Genomics in patients with Japanese Ancestry

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Examples of PGx implementation
-Ethnic differences-

CBZ-induced SJS/TEN & *HLA-B*1502*

CBZ-induced SJS/TEN & *HLA-B*1502*

- *HLA-B*1502* screening could provide a benefit in countries, in which *HLA-B*1502* is relatively prevalent

	HLA-B*1502-positive with alternative medication (N=215)	HLA-B*1502-Negative with CBZ (N=4120)	Estimated historical incidence
CBZ-induced SJS/TEN	0% (0/0)	0% (0/0)	0.23%

Chen P et al, N Engl J Med, 364: 1126-1133, 2011
Chung WH et al, Nature, 428: 486, 2004

- However, CBZ-induced SJS/TEN patients carrying *HLA-B*1502* have not been found in Japanese

(Ozeki T et al, *Hum Mol Genet*, 2011, Kashiwagi M et al, *J Dermatol*, 2008, Kaniwa N et al, *Epilepsia*, 2008)

Biomarker for CBZ-induced SJS/TEN in Japanese

- In Japanese, association with a different allele, HLA-A*3101, has been reported

Ozeki T et al, Human Molecular Genet, 2010

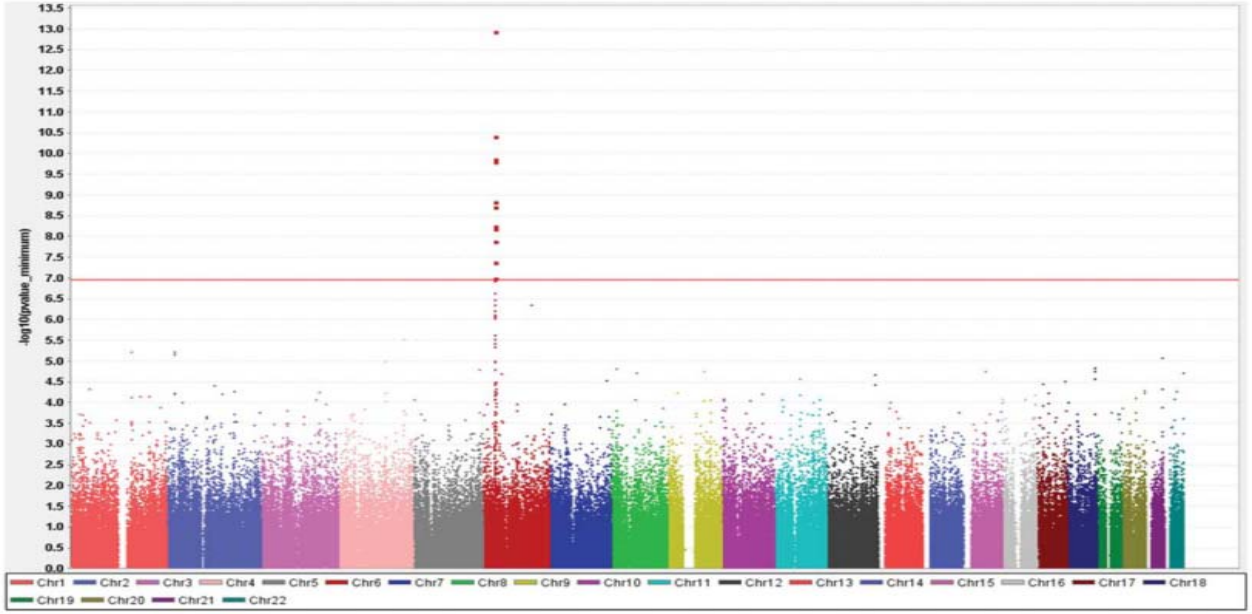


Figure 1. $-\mathrm{Log}_{10}$ *P*-value plots at the GWAS. Each dot represents *P*-value obtained from GWAS using 53 patients with carbamazepine-induced cutaneous adverse drug reactions and 882 subjects of a general population in Japanese. The *Y*-axis represents the $-\log_{10}$ of the minimal *P*-values calculated by Fisher's exact tests for three models: dominant, recessive and allele frequency models in the case–control association study.

