Approach to regulation for NGS-based oncology panel products in Japan

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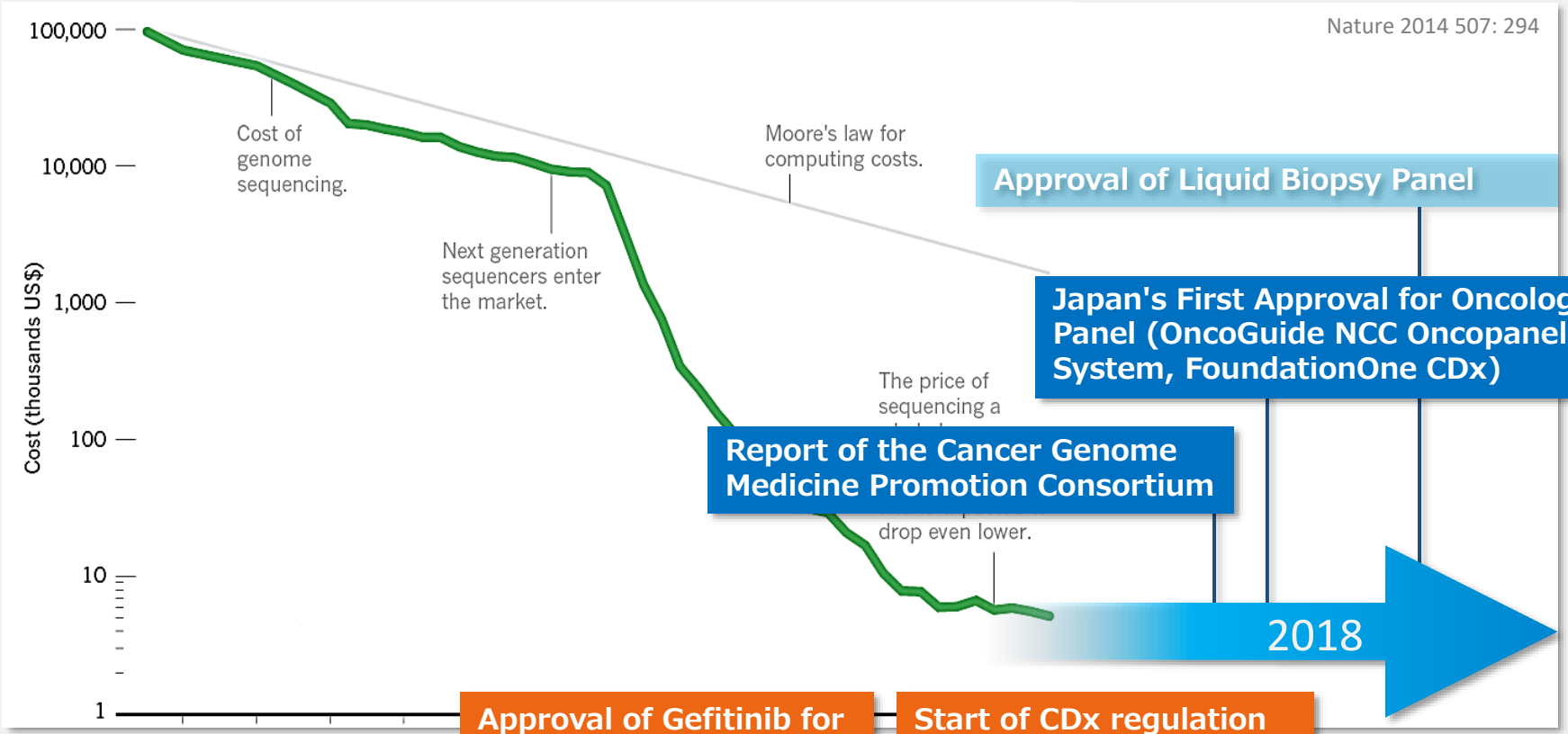
Main points of today's presentation

- Two NGS based oncology panel products have been approved in Japan. Many of the genes carried in oncology panel do not have sufficient clinical evidence. How were products that detect these genes approved as medical devices with clinical performance?
- In oncology panels, it is essential to refer to the DB (i.e., the accumulation of information on existing variants), when interpreting the test results. How should DB be handled in the regulations as a medical device?
- Oncology panels are expected to continue to develop technologically in the future. I hope that this presentation will be a subject for discussion with Taiwanese about more optimized regulation.

