多様化するがんゲノム診断法に対する薬事規制の対応

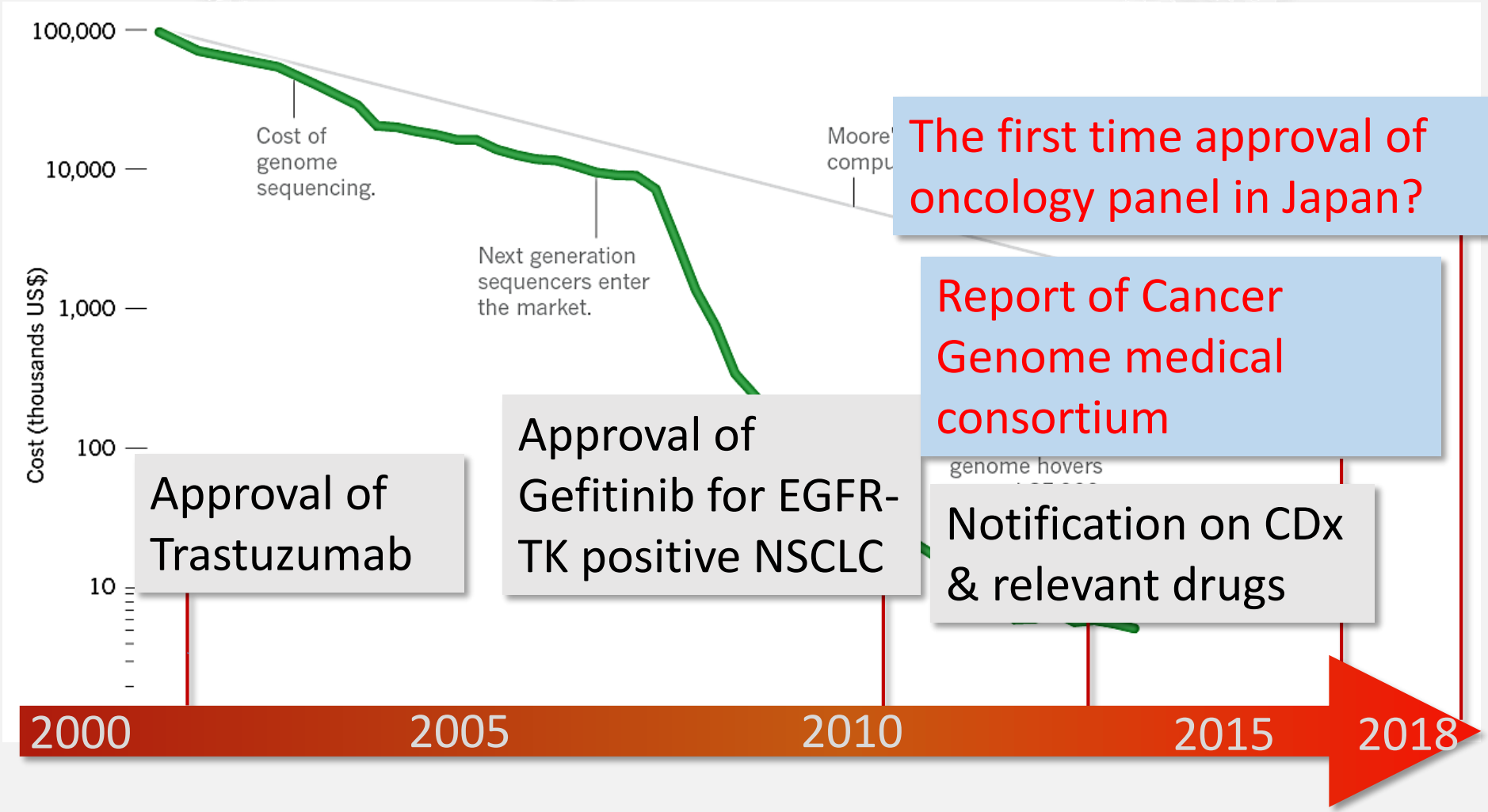
Regulatory Trends toward Approval of Oncology panel in Japan

医薬品医療機器総合機構
体外診断薬審査室
矢花直幸
Naoyuki Yabana　Office of IVD, PMDA

Disclaimer

The views and opinions expressed in this presentation are those of the presenter and should not necessarily represent the views and opinions of the PMDA.

From CDx Era to Oncology Panel Era



The first time approval of oncology panel in Japan?

