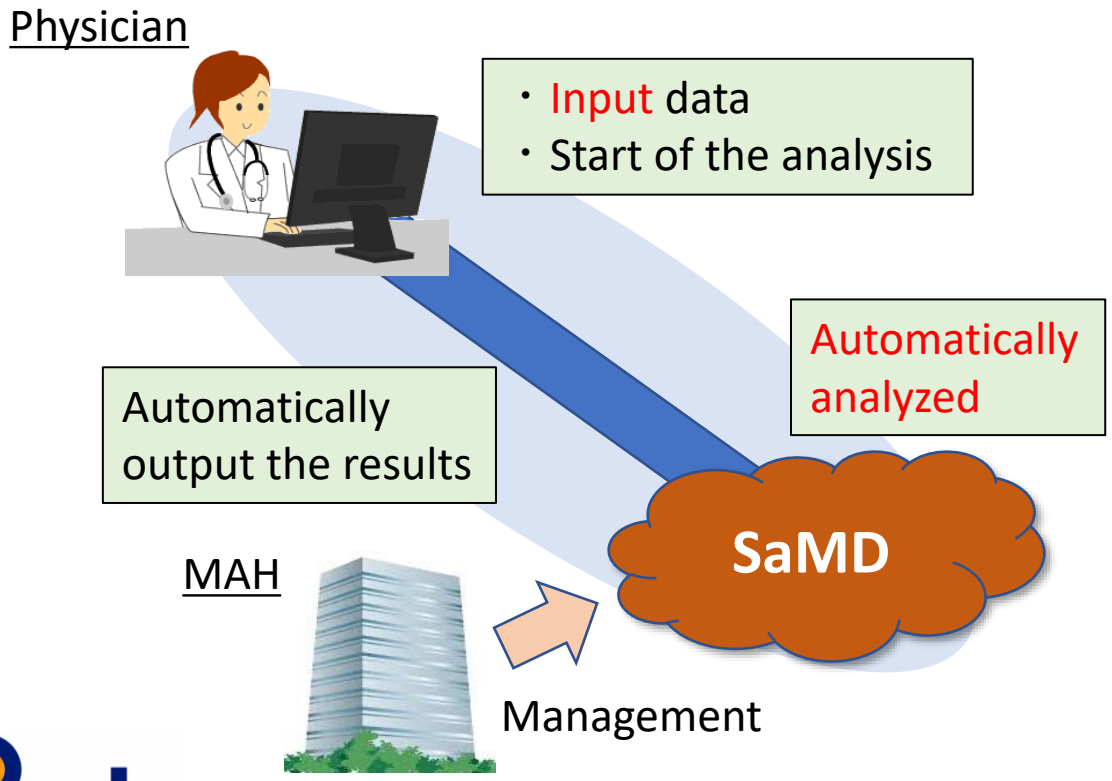
Provision via telecommunications line (Provision of right to use)

SaMD on the cloud managed by the MAH have to be provided as the right to use.