From CDx Era to Oncology Panel Era



CDx vs Comprehensive Genome Profiling

Indication for use	Companion Dx	Comprehensive Genome Profiling (CGP)
Medication based on the diagnostics	Established medication	Medication with potential evidence
Output of the diagnostics system	Interpretation is not acceptable	Interpreted by the expert panel for the clinical significance
Major regulatory evaluation points	Positive and negative predictive values	Analytical performance
medical institutes of implementation	-	Core hospitals for cancer genome precision medicine

Framework of cancer genome precision medicine in Japan

12 core hospitals for cancer genome precision medicine

33 main hospitals and 180 associate hospitals for cancer genome precision medicine

obtain the genome variants data using approved oncology panel (OncoGuide NCC Oncopanel System, FoundationOne CDx)

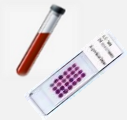
annotation of variants using databases and report the comprehensive genome profile

Finalizing the report of the evidence-based categorization of variants by expert panel

Framework of cancer genome repository and Knowledge DB based medication in Japan

Certified Labs for genomic testing

Analysis using approved oncology panel



specimens

Sequence Data

report

12 core hospitals for cancer genome precision medicine

Clinical info

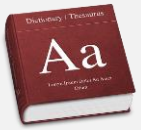
33 main hospitals and 180 associate hospitals for cancer genome precision medicine