Report of Cancer Genome medical consortium

Approval of Trastuzumab

Approval of Gefitinib for EGFR-TK positive NSCLC

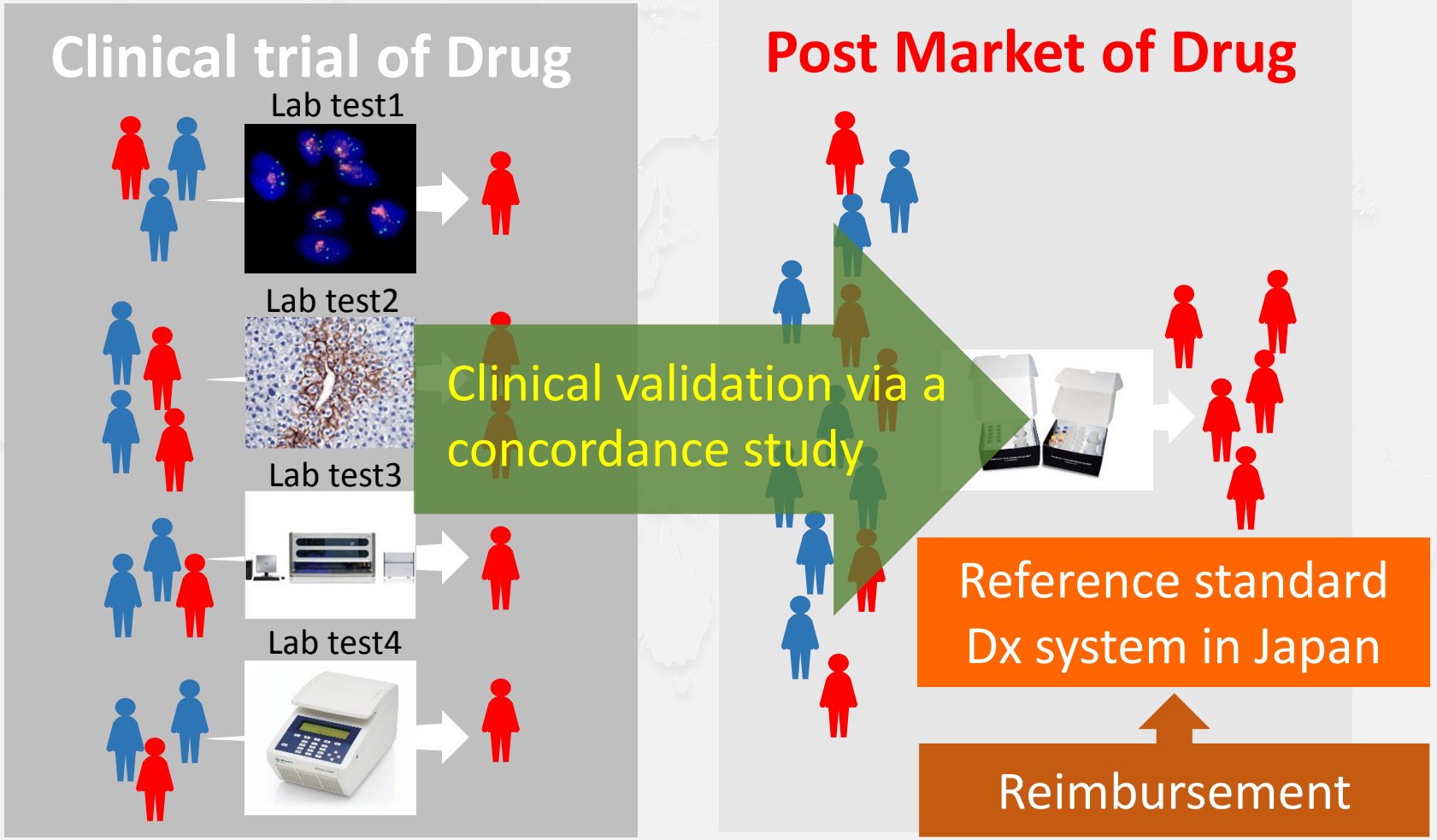
Notification on CDx & relevant drugs

Nature 2014 507: 294

Approved CDxs 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

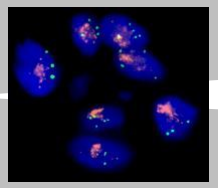
What is the essence of CDx?



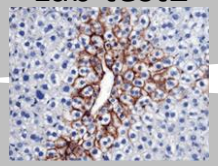
What is the essence of CDx?

Clinical trial of Drug

Lab test1



Lab test2



Lab test3

Lab test4

Post Market of Drug

Follow-on CDx

Clinical validation via a concordance study

Reference standard
Dx system in Japan

Reimbursement

Issues of CDx in Japan

- **One CDx corresponds to One clinical trial.**
  - ✓Not “One CDx to One drug”, nor “One CDx to One biomarker”.
  - ✓e.g. ALK, BRAF, etc
  - ✓Development of “Follow-on CDx for multiple drugs” based on the external concordance study is encouraged.
- **Is it the lab-test for subtype diagnostics or identification of the therapeutic responder?**
  - ✓As the biomarker for drug response is established in long-term clinical use, it could be a test item in a routine medical practice.
  - ✓e.g. HER2 for breast cancer

From One Gene test to Multiplex NGS test – Benefits for Patients

Commercialization of NGS is making the following changes:

- Enabling to obtain a lot of genome information on driver genes including SNV, Ins/Dels, CNA and structural variants.
- Enabling precision medicine based on therapeutic response factors and prognostic factors in addition to CDx.