- Interestingly, similar results were found in European population

McCormack M et al, N Engl J Med, 364: 1134-1143, 2011

CBZ Label in Japan

貯法：
錠　：室温保存
細粒：防湿、室温保存
使用期限：
包装に表示の使用期限内に使用すること
使用期限内であっても、開封後はなるべく速やかに使用すること

向精神作用性てんかん治療剤・躁状態治療剤
処方せん医薬品
（注意－医師等の処方せんにより使用すること）

テグレトール®錠100mg
テグレトール®錠200mg
テグレトール®細粒50%
Tegretol®
カルバマゼピン製剤

承認番号	錠100mg：20300AMZ00826000 錠200mg：20300AMZ00827000 細粒50%：21500AMZ00527000		
	錠100mg	錠200mg	細粒50%
薬価収載	1992年7月	1992年7月	2004年7月
販売開始	1992年7月	1966年3月	1969年3月
再評価結果	－	1975年6月	
効能追加	－	1990年3月	

NOVARTIS

＊＊(6) 日本人を対象としたレトロスペクティブなゲノムワイド関連解析において、本剤による皮膚粘膜眼症候群、中毒性表皮壊死融解症及び過敏症症候群等の重症薬疹発症例のうち、*HLA-A*3101*保有者は58%（45/77）であり、重症薬疹を発症しなかった集団の*HLA-A*3101*保有者は13%（54/420）であったとの報告がある。[4]
漢民族（Han-Chinese）を祖先にもつ患者を対象とした研究では、本剤による皮膚粘膜眼症候群及び中毒性表皮壊死融解症発症例のうち、ほぼ全例が*HLA-B*1502*保有者であったとの報告がある。[5,6] 一方、日本人を対象とした研究において本剤による重症薬疹発症例と*HLA-B*1502*保有との明らかな関連性は示唆されていない。[4]
なお、*HLA-B*1502*アレルの頻度は漢民族では0.019-0.124、日本人では0.001との報告がある。[7]

- Results of Genome-Wide Association Study (GWAS) in Japanese population
  - HLA-A*3101 is associated with CBZ-induced serious cutaneous adverse events including SJS/TEN
- The association with HLA-B*1502 is revealed in Han-Chinese, but not in Japanese

