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PMDA Perspectives on Companion Diagnostics Development in Japan

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Presentation Topics

- CDx Regulation in Japan
- CDx Development and Evaluation
- Current Challenges and Future Perspectives

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Notification and Administrative Notice

Issue date	Title
July 1, 2013	Notification on Marketing Authorization Application of In Vitro Companion Diagnostics and Corresponding Therapeutic products
	Questions and Answers on Companion Diagnostics and Corresponding Therapeutic products
Dec 26, 2013	Technical Guidance on Development of In Vitro Companion Diagnostics and Relevant Drugs
Feb 29, 2014	Points to consider on Marketing Authorization Application Form of Companion Diagnostics
Mar 28, 2014	Questions and Answers on Marketing Authorization Application Form of Companion Diagnostics
June-July 2018	Questions and Answers on Application Dossier of Companion Diagnostics (in preparation)

http://www.pmda.go.jp/english/rs-sb-std/standards-development/cross-sectional-project/0005.html

Notification and Administrative Notice

2013.7.1 Notification

- Definition of CDx
  A companion diagnostic is an in vitro diagnostic reagent or device essential for the safe and effective use of a corresponding therapeutic product
- Contemporaneous MAA of CDx and therapeutic product

2013.12.24 Administrative Notice

＜Technical Guidance＞

- Points to consider for CDx development
- Evaluation of analytical and clinical performance

2014.2.19 2014.3.28 Notification

- Description of Application Form

2018 July? Administrative Notice

What should be described in application dossier

Encourage sharing of the necessary data or information between drug and CDx sponsor

CDx Approved in Japan

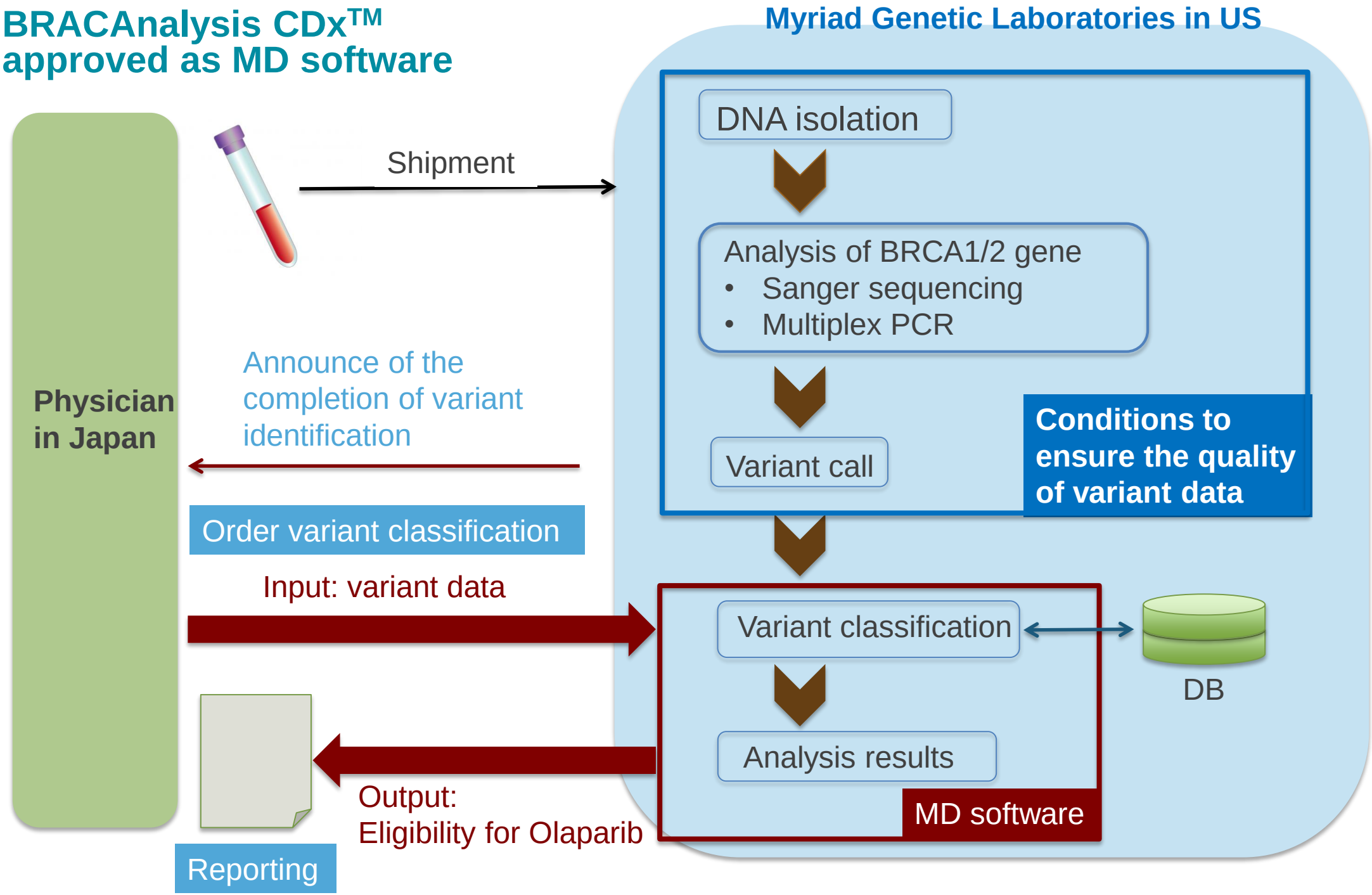
CDx Trade Name	Corresponding drug	Biomarker
POTELIGEO TEST IHC/POTELIGEO TEST FCM	mogamulizumab	CCR4 protein
Cobas BRAF V600 mutation test	vemurafenib	BRAF mutation
Histofine ALK iAEP kit	alectinib	ALK protein
Vysis ALK Break Apart FISH probe kit	crizotinib and alectinib	ALK fusion
THxID BRAF kit	dabrafenib/trametinib	BRAF mutation
Cobas EGFR mutation test v2.0	osimertinib	EGFR mutation
OncoGuide AmoyDx ROS1 Gene Fusions Detection Kit	crizotinib	ROS1 fusion (RNA)
PD-L1 IHC 22C3 pharmDx [Dako]	pembrolizumab	PD-L1 protein
Ventana OptiView ALK (D5F3)	crizotinib and ceritinib	ALK protein
MEBGEN RASKET-B kit	cetuximab and panitumumab	KRAS and NRAS mutation
BRACAnalyis CDx	olaparib	BRCA1 and BRCA2 mutation
Oncomine Dx Target test	dabrafenib/trametinib	BRAF mutation