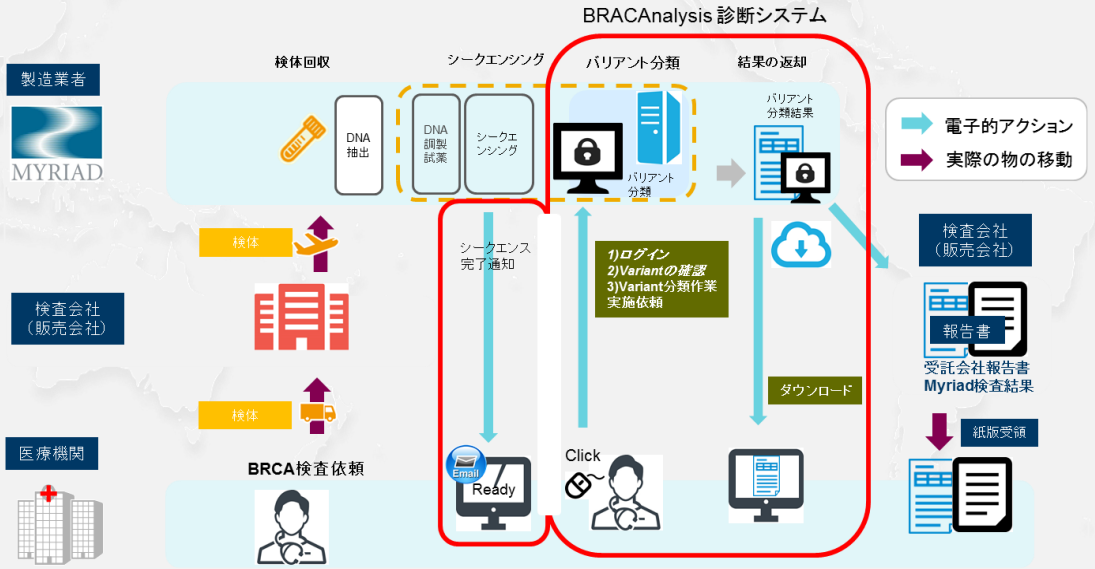
From One Gene test to Multiplex NGS test – Challenges in Lab tests

Clinical implementation of NGS is making the following changes:

- Drastic increase of information for annotation and interpretation of variants requisites the reference databases.
- Establishment of clinical field for the genome precision medicine which interprets the genome profile and selects optimal medication.
- Emergence of various type of diagnostic system, i.e. single-site assay performed at marketing authorization holder's lab.

Case1: BRACAnalysis CDx™ （BRACAnalysis診断システム）

- 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.
- Annual post-marketing report on summary of newly variant classification is requested.



BRACAnalysis診断システム審査報告書
（http://www.pmda.go.jp/medical_devices/2018/M20180420001/navi.html）

Case2: Oncomine™ Dx Target Test （オンコマイン Dx Target Test CDxシステム）

- This assay is indicated to CDx on 3 genes (BRAF, ROS1, EGFR). Also indicated to qualitative diagnostic tests of 23 genes for patients who have already been considered for all appropriate therapies in US SSED.
- Approved as CDx system for Tafinlar/Mekinist in Japan in 2018. The test result of other genes on the panel could be provided for clinical research use only.
- First NGS-based CDx in Japan.

Case3: NCC Oncopanel

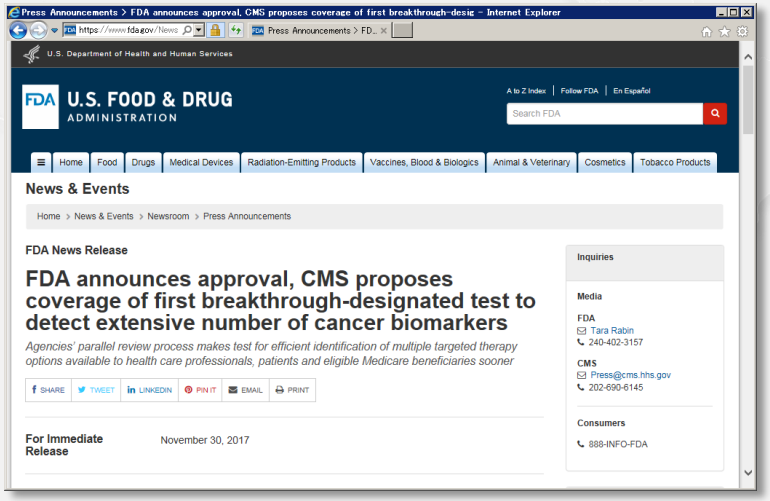
- This NGS-based IVD system is developed mainly by the National Cancer Center, and has received designation under the Sakigake Designation System in 2017.
- This assay detects SNV, Ins/Dels, CNA and gene rearrangements of 114 driver genes.