Clinical meaningfulness of HLA-A*3101 on patient selections is still unknown

Other Examples

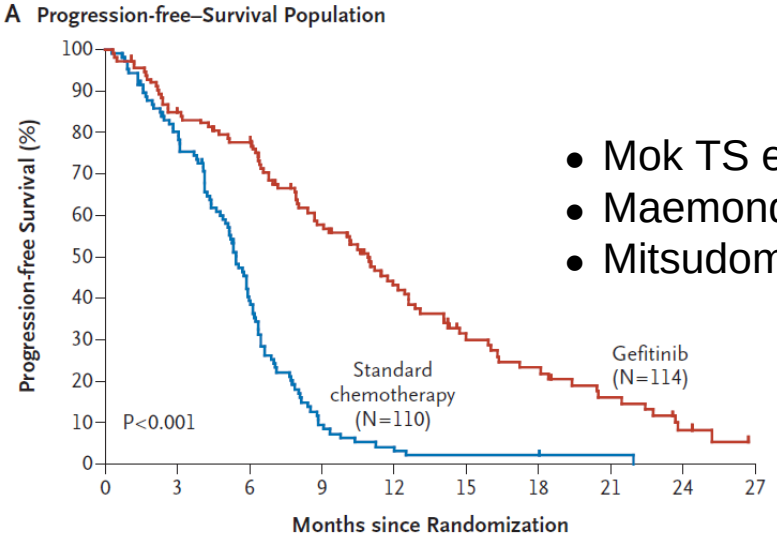
Gefitinib & *EGFR* Mutation

- Higher EGFR mutation rate in Asian population

Asian	**30–40%**
Non-Asian	5–10%

Mitsudomi T eta al., Cancer Sci. 12:1817-24, 2007

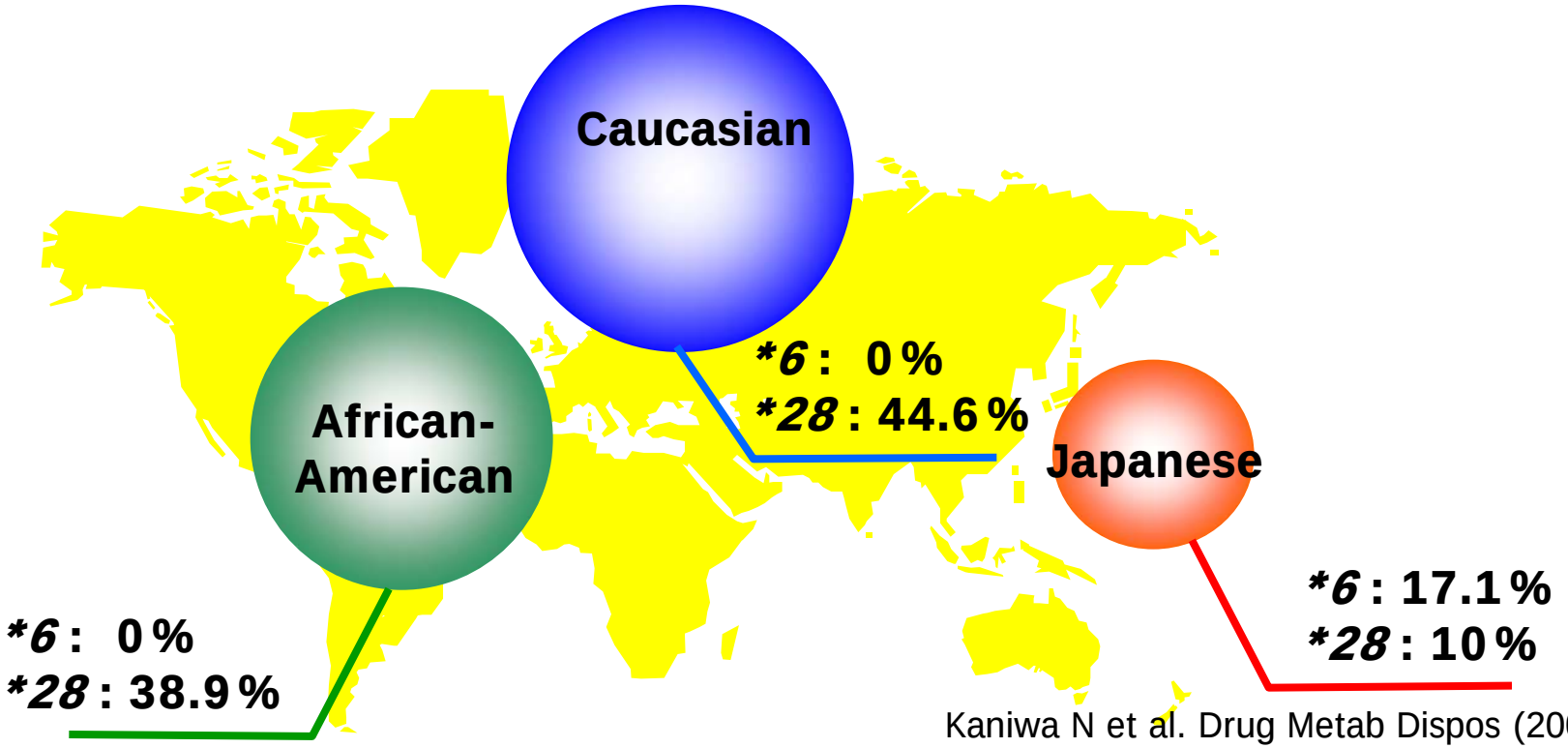
- Higher efficacy of gefitinib has been confirmed in non-small cell lung cancer patients with EGFR mutation, mainly in Asian population