Differences between the provision of SaMD and analysis services

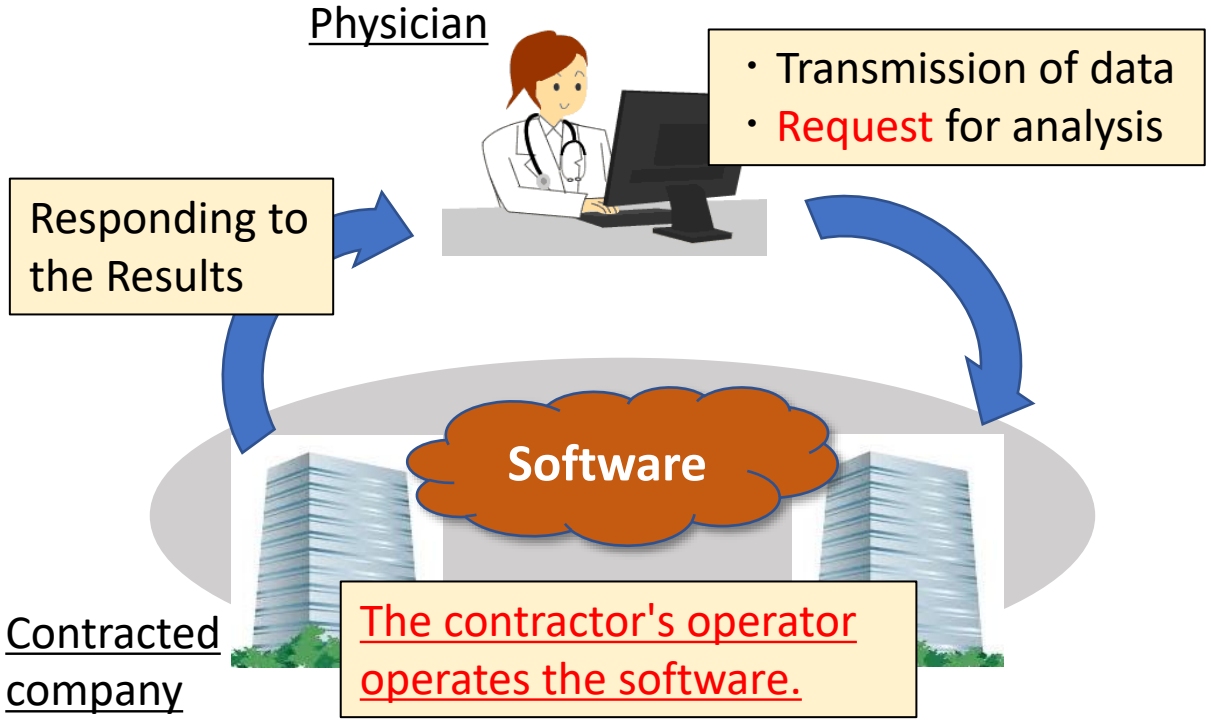
Provision of SaMD via telecommunications line

(in principle) Physician manipulates the SaMD directly.