CKDB report

Center for Cancer Genomics and Advanced Therapeutics: C-CAT

Cancer genomics info repository

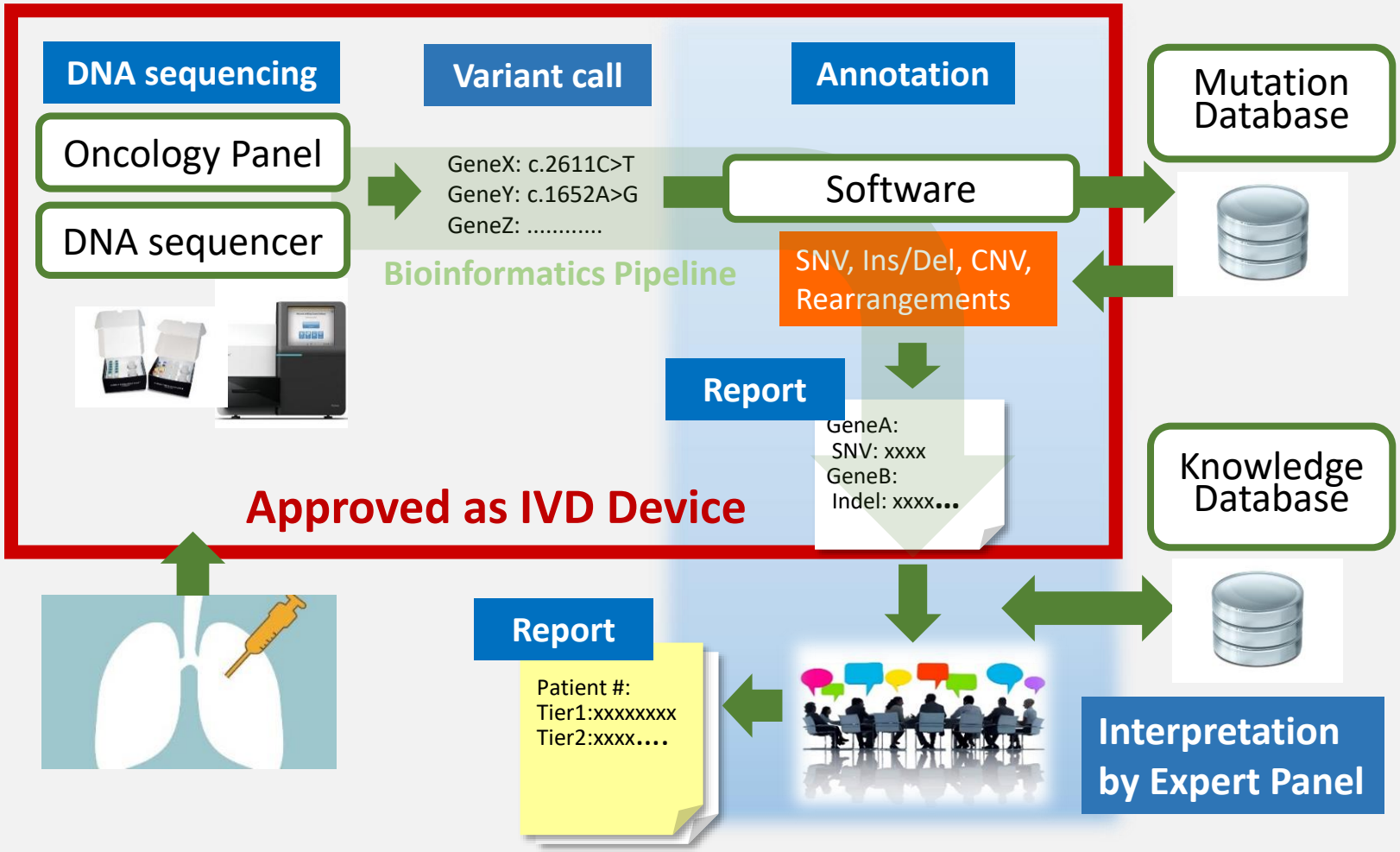