as of June 26,2018

Approval of BRACAnalysis CDx™

- Approved in March 2018 as **medical device software**
- Intended use: aid in identifying breast cancer patients eligible for treatment with Lynparza (olaparib)
- Conditions of approval
  - Submission of annual report on the evaluation of the robustness of the variant classification process, classification changes and newly identified variants.
  - Assurance of cyber security and patient privacy

BRACAnalysis CDx™ approved as MD software



Presentation Topics

- Regulation of CDx in Japan
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CDx Development

- Early stages of the therapeutic product (TP) development
  - Rationale for therapy targeted to a biomarker positive or negative population
  - Determination of the clinical cutoff
- Prior to Major Efficacy Trial
  - Analytical validation studies should be completed.
  - Variables that affect the test result should be specified and controlled.
- Later Stages of the TP development
  - Evaluation of clinical performance of the candidate CDx
  - Confirmation of the cut-off value

Evaluation of CDx

Basic Principles:

- CDx should provide accurate and reproducible results.
- CDx should be able to identify a population expected to benefit from the therapeutic product.

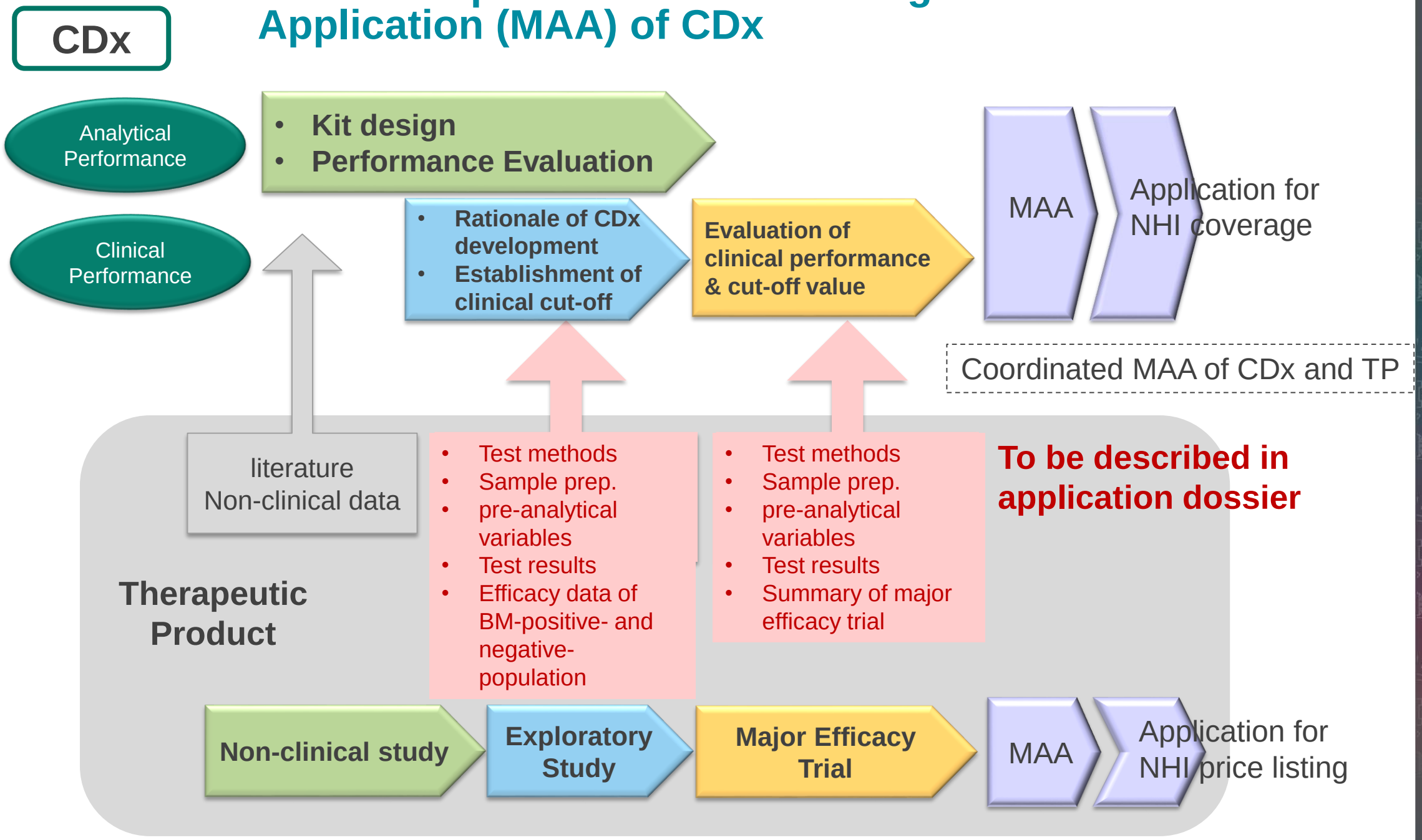
- Analytical Performance
  - Accuracy
  - Precision(repeatability and reproducibility)
  - Specificity
  - Detection Limit
  - Interfering substances
  - Cross-contamination
  - Robustness
- Clinical Performance

What to be described in application dossier

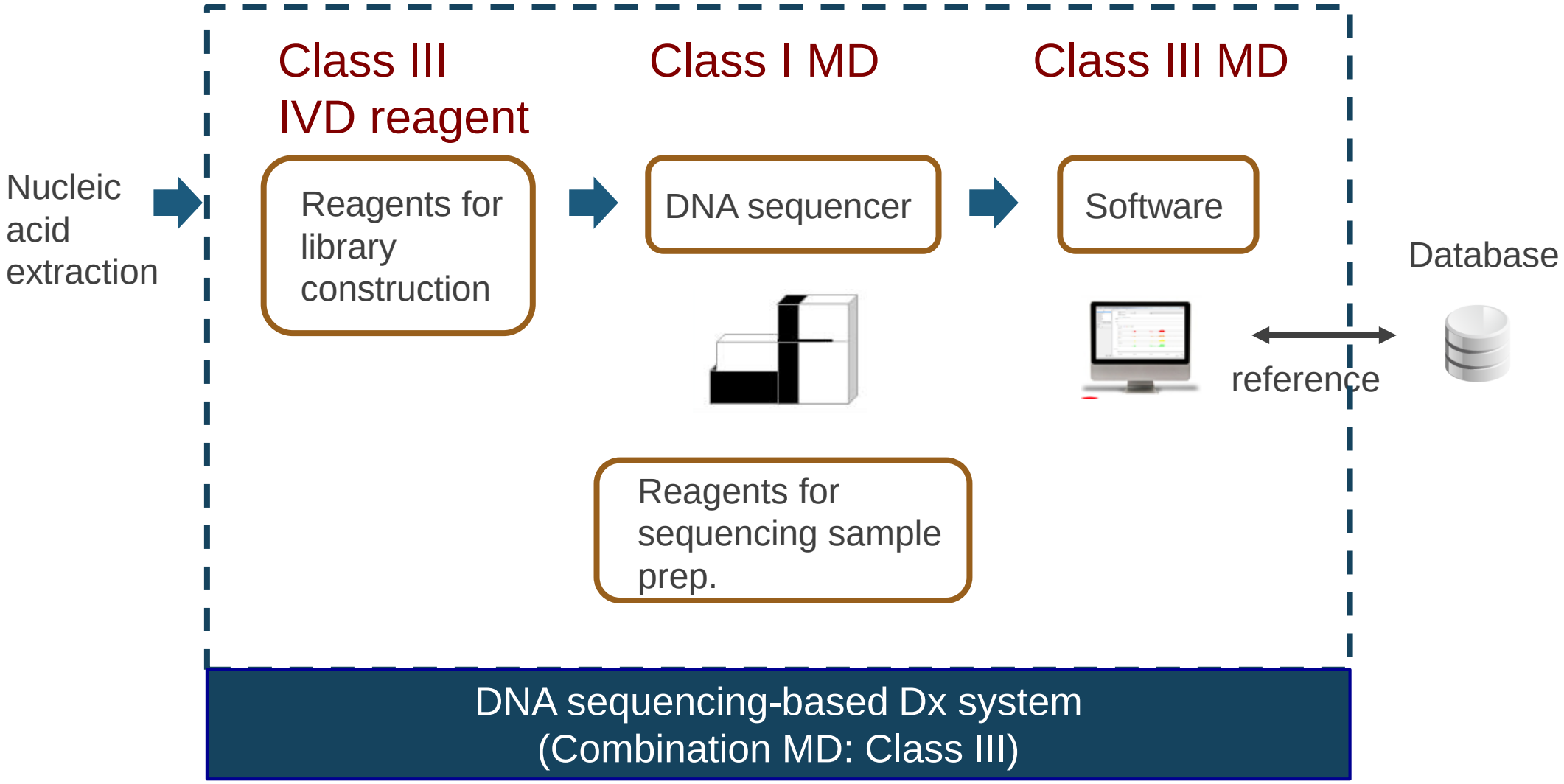
New Administrative Notice expected to be issued in July

