PMDA Perspectives on CDx

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   - ✓ Basic principles for CDx development
   - ✓ Challenges and observation

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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

- What should be described in Application Form

2018.7.3 Administrative Notice

- What should be described in application dossier
- Encourage sharing of the necessary data or information between drug and CDx sponsor

https://www.pmda.go.jp/english/rs-sb-std/rs/0006.html

CDx Approved in Japan

as of Aug 20, 2019

CDx Trade Name	Corresponding drug	BM to be tested
POTELIGEO TEST IHC/POTELIGEO TEST FCM	mogamulizumab	CCR4 protein
Cobas BRAF V600 mutation test	vemurafenib	BRAF mutation
Histofine ALK iAEP kit	alectinib, crizotinib	ALK protein
Vysis ALK Break Apart FISH probe kit	crizotinib and alectinib	ALK fusion
THxID BRAF kit	dabrafenib/trametinib (melanoma) encorafenib/binimetinib	BRAF mutation
Cobas EGFR mutation test v2.0	gefitinib, erlotinib, afatinib, 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)	alectinib, ceritinib,crizotinib	ALK protein
MEBGEN RASKET-B kit	cetuximab, panitumumab	KRAS and NRAS mutation
BRACAnalyis CDx	olaparib (ovarian cancer, breast cancer)	BRCA1 and BRCA2 mutation

CDx Trade Name	Corresponding drug	BM to be tested
Oncomine Dx Target Test	dabrafenib/trametinib (NSCLC)	BRAF mutation
	gefitinib, erlotinib, afatinib, osimertinib	EGFR mutation
	crizotinib, alectinib	ALK fusion
	crizotinib	ROS1 fusion
MSI kit (FALCO)	pembrolizumab	MSI-High
LeukoStrat CDx FLT3 Mutation Assay	gilteritinib, quizartinib	FLT3 mutation
FoundationOne CDx	gefitinib, erlotinib, afatinib, osimertinib	EGFR mutation
	vemurafenib, dabrafenib/trametinib(melanoma)	BRAF mutation
	trastuzumab	HER2 amplification
	alectinib, crizotinib, ceritinib	ALK fusion
	cetuximab, panitumumab	KRAS and NRAS mutation
	entrectinib	NTRK fusion
Therascreen EGFR mutation detection kit RGQ	gefitinib, erlotinib, afatinib,dacomitinib	EGFR mutation

https://www.pmda.go.jp/english/rs-sb-std/rs/0006.html

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:

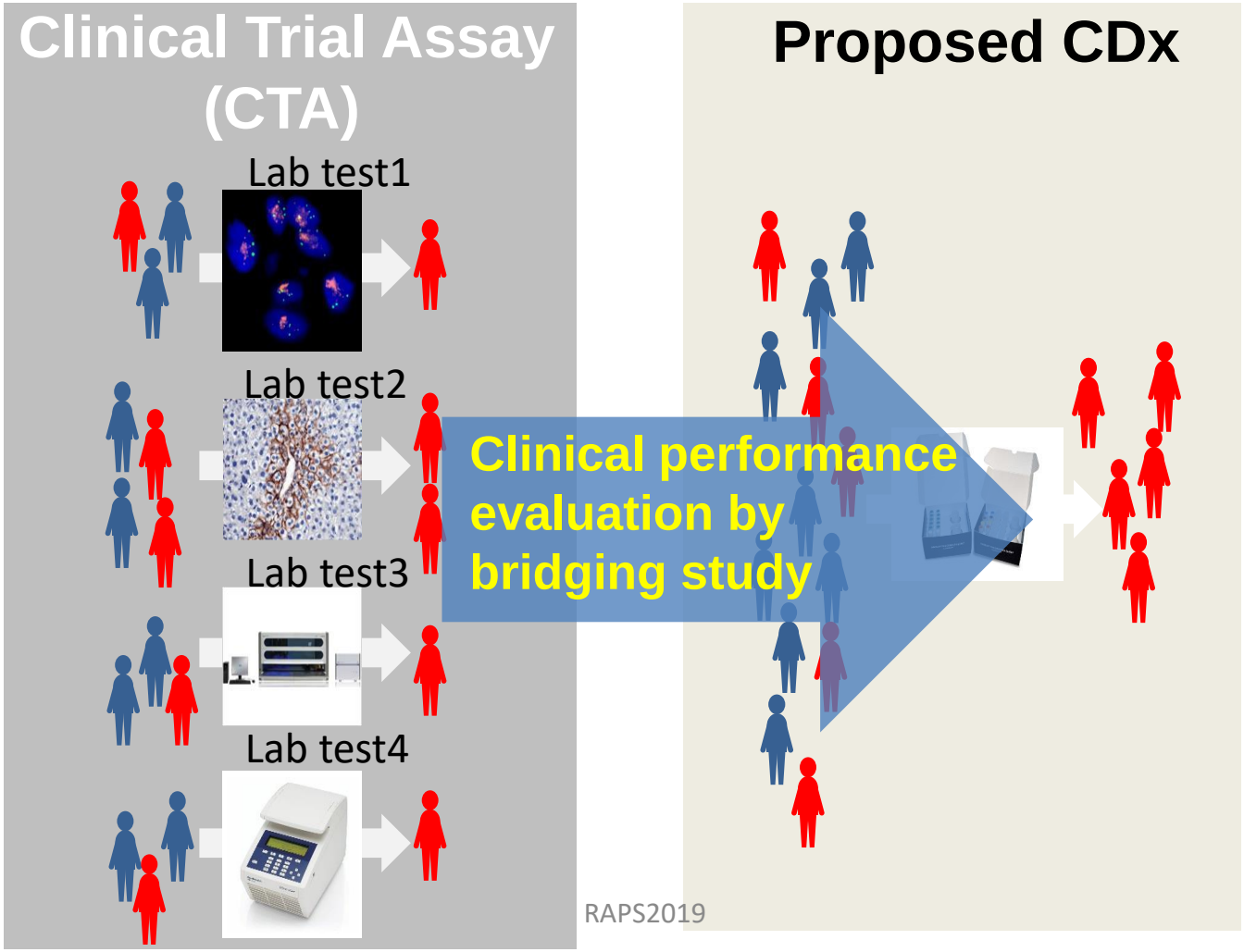
- CDx should provide accurate and reproducible results. (analytical performance)
- CDx should be able to identify a population expected to benefit from the therapeutic product. (clinical performance)

- Analytical parameters to be considered:
  - Accuracy
  - Precision(repeatability and reproducibility)
  - Detection Limit
  - Interfering substances…etc.

Technical Guidance
https://www.pmda.go.jp/files/000153149.pdf

Bridging Study

If the proposed CDx was not used in the major efficacy trial(s), generally, a bridging study would be needed to demonstrate high concordance with clinical trial assay(s).



What should be evaluated in the bridging study?

In principle,

- PPA and NPA between CTAs and the proposed CDx using the original clinical trial samples
- Comparability of efficacy of the therapeutic product between CTA identified- and the proposed CDx identified- population