114 mutation・amplification (whole exon)					13 fusion genes
ABL1	CRKL	IDH2	NF1	RAC2	ALK
ACTN4	CREBBP	IGF1R	NFE2L2/Nrf2	RAD51C	AKT2
AKT1	CTNNB1/b-catenin	IGF2	NOTCH1	RAF1/CRAF	AKT3
AKT2	CUL3	IL7R	NOTCH2	RB1	BRAF
AKT3	DDR2	JAK1	NOTCH3	RET	ERBB4
ALK	EGFR	JAK2	NRAS	RHOA	FGFR2
APC	ENO1	JAK3	NRG1	ROS1	FGFR3
ARAF	EP300	KDM6A/UTX	NTRK1	SETBP1	NRG1
ARID1A	ERBB2/HER2	KEAP1	NTRK2	SETD2	NTRK1
ARID2	ERBB3	KIT	NTRK3	SMAD4	NTRK2
ATM	ERBB4	KRAS	NT5C2	SMARCA4/BRG1	PDGFRA
AXIN1	ESR1/ER	MAP2K1/MEK1	PALB2	SMARCB1	RET
AXL	EZH2	MAP2K2/MEK2	PBRM1	SMO	ROS1
BAP1	FBXW7	MAP2K4	PDGFRA	STAT3	
BARD1	FGFR1	MAP3K1	PDGFRB	STK11/LKB1	
BCL2L11/BIM	FGFR2	MAP3K4	PIK3CA	TP53	
BRAF	FGFR3	MDM2	PIK3R1	TSC1	
BRCA1	FGFR4	MDM4	PIK3R2	VHL	
BRCA2	FLT3	MET	POLD1		
CCND1	GNA11	MLH1	POLE		
CD274/PD-L1	GNAQ	MTOR	PRKCI		
CDK4	GNAS	MSH2	PTCH1		
CDKN2A	HRAS	MYC	PTEN		
CHEK2	IDH1	MYCN	RAC1		

2017.10.4　厚生労働省 がん診療連携拠点病院等の指定要件に関するWG資料

Case4: FoundationOne CDx™

- This assay is NGS-based IVD test that can detect genetic mutations in 324 genes and two genomic signatures *i.e.* MSI and TMB in any solid tumor type.
- This assay provides the information of 6 CDx genes and can identify which patients with any of five tumor types may benefit from 17 different FDA-approved targeted treatment options.
- Submitted to MHLW in March 2018 and under the review of PMDA.



Framework of cancer genome precision medicine in Japan

11 core hospitals for cancer genome precision medicine

Approx. 100 associate hospitals for cancer genome precision medicine

obtain the genome variants data using the oncology panel

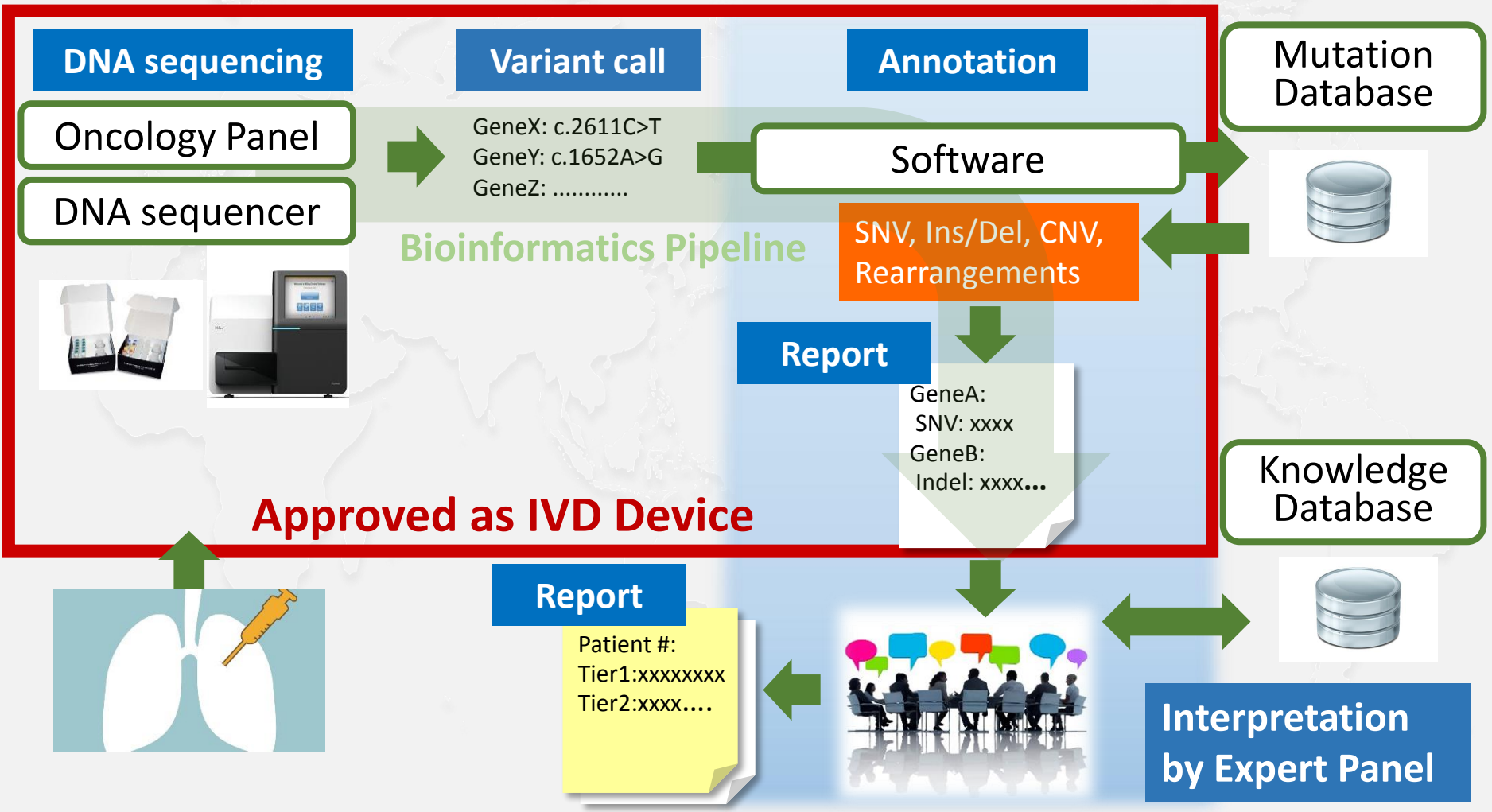
annotation of variants using databases and report the comprehensive genome profile