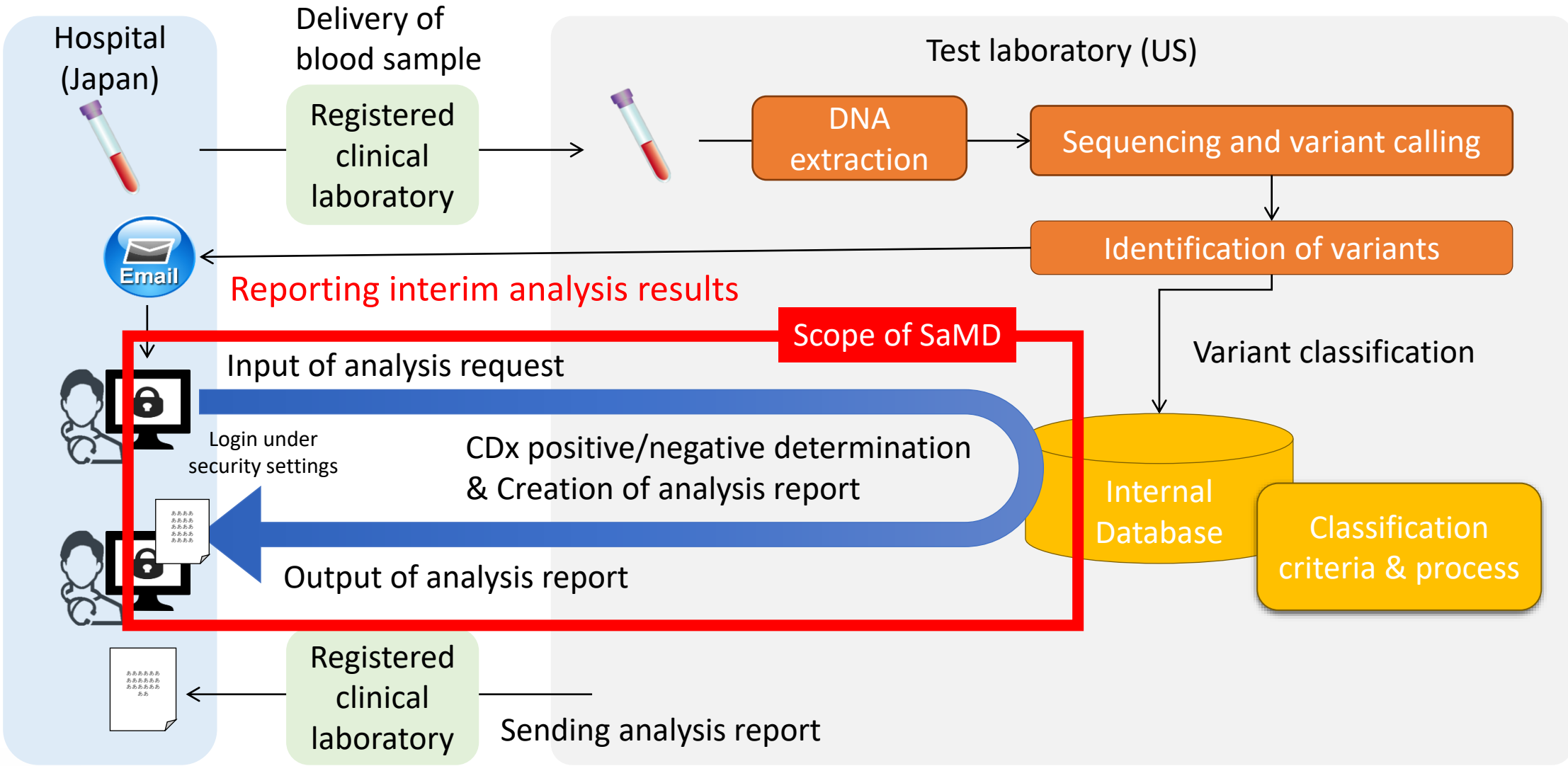


Provision of analysis services (Contract Analysis)

Physician only requests analysis and does not operate.