Challenges and Observation

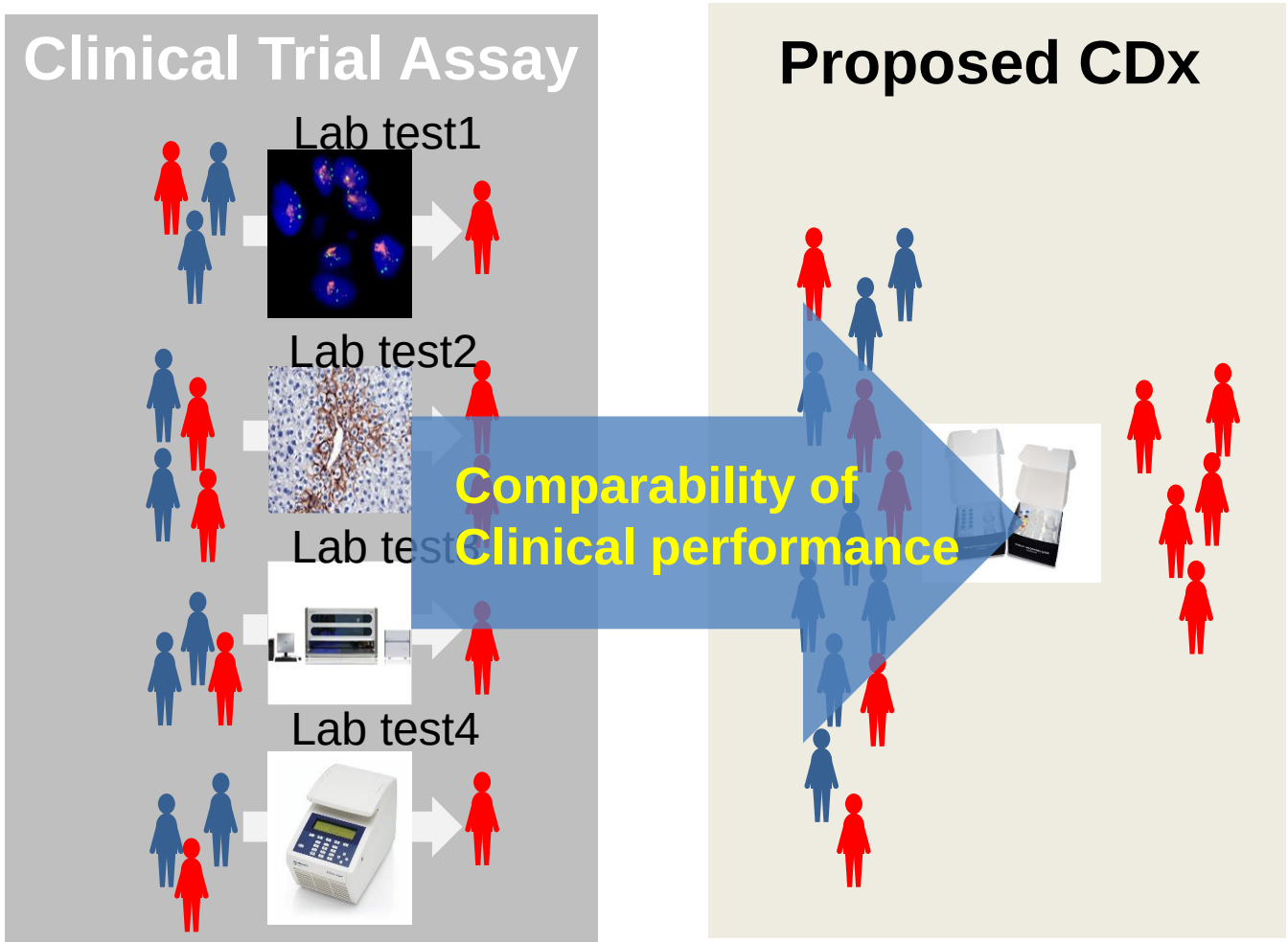
- Concordance study only using CTA*-positive samples

  *Clinical Trial Assay

  - Evaluation of NPA is expected based on the available evidence (e.g. concordance study with BM-negative samples, literature)
- Limited Availability of Clinical Samples
  - Concordance study using clinical samples with the same patient background is expected.

Role of originally approved CDx

The originally approved CDx should be served as standard diagnostic test to identify patients for whom the efficacy and safety of the therapeutic product are expected as in the major efficacy trial.



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Exploring New Regulatory Approach for Interchangeable CDx

Background

- Multiple CDxs are developed independently for oncology therapeutic products of which indications including the target mutation(s) are the same (e.g. EGFR mutation kits).
- Among those companion diagnostics, some are already shown to be comparable.

In such cases, **interchangeable use of CDx could be possible.**

To optimize the clinical use of CDx, PMDA is now considering a new regulatory approach, including the regulation for ‘interchangeable CDx’.

EGFR mutation detection kit approved in Japan

CDx	gefitinib	erlotinib	afatinib	osimertinib	dacomitinib
Therascreen EGFR mutation detection kit RGQ	x	x	x		x
Cobas EGFR mutation test v2.0	x	x	x	x	x
FoundationOne CDx	x	x	x	x	
Oncomine Dx Target Test	x	x	x	x (1^{st} line)	

as of Sep 10, 2019

e.g. concordance study of cobas v2

reference IVD	IVD-A	IVD-B
PPA	100% (59/59)	100% (59/59)
NPA	98% (58/59)	100% (59/59)
Overall concordance	99%(117/118)	100% (118/118)