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

CDx vs Comprehensive Gene Profile (CGP)

Indication for use	CDx	CGP
Assumed Medication	Established medication with strong evidence	Medication with potential evidence
Output of the diagnostics system	Directly judge the eligibility for corresponding approved drug	Interpreted by the expert panel for the clinical significance
Assumed medical institutes of implementation	-	Medical institutes with expert panels, i.e. core hospitals for cancer genome precision medicine
Major Regulatory evaluation points	Positive and negative predictive values	Analytical performance based on validated accuracy, reproducibility, repeatability etc.

Typical Schematic Flow of Medication using Oncology Panels



Points to Consider in Reviewing Oncology Panels

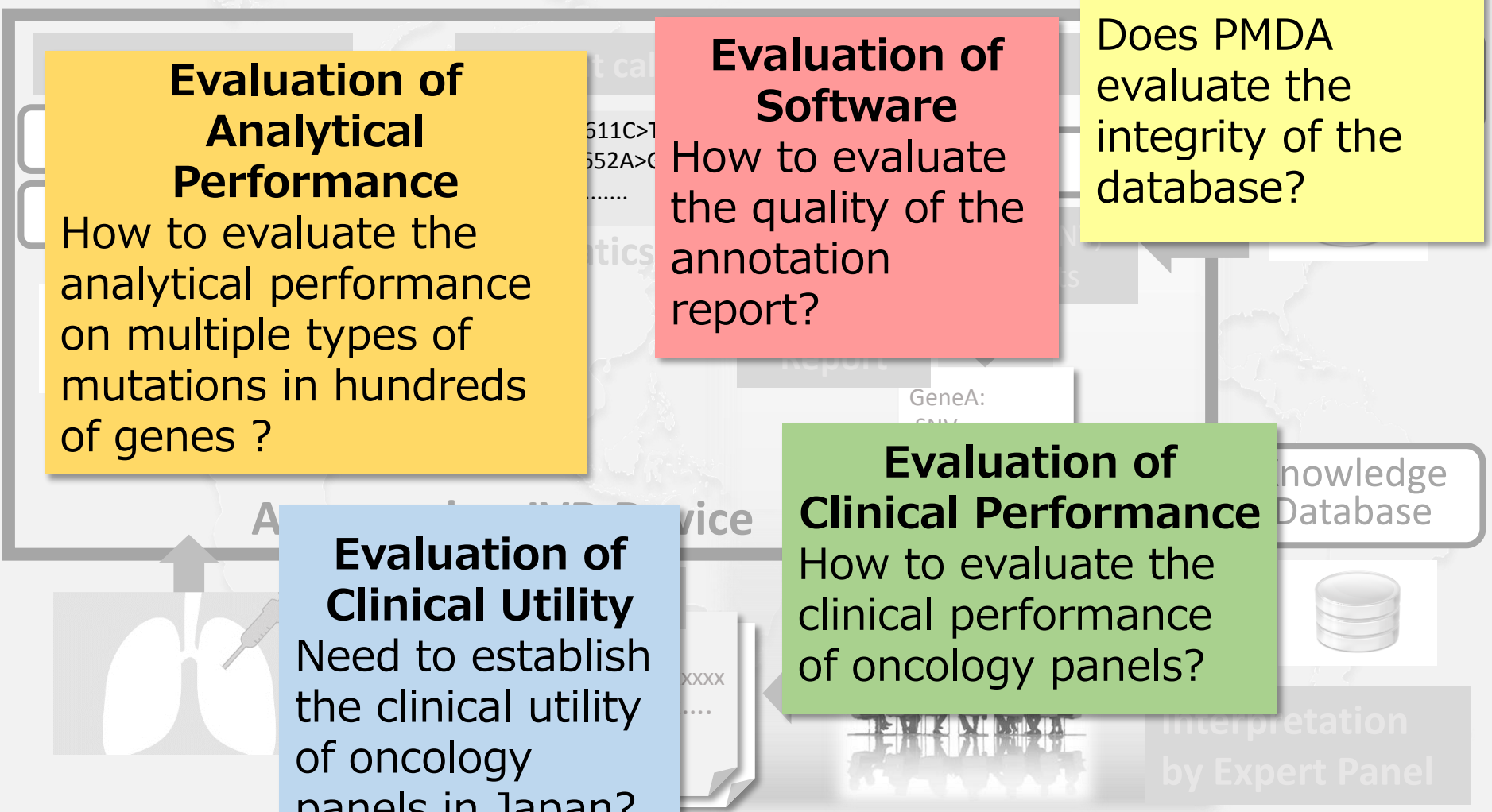
Evaluation of Analytical Performance
How to evaluate the analytical performance on multiple types of mutations in hundreds of genes ?