- Rationale for clinical cut-off based on exploratory trial data in which both biomarker positive and negative patient were enrolled
- Description of CTA methods used to establish clinical cut-off based on exploratory trial
- Rationale of the clinical cut-off for patient enrollment in major efficacy trial, taking into consideration of the impact of the difference between CTA and the candidate CDx (basically based on concordance study)

Data to be provided for Marketing Authorization Application (MAA) of CDx



Regulatory Framework of DNA Sequencing-based Dx System



Evaluation of NGS-based CDx

- **Basic principles are the same as conventional CDx.**
  - CDx should provide accurate and reproducible results.
  - CDx should be able to identify a population expected to benefit from the therapeutic.
- **Validation approach considering the characteristic feature of NGS-based system could be possible.**

Evaluation of NGS-based CDx

- In principle, clinical specimen should be used to evaluate analytical performance.
- For rare variants, use of contrived sample could be acceptable if the scientific rationale is provided.
- It is acceptable to evaluate analytical performance for the representative subset of variants if scientific rationale is provided.
  - the representative subset of variants should cover the range of variants to be detected by the system.
  - Variant type (SNV, indels, CNV, fusion), genome context, length should be considered.

Follow-on CDx

- Comparability of clinical performance of follow-on CDx to the original CDx could be demonstrated by analytical concordance study.
- Reference in concordance study should be the originator product of which clinical performance is demonstrated based on clinical trial data of the corresponding TP.
  - Approved follow-on CDx should not be a reference in concordance study.

<Possible Issues>

- Acceptability of the reference CDx approved outside of Japan (e.g. US-approved but not Japan-approved CDx)