Discussion Paper on New Regulatory Approach

Main proposals are:

- Regulation for 'interchangeable CDx' (Group Companion Diagnostics)
- Strategy for drug development using Group CDx

Definition of 'Group Companion Diagnostics'

- Companion diagnostics for the therapeutic products approved for the same indication including the biomarker status (e.g. EGFR-TKI).
- CDx of which interchangeability is considered acceptable based on:
  - ✓ publically available information of the concordance with other member of CDx in the group
  - ✓ guideline for health care professionals

Regulatory Process for Group CDx designation

1. Release of the draft Notification on the designation of specific ‘Group CDx’ by MHLW/PMDA, based on the request or proposal from stakeholders (e.g. EGFR mutation kit for EGFR-TKI)

2. Public comments on the draft Notification

3. Publication of Notification on ‘Group CDx’

Submission of marketing application supplement for indication as Group CDx based on the Notification

If evidence is sufficient to conclude that the approved companion dignostics are interchangeable..

Group CDx for EGFR-TKI

CDx	gefitinib	erlotinib	afatinib	osimertinib	dacomitinib
Therascreen EGFR mutation detection kit RGQ	X	X	X	X	X
Cobas EGFR mutation test v2.0	X	X	X	X	X
FoundationOne CDx	X	X	X	X	X
Oncomine Dx Target Test	X	X	X	X	X

?

＜indications for use＞

The test is intended to be used to select patients with NSCLC for whom **EGFR tyrosine kinase inhibitors** is indicated.

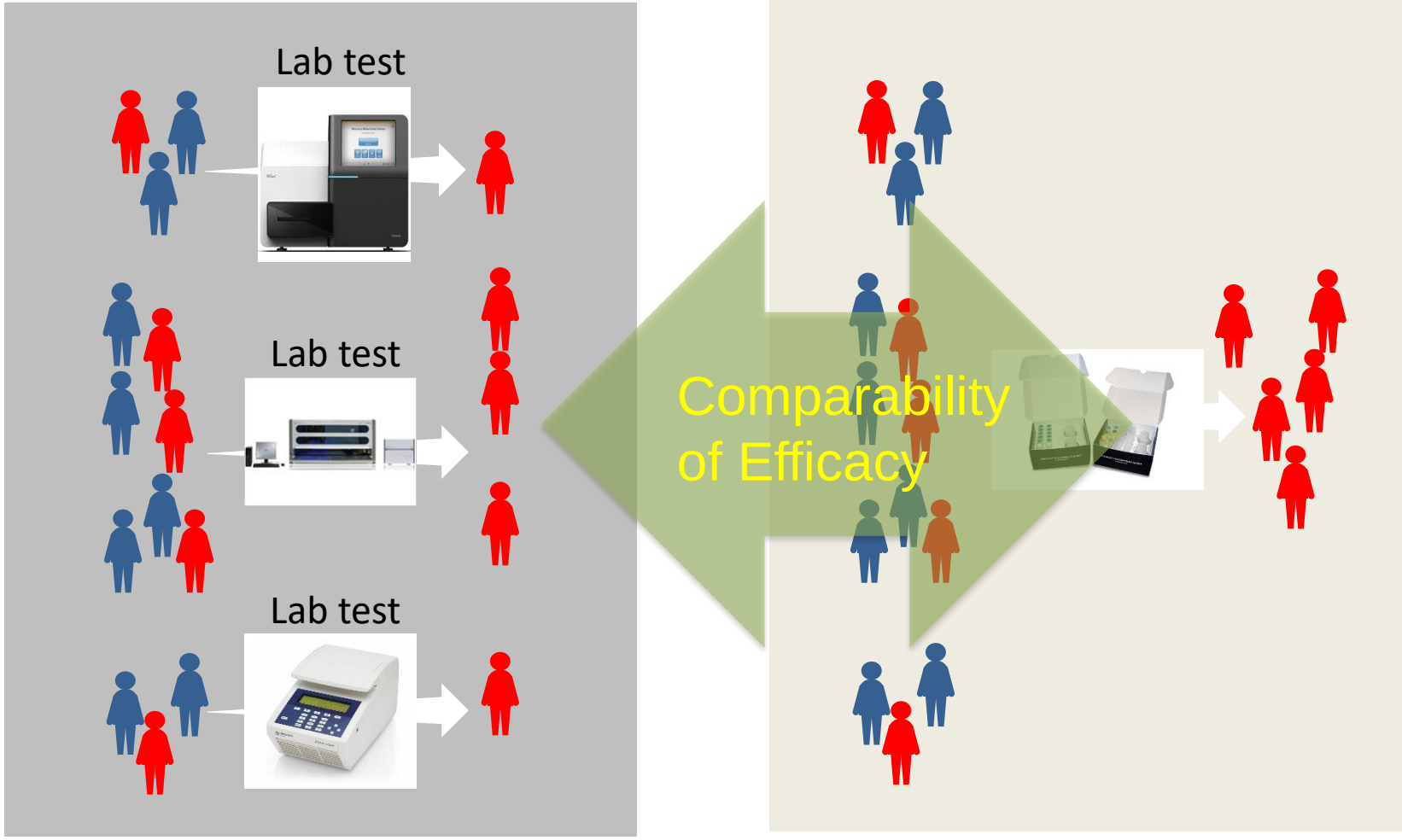
New Drug Development using Group CDx (e.g. new EGFR-TKI)