CKDB



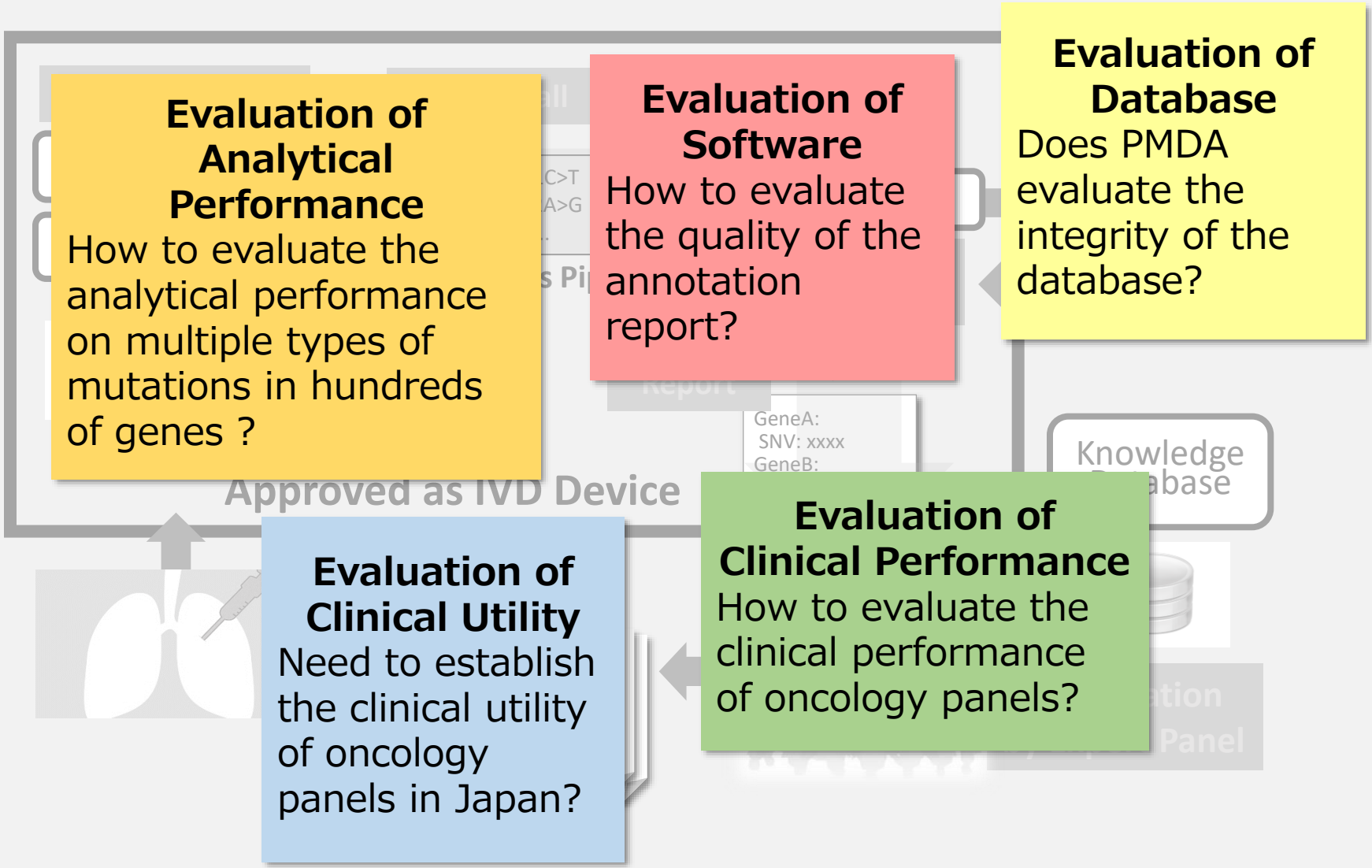
Development of new drugs, bio-markers and diagnostics systems