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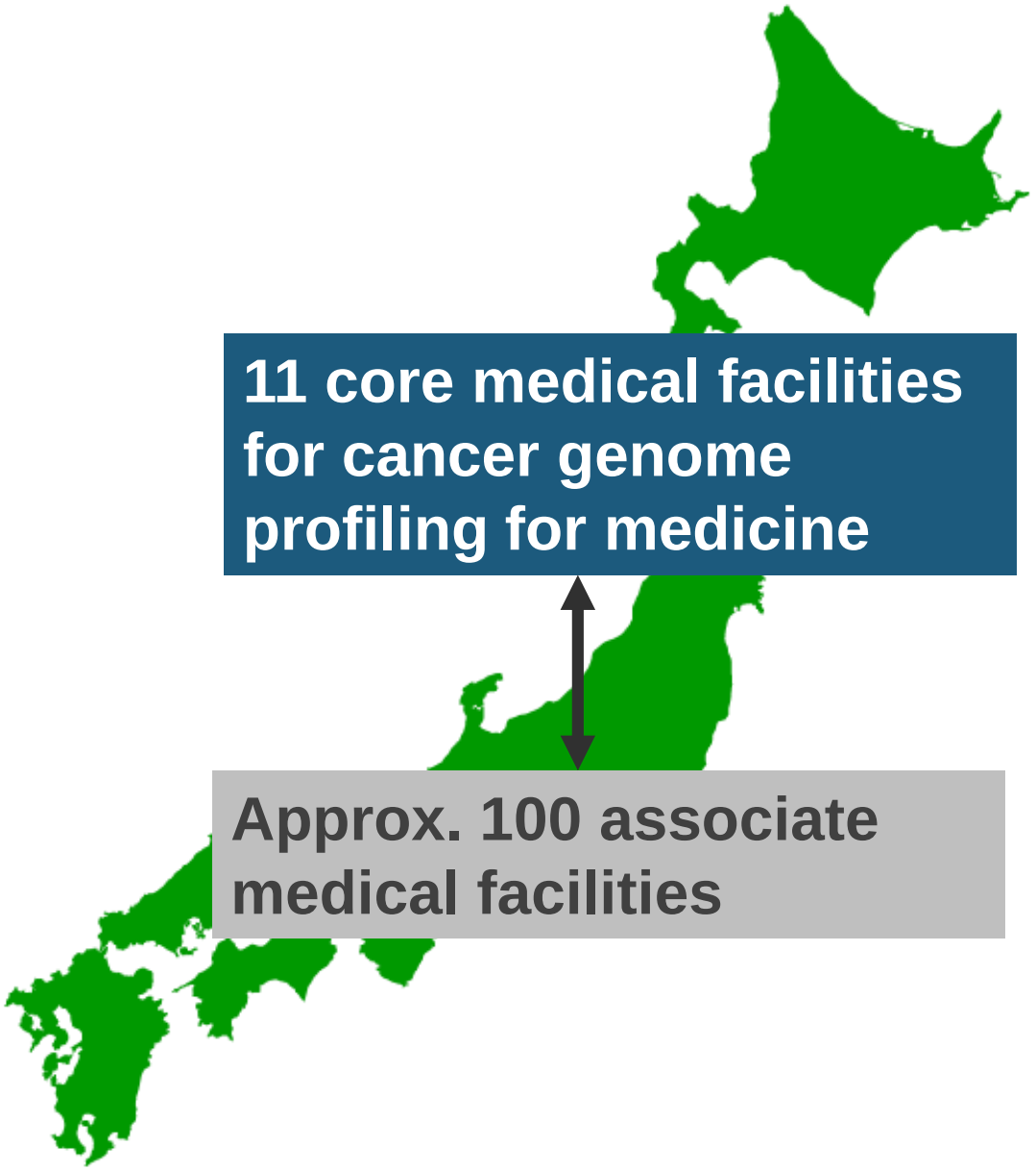
Challenges in CDx evaluation

- Pan-cancer claim
  - Availability of specimens
  - How to provide evidence to support test performance for all tumor types
- CDx development in rare disease
  - How to ensure analytical and clinical performance with limited specimens
  - How to conduct bridging study

Challenges after implementation of oncology panel into clinical settings

- Possibility to identify patients eligible for TP using oncology panel in medical facilities
  - Use of panel result is expected by physicians considering early patient access to TP and the limitation of clinical specimen
  - Measures to ensure the safety and efficacy of the corresponding TP are necessary.
- Possibility to establish standards for comparability evaluation
  - Comparability of genetic tests, especially for NGS-based tests