① Cases of SaMD provided via telecommunications line



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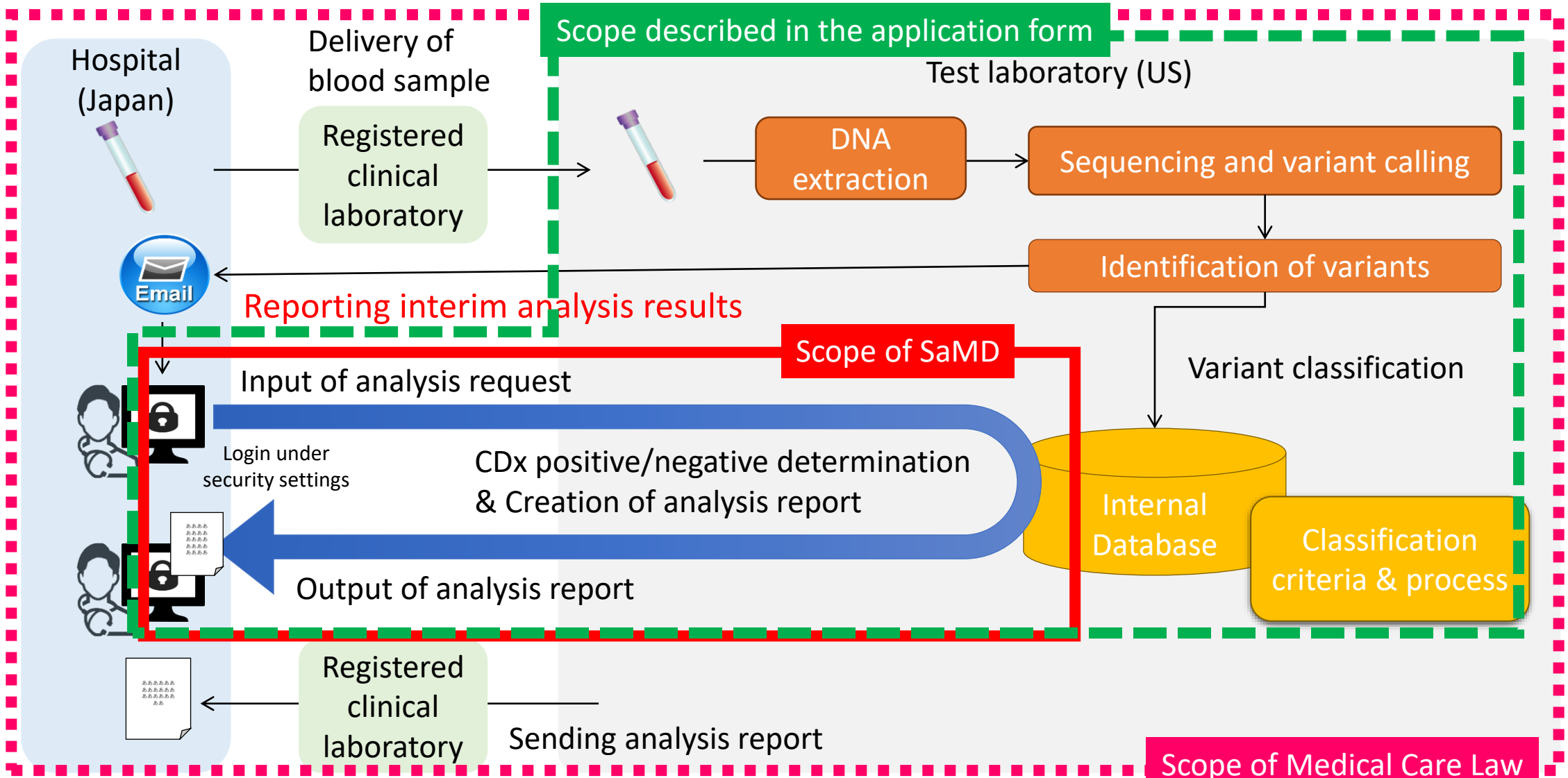
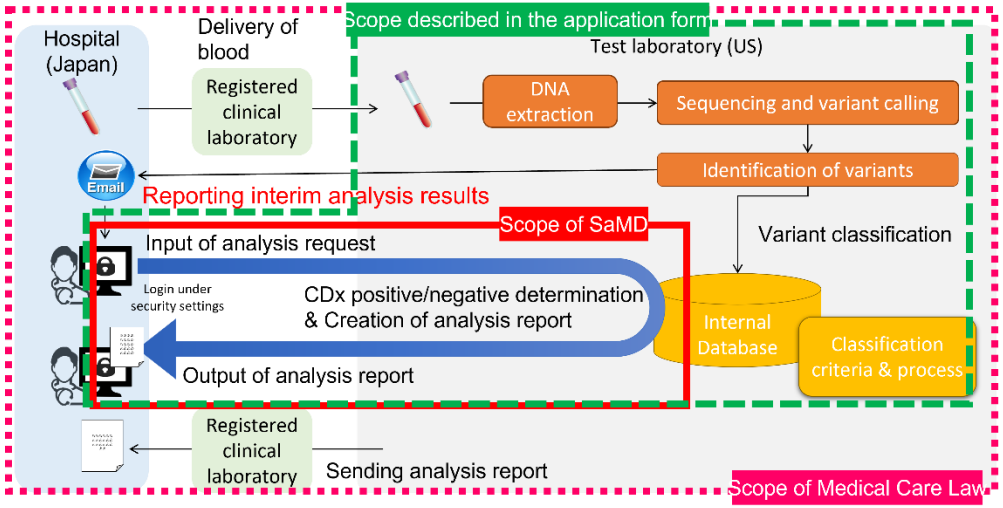


① Cases of SaMD provided via telecommunications line

In principle, the scope of regulation of SaMD is limited to the range in which data is input via a telecommunication line and analysis results are output. However, it is important to ensure the quality of the entire test.

＜Solution＞

- The process of variant analysis and classification is specified in the remarks column of the application form as a requirement for the quality control of the input information of the SaMD.
- Approval conditions were given so that pharmaceutical procedures are required when the requirements in the remarks column are changed.
- The scope of examination, QMS, and GVP is the same as that of products distributed in Japan.
- Although it is outside the scope of the Pharmaceuticals and Medical Device Law, it is necessary to appropriately control the accuracy based on the Medical Care Law.



② Cases in which methods such as variant classification were approved

It is necessary to ensure the quality of not only the variant analysis but also the variant classification. On the other hand, the evidence of variant classification is always updated and the treatment strategy should be determined based on the latest information.