Maximize treatment opportunity in collaboration with core and associated hospitals

Typical Schematic Flow of Medication using Oncology Panels



Typical Schematic Flow of Medication using Oncology Panels



Review Policies

Clinical Utility is already established by the report of Cancer Genome Medical Consortium, and also demonstrated in the medication under advanced medical care.

Clinical Performance = **Analytical Performance**

Recognized but not evaluated: Public Database
Evaluated in the review and Recognized : In-house database
Evaluated in the review and Approved: Bioinformatics Pipeline

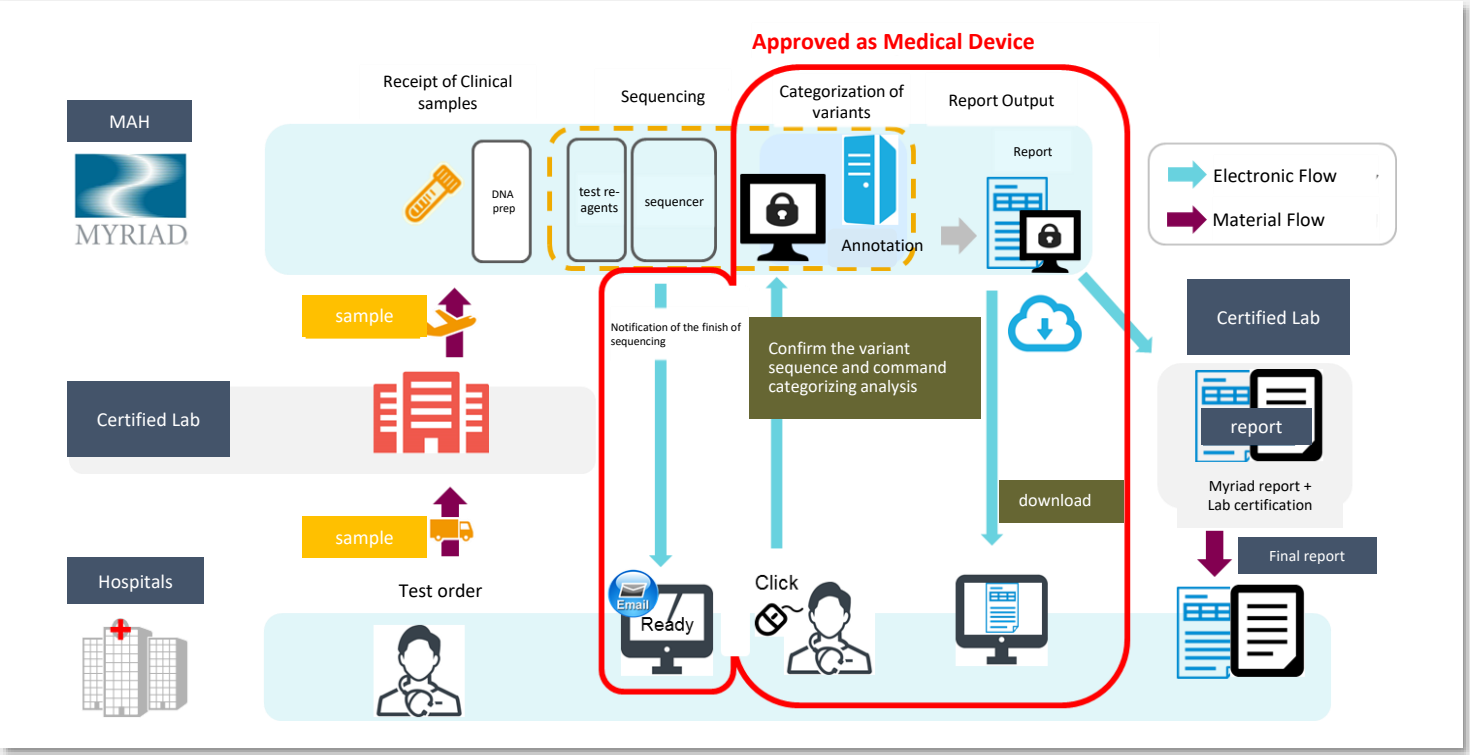
Evaluation of Software
Quality of the annotation report is evaluated based on the design and the validation reports of NGS test and bioinformatics pipeline.

Regulatory Evaluation of Genome Database

	System referring to In-house confidential DB	System referring to Public DB
Evaluation Points of DB in Review Process	● Validation of DB construction and update.	● Not subject to evaluation. ● Should be recognized in the approval dossier
What is regulatory approved?	● Analysis Pipeline ● DB construction and update procedure	● Analysis Pipeline
Post-marketing requirement	Annual Reports including following contents are required ● Newly registered variants ● Updated classification of variants ● Compliance to the approved procedure	No post-marketing requirement