Evaluation of Software
How to evaluate the quality of the annotation report?

Evaluation of Database
Does PMDA evaluate the integrity of the database?

Evaluation of Clinical Utility
Need to establish the clinical utility of oncology panels in Japan?

Evaluation of Clinical Performance
How to evaluate the clinical performance of oncology panels?



Pharmaceuticals and Medical Devices Agency

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.

Analytical Validity

- Accuracy should be stated in terms of Positive Percentage Agreement and Positive Predictive Value using reference samples or reference methods for each mutation type (e.g. SNVs, Ins/Dels, CNAs, structural variants) .
- How to select the reference method (orthogonal method) in Japan?

Example: FoundationOne CDx SSED Table 6

Variant Type	F1CDx+/ evNGS+	F1CDx- /evNGS+	F1CDx+ /evNGS-	F1CDx- /evNGS-	PPA*(95%CI)	NPA*(95%CI)
All short variants	1282	73	375	284218	94.6% (93.3%-95.8%)	99.9% (99.9%-99.9%)
Substitutions	1111	39	334	242540	96.6% (95.4%-97.6%)	99.9% (99.8%-99.9%)
Indels	171	34	41	41678	83.4% (77.6%-88.2%)	99.9% (99.9%-99.9%)

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?

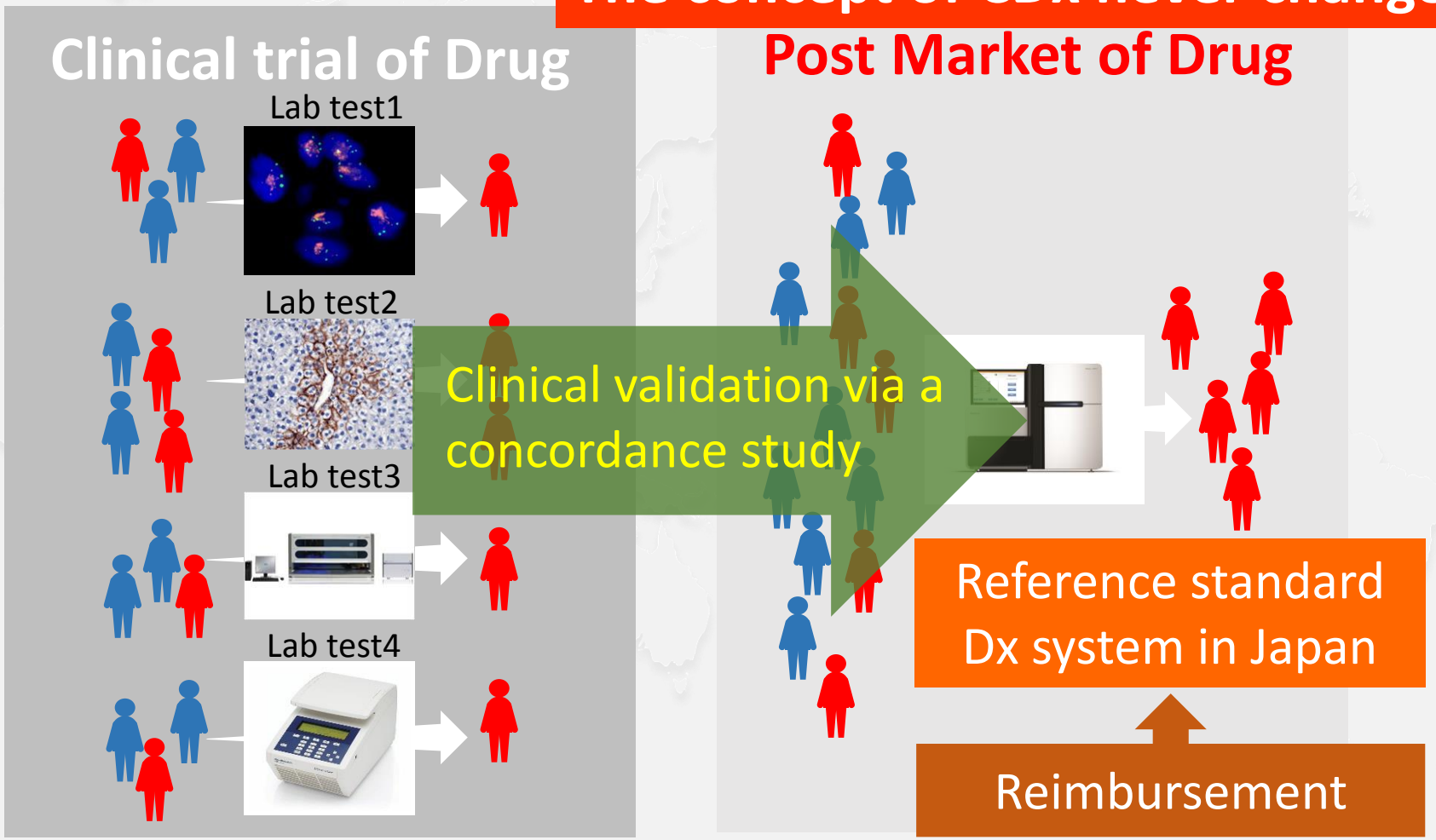
New CDx for marker X is approved to identify the patients for the new drug. Marker X has already been measured using approved oncology panel to obtain the CGP. Is it possible to identify the patients for the new drug based on the result report of the CGP without using CDx for marker X?