Cancer Genome Consortium for Medicine in Japan



11 core medical facilities for cancer genome profiling for medicine

Approx. 100 associate medical facilities

Genome profiling using oncology panel

↓

Annotation of variants using DB

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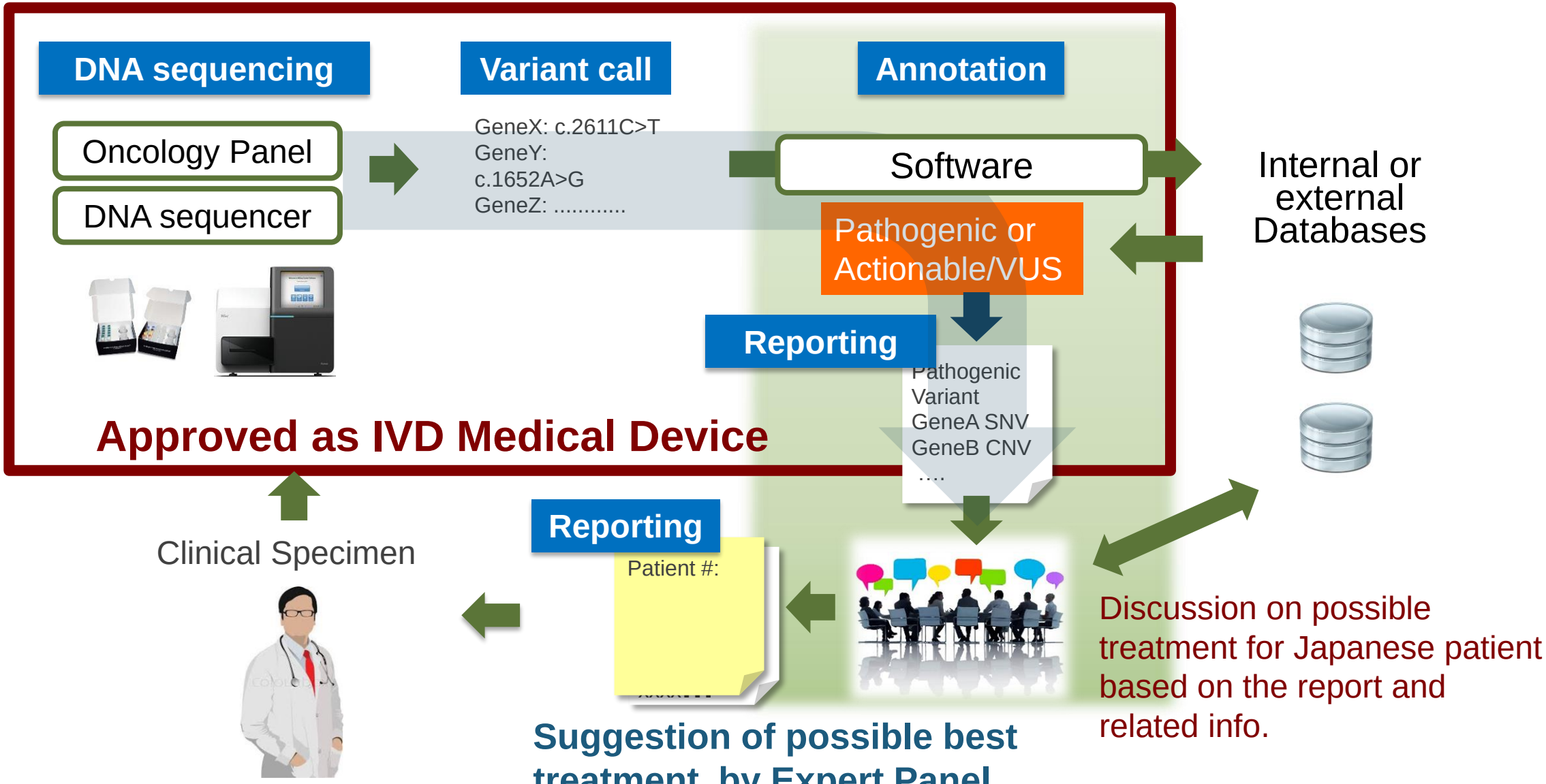
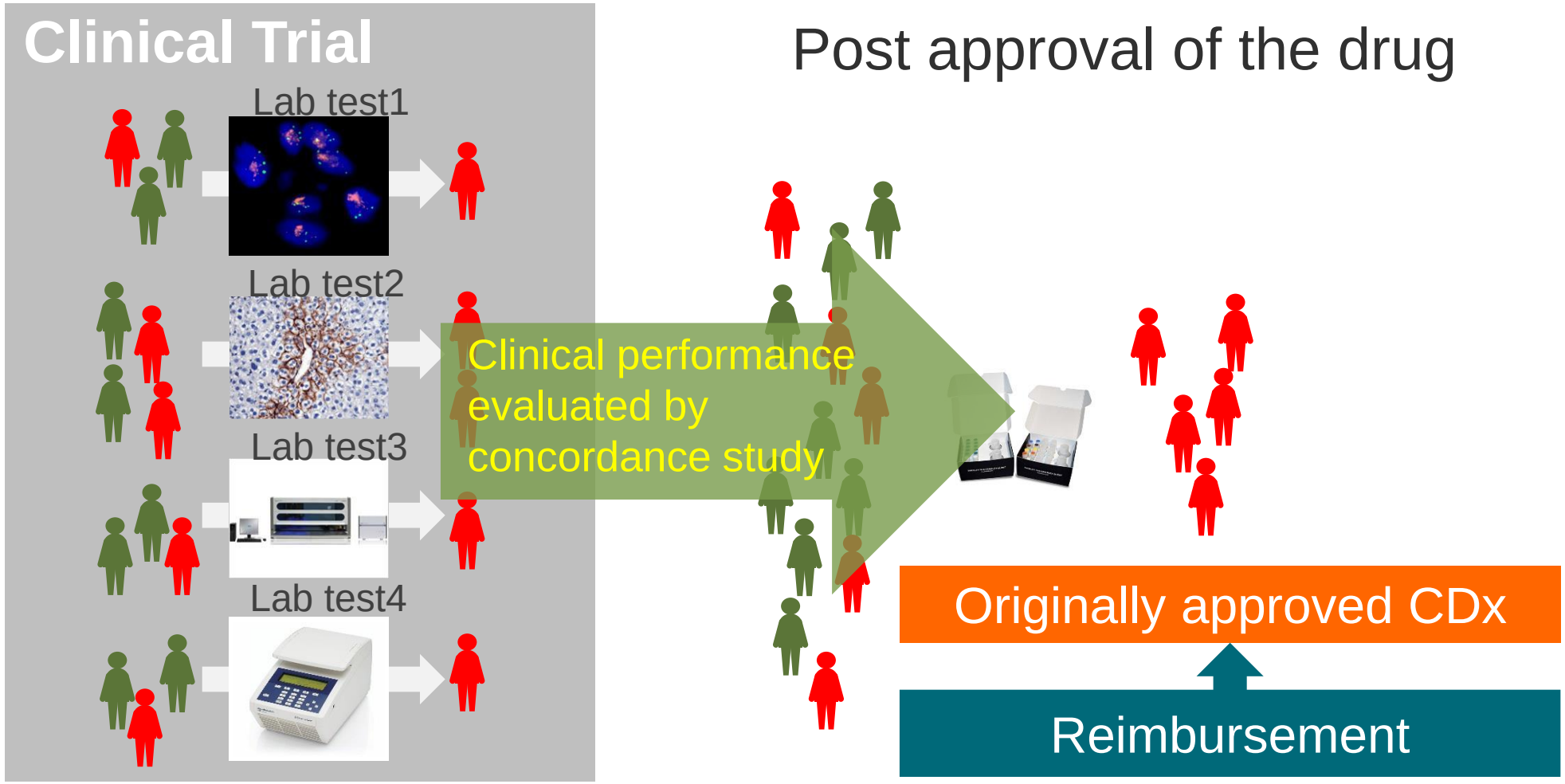
Evaluation of variant annotation and reporting of the possible best treatment by expert panel