Case1: BRACAnalysis CDx™

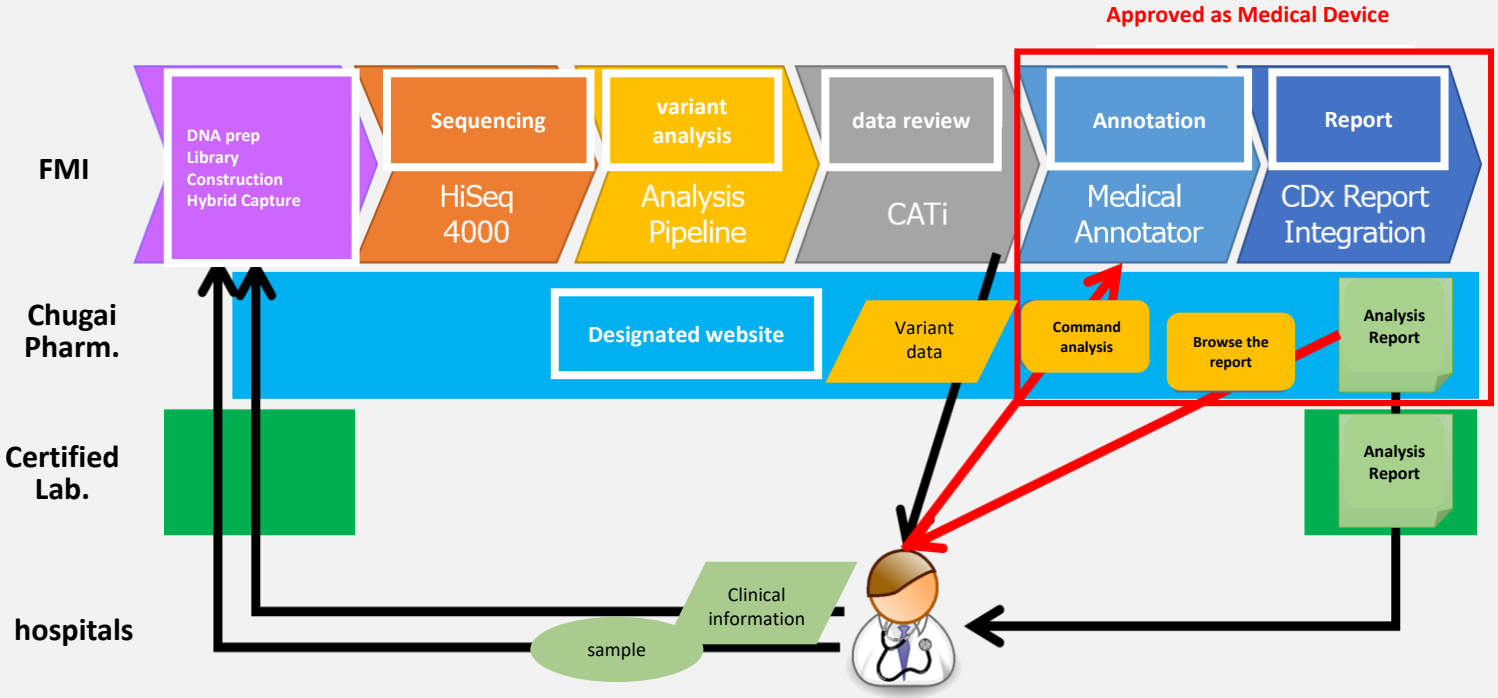
- This assay identifies breast cancer patients with deleterious or suspected deleterious germline BRCA mutation from more than 19,000 variants. Approved as CDx system for Olaparib in 2018 in the category of software as a medical device.



Modified from the Review Report
(http://www.pmda.go.jp/medical_devices/2018/M20180420001/navi.html)