- Mok TS et al. N Engl J Med, 361:947-957, 2009
- Maemond M et al., New Engl J Med., 362: 2380-8, 2010
- Mitsudomi T et al, Lancet Oncol, 11: 121-8, 2010

Irinotecan & *UGT1A1* Alleles

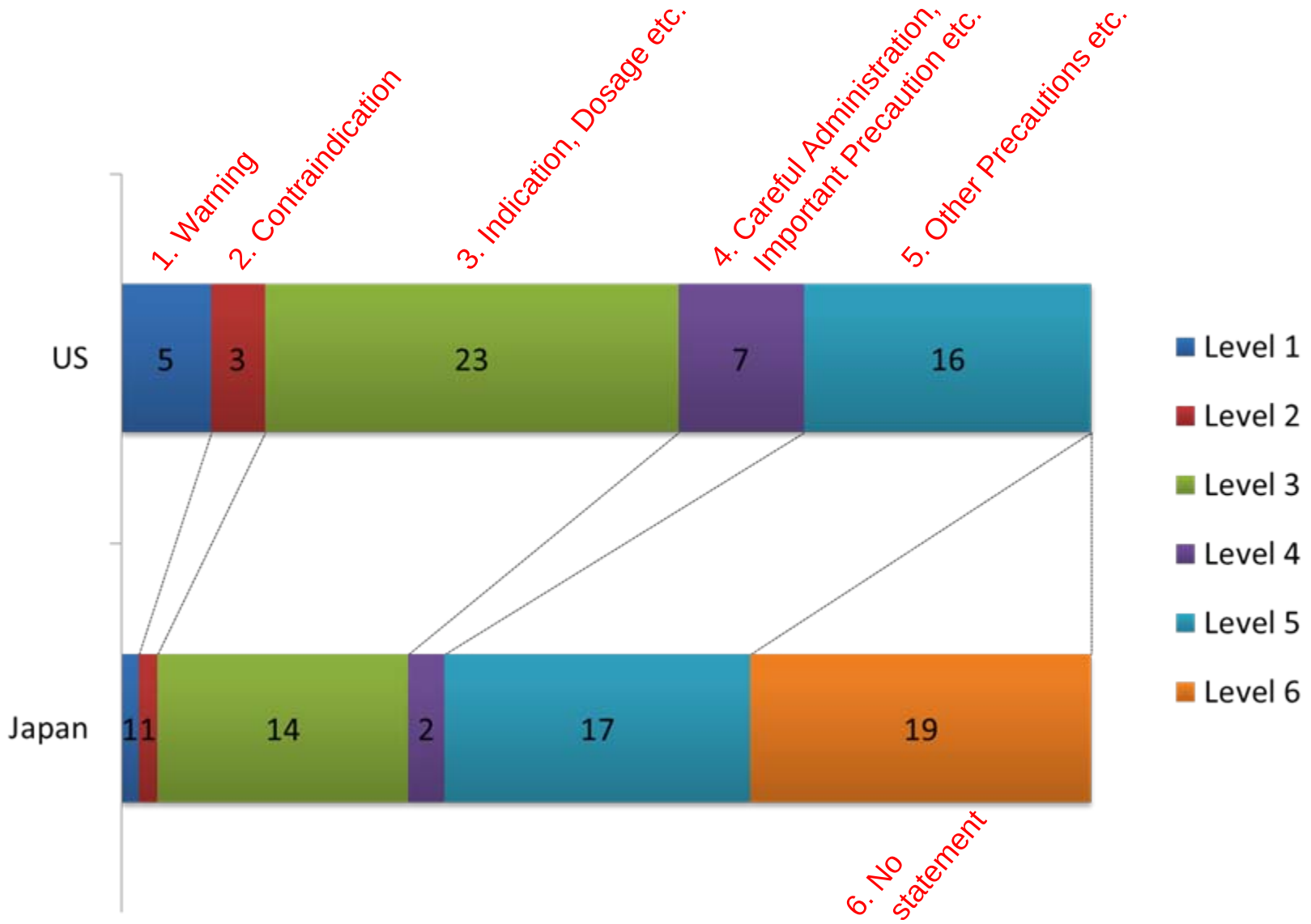
- Higher prevalence of UGT1A1*6 (lower activity) in Japanese
- The Japanese Label includes the information of *6 in addition to *28