Implementation of Oncology Panel in Japanese Clinical Setting



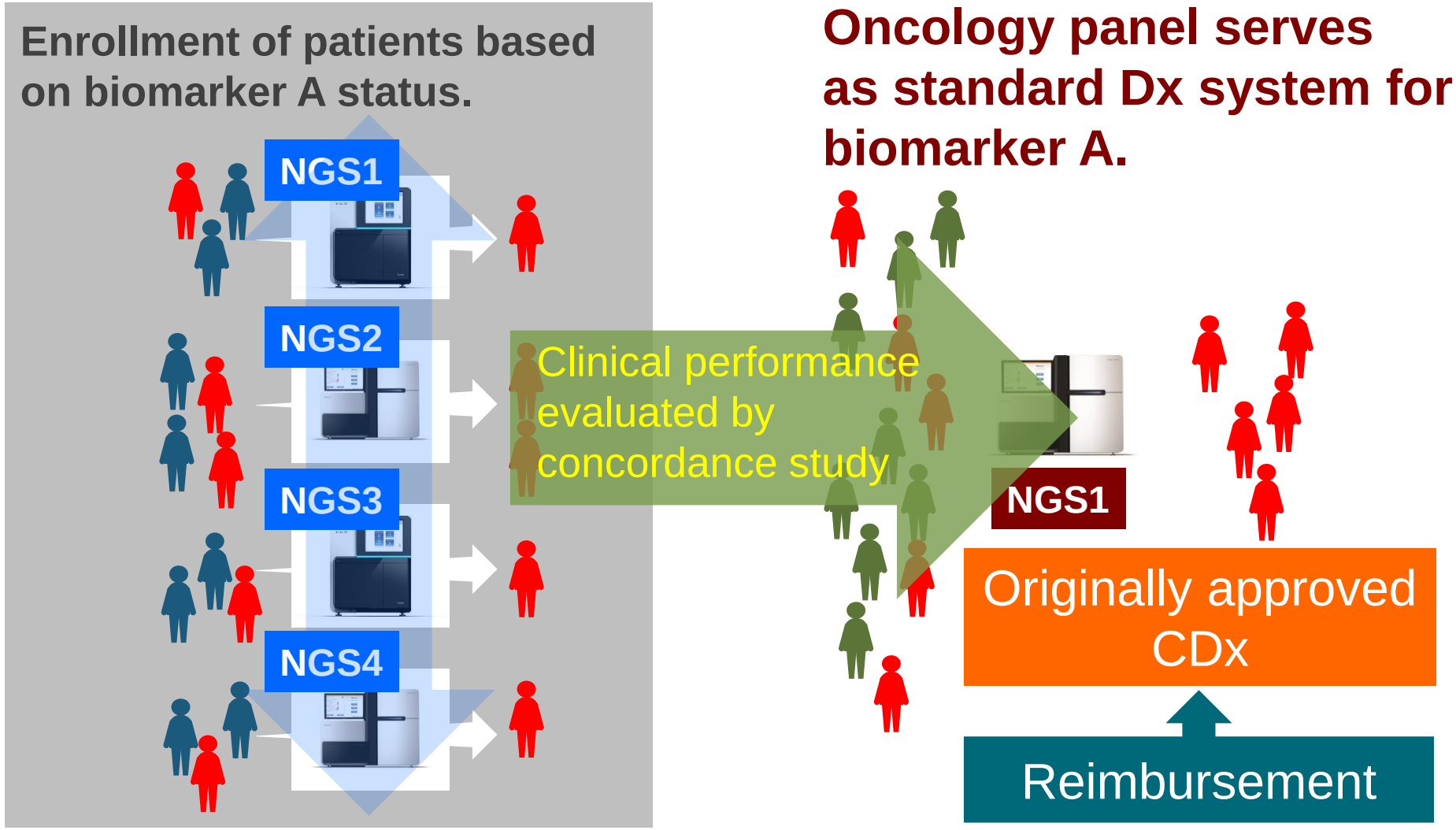
Role of approved CDx

- **Originally approved CDx serves as standard Dx system to ensure the safety and efficacy of TP.**