The specific procedure and criteria of variant classification were fixed. And so that when the referenced information is updated, the classification can be changed accordingly.

Fixed factors

- Procedure of variant classification
- Classification criteria for variant classification
- Referenced public databases on which the variant classification is based
- Qualification requirements for operators to update and manage internal databases

Variable factors

- Contents of updated internal databases
- Operators who updates and manages the internal database*

＊ Verification testing is required to demonstrate that the judgment does not differ between operators who update and manage the internal database.

② Cases in which methods such as variant classification were approved

As an important point, the correctness of the changed variant classification results must also be ensured.

If all of the following conditions are met, an approval condition filing the annual report to justify the classification results has to be attached.

1. Private internal databases will be used.
2. The internal database will also be updated based on the update of the referenced public database.
3. The output directly reflects on the decision of treatment strategies, such as CDx.

Comprehensive genome profiling tests does not meet the requirement 3 and does not require an annual report because the treatment strategies is determined by the expert panel.

③ Cases in which output of not approved results was accepted

Multi-gene panel testing

Gene A = Biomarker for CDx

Gene B = Uncertain clinical significance

Gene C = Uncertain clinical significance

DNA sequencer diagnostic system is capable of detecting multiple genetic variations simultaneously, including genetic variations of uncertain clinical significance. Although detecting genetic variations of uncertain clinical significance is not eligible for approval, providing the results as reference information is acceptable only when the physician considers it necessary. In such circumstances, caution must be exercised so that physicians are appropriately informed that the clinical significance of those genetic variations and analytical validity of the system for those variations are unknown.

"Legislation Notice to Applicants for Marketing Authorization of DNA Sequencers and Related Products Utilized for Genetic Testing Systems" (PSEHB/MDR/MPED Notification issued on April 28, 2016)

③ Case in which all output results were included in the approval range

Multi-gene panel testing

Gene A = Biomarker for CDx

Gene B = Uncertain clinical significance

Gene C = Uncertain clinical significance

Preconditions for use in the decision of treatment strategies by expert panels

For comprehensive genome profiling tests, all the target genes for analysis were included in the approved range if the following points were identified:

- Genes with high evidence levels in the guidelines are covered.
- Even for genes with low evidence level, the test results must be registered in an official database such as C-CAT, and must be ready to be used for research.
- The analytical performance of representative genes covering the variant type (SNV, Indel, CNA, Rearrangement, TMB, etc.) to be detected is evaluated.

Future Responses to the SaMD for Genomic/Genetic Testing

＜ Assumed case ① ＞

Programs that perform only variant analysis and/or medical annotation based on arbitrary sequencing results performed at each site

- The quality assurance until sequencing analysis is the key to approving these SaMD.
- Quality standards such as Q30, Depth of coverage, Uniformity of coverage, Mapping quality, and On-target rate exist, but it is necessary to investigate whether they are sufficient or not.

Future Responses to the SaMD for Genomic/Genetic Testing

＜Assumed case ②＞

Whole Genome Analysis

"Action Plan for Whole Genome Analysis 2022", MHLW, 30 Sep. 2022

○Quality control

Sequencing companies will evaluate the quality and quantity of the data before human genome mapping on the basis of the criteria established by the Expert Committee to obtain data that meet the reference values. Sequencing companies will be under the obligation to cooperate with external accuracy management carried out by the MHLW Science Research Group for promotion of whole genome analysis of cancer and establishment of a system for technology assessment related to whole genome analysis of each individual patient and its clinical application, a center for data analysis and storage, information security and patient confidentiality, and Ethical Legal and Social Implications (ELSI) (tentative name), using the sequencing accuracy values, the relevant summary values, and the pre-mapping quality control values of sequencing companies.

Personal summary

- To date, various efforts have been made within the scope of the Pharmaceutical and Medical Devices Law in accordance with the actual conditions and needs of medical field.
- The purpose of each effort was to ensure the quality of clinical testing.
- Ensuring quality may become an important issue for increasingly sophisticated and diverse testing in the future.
- We believe that it’s time for industry, government and academia to tackle this problem together.