- Once approved as Group CDx, sPMA is not required to change indications for use.
- In this case, it is expected that the drug sponsor provides rationale for the development using group CDx in NDA.

Example1: enrollment using one of the Group CDx

Example2:
Enrollment with various CTAs

Central testing with one of the Group CDx



Comparison with FDA Draft Guidance

‘Developing and Labeling In vitro Companion Diagnostic Devices for a Specific Group or Class of Oncology Therapeutic Products’

Same concern

‘FDA is concerned that the current situation is not optimal for patient care because a clinician may need to order a different companion diagnostic (i.e., one that includes other therapeutic products on the label), obtain an additional biopsy(ies) from a patient, or both, to have additional therapy treatment options.’

Same Goal

- ✓ Flexibility for clinicians in choosing the most appropriate therapeutic product based on a patient’s biomarker status
- ✓ Our current idea on indications for use of EGFR mutation kit is similar to FDA’s proposal.

Comparison with FDA Draft Guidance

‘If evidence is sufficient to conclude that the CDx is appropriate for use with a class of therapeutic products, the intended use should name the therapeutic class.’

A specific group or class of therapeutic products

CDx	gefitinib	erlotinib	afatinib	osimertinib	dacomitinib
Therascreen	x	x	x	x	x
cobas	x	x	x	x	x
FO	x	x	x	x	x
Oncomine	x	x	x	x	x

＜indications for use＞

‘identifying patients with NSCLC whose tumors have EGFR exon19 del or exon21 (L858R) substitution mutations and are suitable fro treatment with a tyrosine kinase inhibitor approved by FDA for that indication’

FDA DRAFT Guidance
The factors to support broader labeling claim

1. Whether a specific group or class of TPs can be defined for which CDx will identify an appropriate patient population
2. Detailed understanding of mechanism of action of TP and interaction between TP and biomarker(s) at the mutation level
3. Sufficient clinical experience with at least two TPs for the same biomarker-informed indications
4. Analytical validity of CDx across the range of biomarkers that inform the indication
5. Clinical validity for each TP

- No.1-5 will be similarly considered by MHLW/PMDA to designate the group CDx.
- No.5 could be ensured by the concordance test result between members of the group.

Schedule for the Implementation of new CDx Regulation in Japan

Current schedule

1. Release of discussion paper on new CDx regulation for comments from industries and academia (comment deadline: mid-September)
2. Companion diagnostic workshop in December 20, 2019

3. Administrative Notice on regulation of group CDx in 2020
4. Process for the designation of each group CDx will start in 2020 (hopefully).

Summary and Future Perspectives

- PMDA is considering the regulatory approach to further support the advancement of precision medicine in Japan.

- New regulation for interchangeable CDx (Group CDx) has been proposed asking for public comments and will be implemented in 2020.

- As for genetic testing, PMDA is also considering the possibility to evaluate the comparability of clinical performance between follow-on CDx and the original CDx based on LOD, as an alternative to concordance study.

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