CDx vs Comprehensive Gene Profile (CGP)

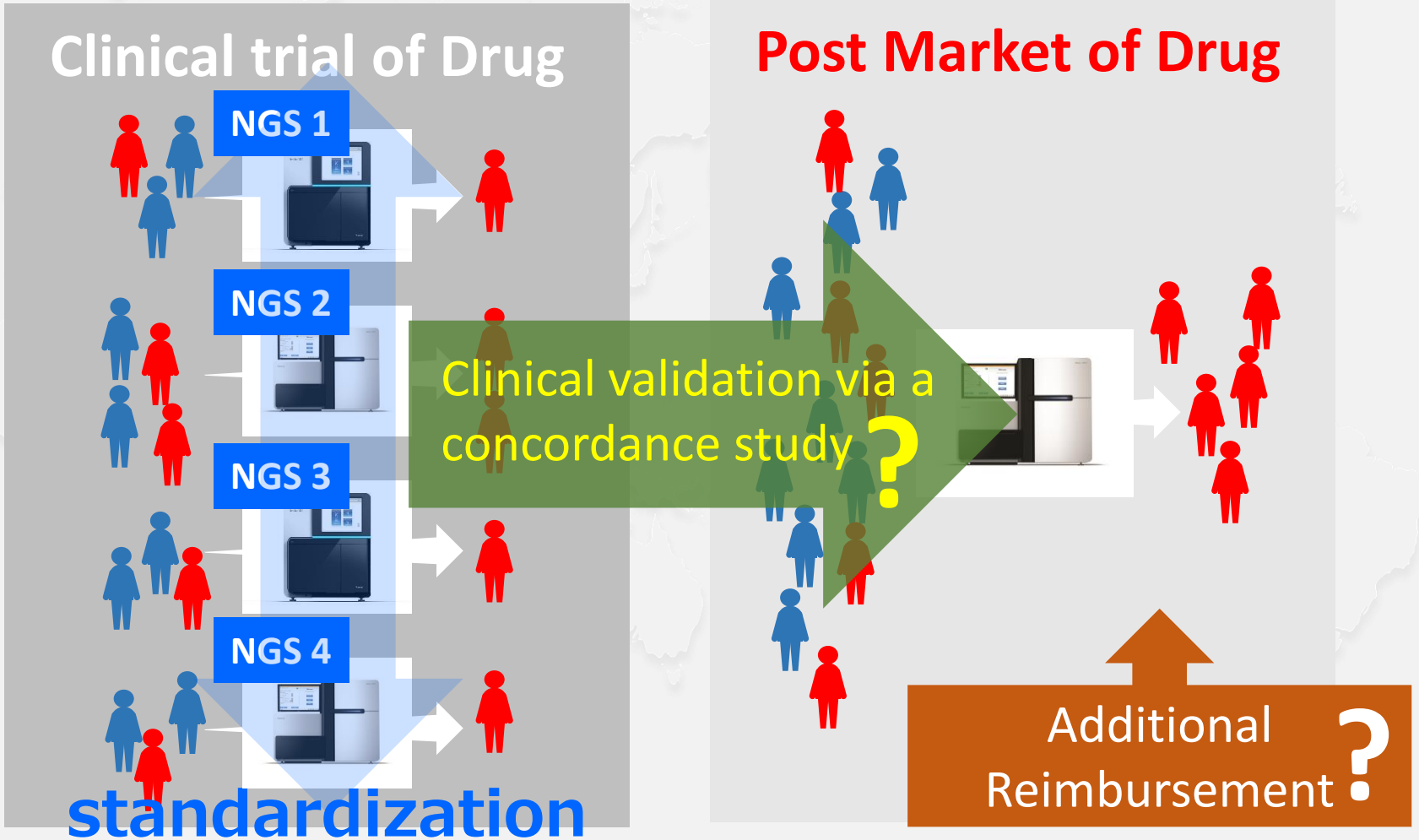
Indication for use	CDx	CGP
Assumed Medication	Established medication with strong evidence	Medication with potential evidence
Output of the diagnostics system	Directly judge the eligibility for corresponding approved drug	Interpreted by the expert panel for the clinical significance
Assumed medical institutes of implementation	-	Medical institutes with expert panels, i.e. core hospitals for cancer genome precision medicine
Major Regulatory evaluation points	Positive and negative predictive values	Analytical performance based on validated accuracy, reproducibility, repeatability etc.