Kaniwa N et al. Drug Metab Dispos (2005)

Comparison of the label between Japan and US

Comparing grading levels of the contexts between Japan and the US



Otsubo Y et al, Drug Metab Pharmacokinet, 27: 144-151, 2012

Examples of grading differences of drug/BM-context between Japan and the US

		JAPAN	USA	Possible reason
Warfarin	CYP2C9	Information only (Clinical Pharmacology)	Indication and Usage	Clinical evidence in Japanese
Carbamazepine	HLA-B*1502	Information only (Other precaution)	Boxed Warning	Genetic difference
Capecitabine	DPD	Information only (Other precaution)	Contraindication	Genetic difference Availability of diagnostic agent

Otsubo Y et al, Drug Metab Pharmacokinet, 27: 144-151, 2012

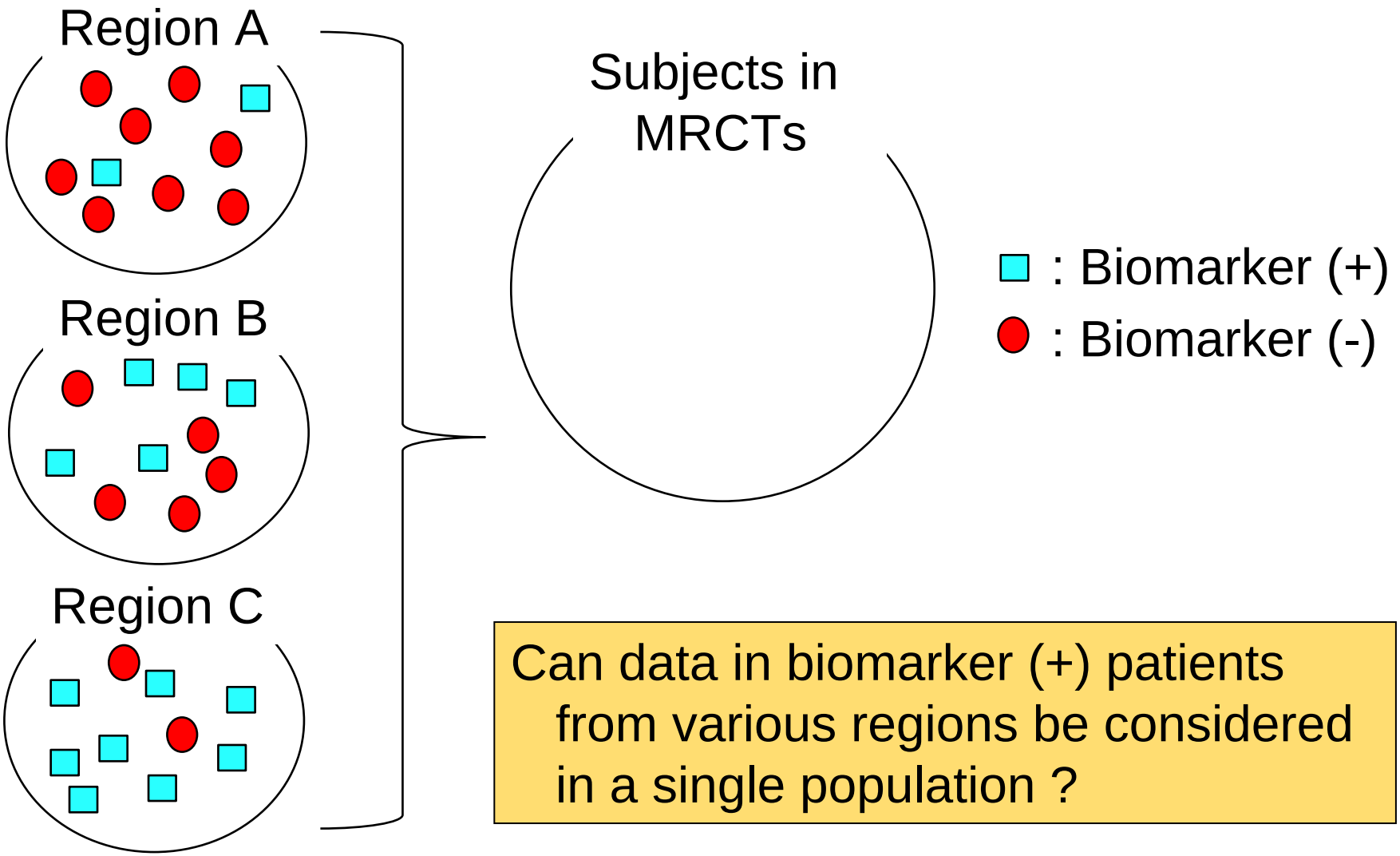
Factors to cause similarities/differences