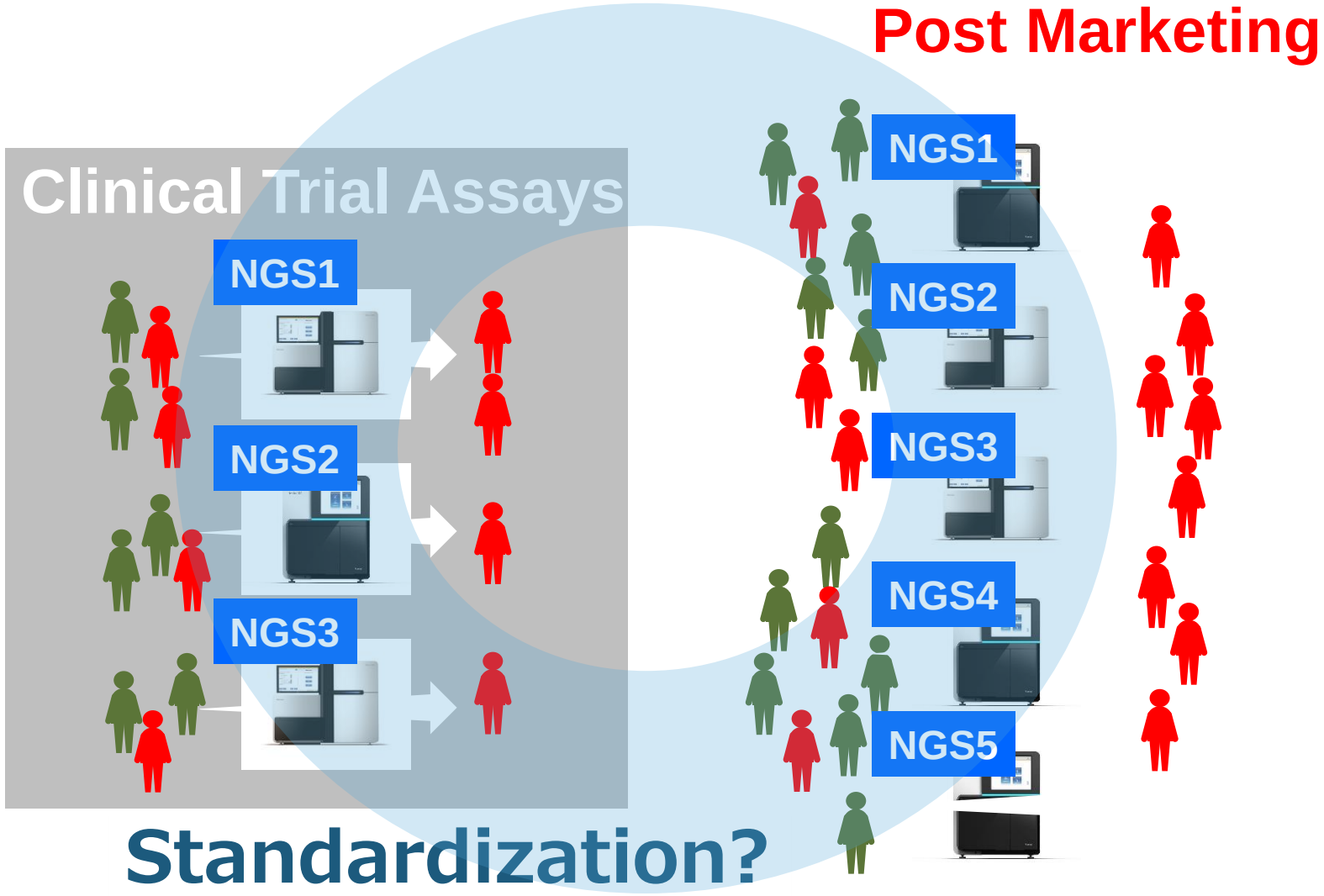
After implementation of oncology panel,

The requirement for the diagnostic system to ensure the safety and efficacy of the corresponding therapeutic product will NOT change.



Further more..

Is it possible to ensure the clinical efficacy and safety of therapeutic product by the establishment of comparability standards?



Summary

- New administrative notice will be issued soon to clarify the scientific data and justification to be provided in application dossier.
- PMDA expects the new administrative notice will be used as a tool to facilitate the communication and data sharing between drug and CDx sponsors.

- Along with for the implementation of oncology panel into medical setting in near future, how to evaluate the comparability of NGS-based tests for CDx use is under discussion.

Thank You

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