After the clinical implementation of Oncology Panels

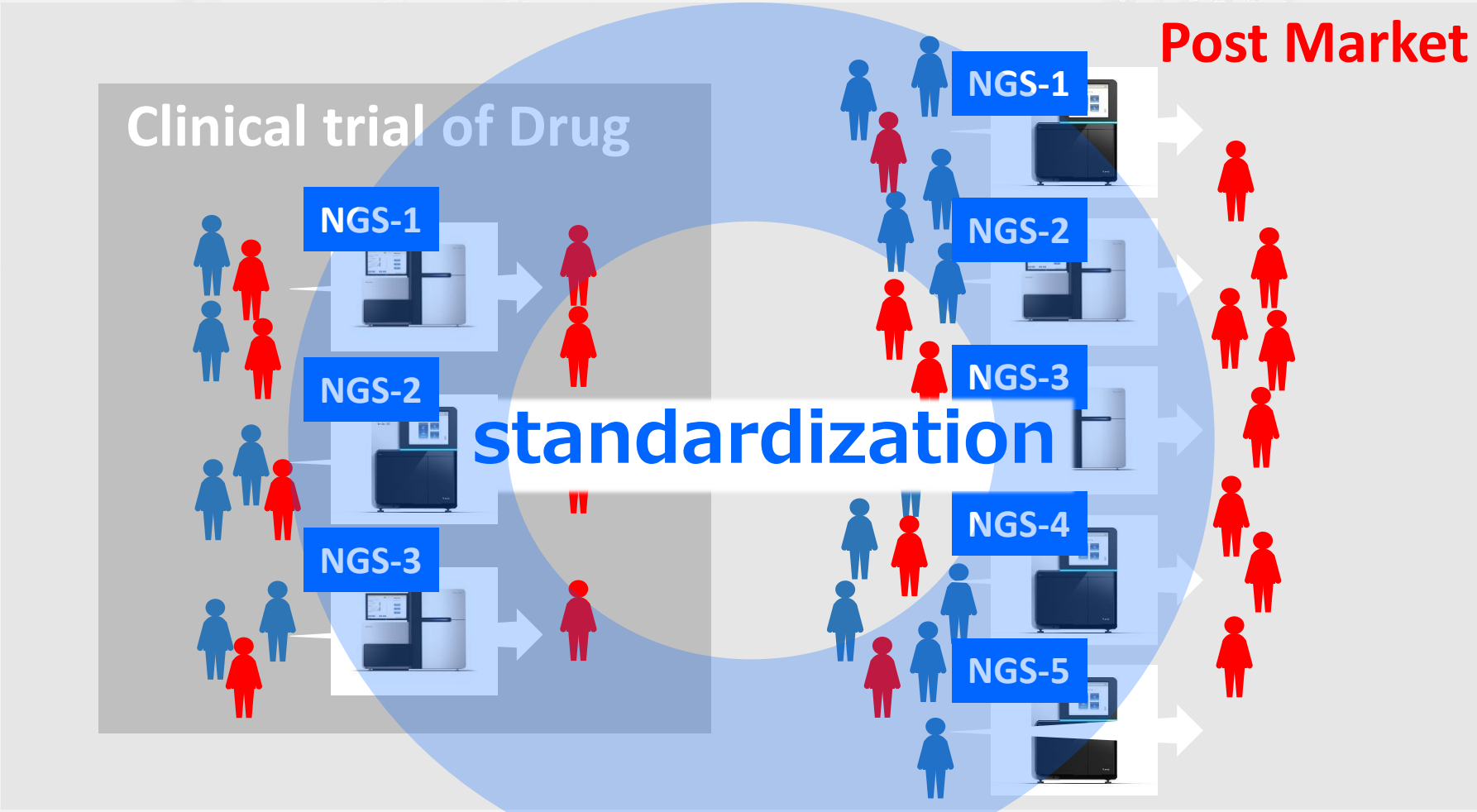
The concept of CDx never changes



CDx in the Oncology Panel Era?



Near Future World With No More CDx



Conclusion

- Along with the promotion of the cancer genome precision medicine, movement to provide the approved oncology panel in medical practice is progressing.
- Review policies for evaluation of the oncology panel in PMDA are being established.
- The emergence of oncology panels does not change the regulatory need for CDx system in Japan, however the standardization of panels in the future could lead to the equivalence of NGS-based tests and possibly the shift in CDx-based regulatory framework.