	Number of contexts with grading difference (%)	Number of contexts without grading difference (%)	P value
Biomarker type			0.0048
ME (n = 30)	24 (80%)	6 (20%)	
PT (n = 18)	6 (33%)	12 (67%)	
Others (n = 6)	3 (50%)	3 (50%)	
Aim of biomarker use			0.0008
Efficacy (n = 21)	7 (33%)	14 (67%)	
Safety (n = 33)	26 (79%)	7 (21%)	
Therapeutic area			0.0025
Oncology (n = 20)	7 (35%)	13 (65%)	
Others (n = 34)	26 (76%)	8 (24%)	
Year of outcome in Japan			0.0104
Before 1993 (n = 18)	16 (89%)	2 (11%)	
1994 - 2003 (n = 11)	6 (55%)	5 (45%)	
After 2004 (n = 25)	11 (44%)	14 (56%)	
Company type			0.21
EU&US-based company (n = 33)	18 (55%)	15 (45%)	
Japan-based company (n = 21)	15 (71%)	6 (29%)	
PGx evidence for the Japanese in Japanese PIs			0.0002
Data on clinical endpoints (n = 13)	2 (15%)	11 (85%)	
PK data only (n = 6)	3 (50%)	3 (50%)	
None (n = 35)	28 (80%)	7 (20%)	

Otsubo Y et al, Drug Metab Pharmacokinet, 27: 144-151, 2012

Challenges in PGx-guided drug development & Ethnic factors

PGx-based data evaluation in Multi-Regional Clinical Trials (MRCTs)



Can data in biomarker (+) patients from various regions be considered in a single population ?

MRCTs with PGx

- In the era of globalization of drug developments
  - Encourage a sponsor to
    - Use PGx in global clinical trials
    - Include major ethnicities from an early stage of drug developments
    - Discuss with PMDA about a development strategy with PGx