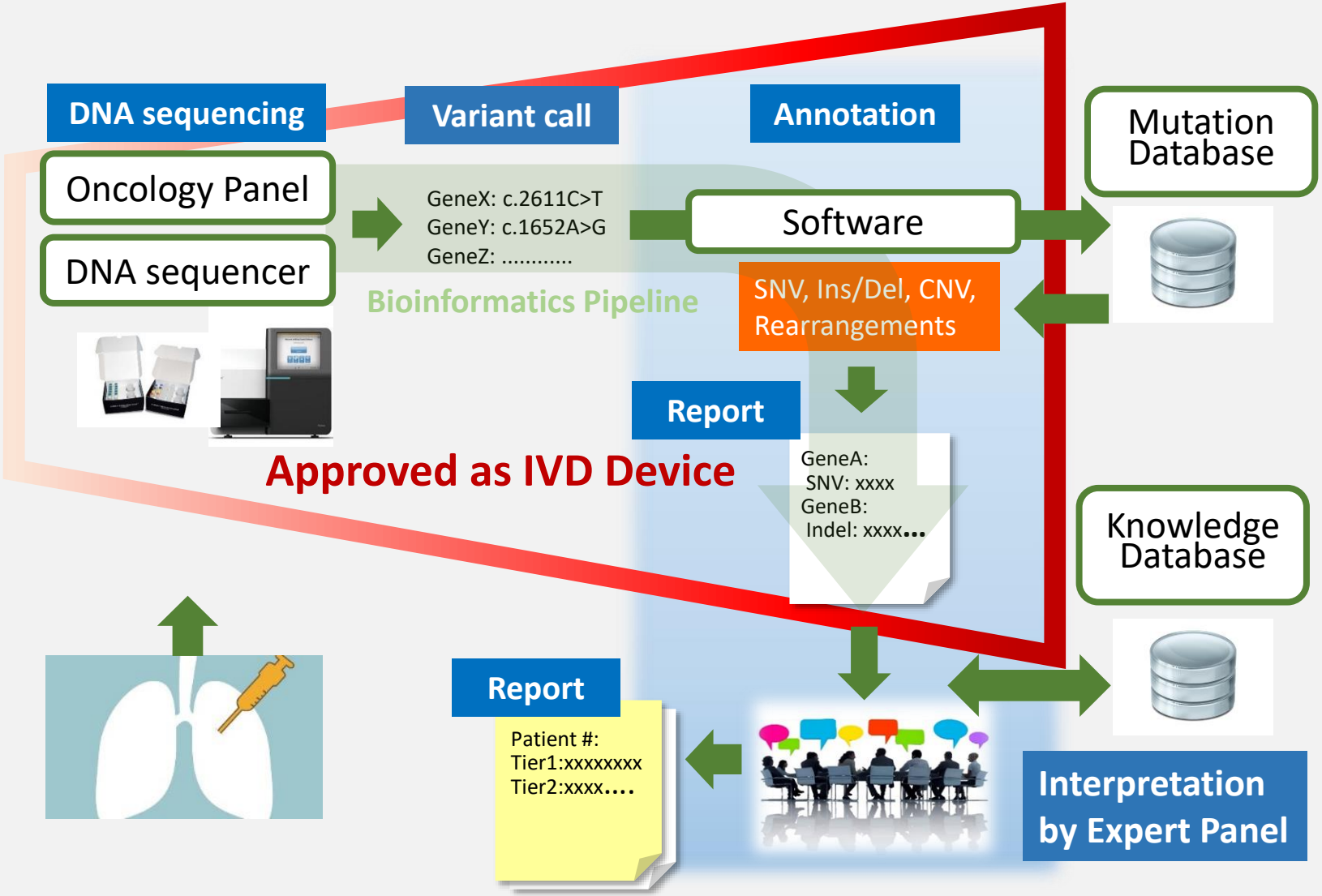
Case2: FoundationOne CDx

- This analysis program annotate the variants of DNA sequences of tumor tissue samples sent to FMI in the United States, based on the reference to the database, and output as a clinical report, using the analysis results.



Modified from the Review Report
（http://www.pmda.go.jp/medical_devices/2019/M20190123001/450045000_23000BZX00403_A100_1.pdf）

The weighting in the review process is shifting to software



What would happen after the clinical implementation of Oncology Panels?

Marker X-positive patients were selected for the phase 3 study in the development of new drug. Marker X has already been measured using approved oncology panel to obtain the comprehensive gene profile (CGP). Is it required to apply new CDx for marker X for approval application of the new drug?

New CDx for marker X is approved to identify the patients for the new drug. Marker X has already been measured using approved oncology panel to obtain the CGP. Is it possible to identify the patients for the new drug based on the result report of the CGP without using CDx for marker X?

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Summary

- In Japan, the panel test, for which there is insufficient clinical evidence, was approved on the premise that the framework of cancer genome precision medicine will be established and clinical development of new treatments will be promoted.
- In Japan, CDx and CGP tests are classified differently, and the latter is approved only on the basis of analytical performance.
- For oncology panel products, the importance of the bioinformatics pipeline is high, including the detection of mutations in the obtained sequencing data and database reference for interpretation of mutations, and the focus of the review is shifting to software.