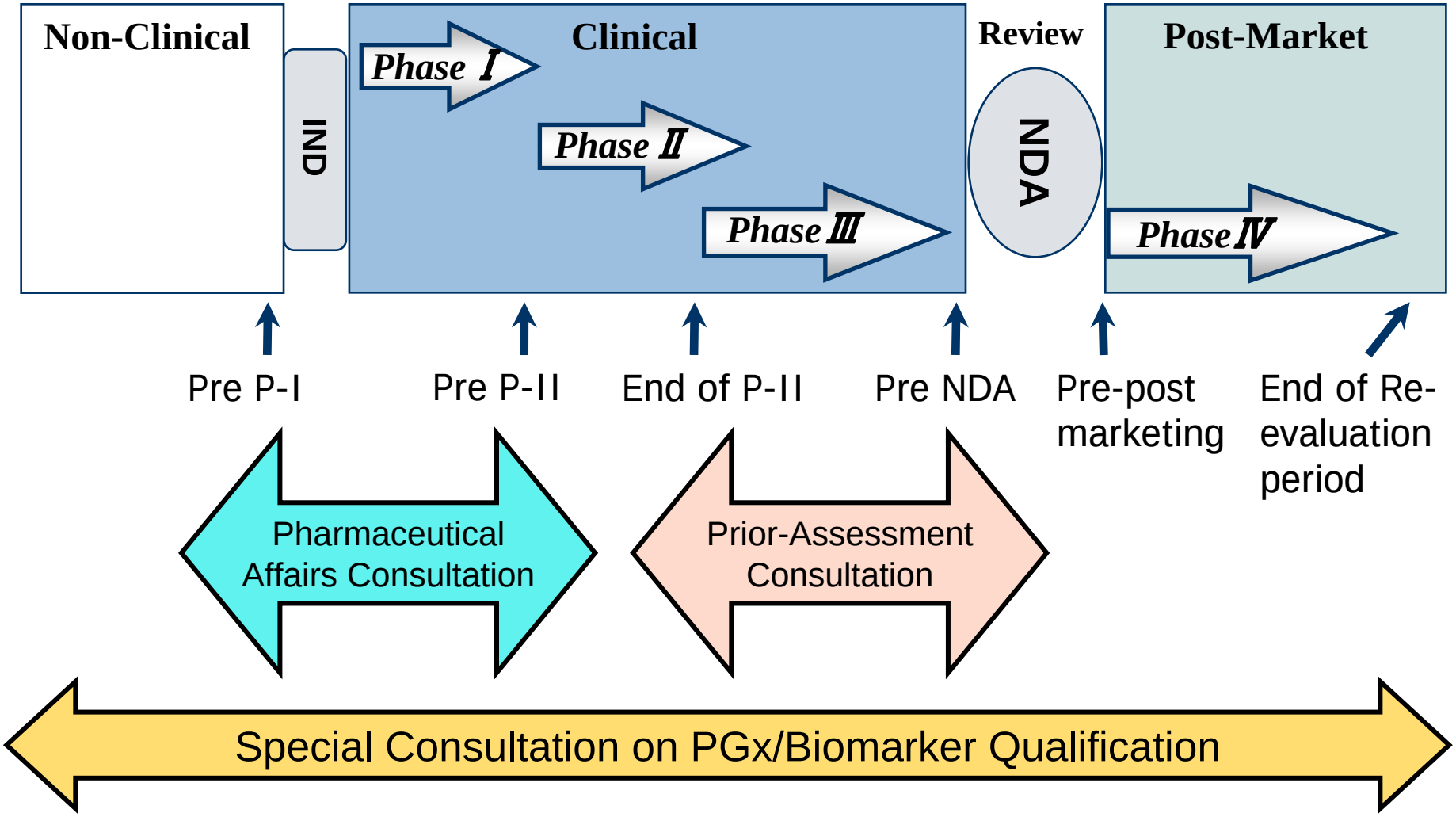
Conduct a confirmatory trial after having grasped impacts of PGx in drug responses

PGx information in a drug label

- What evidence is needed to describe a practical guidance for a safety biomarker, such as dose adjustment and patient selection?
  - Which section and what level of warning?:
    - contraindication, indication, dosage, clinical pharmacology, etc.
    - requirement, recommendation, information only

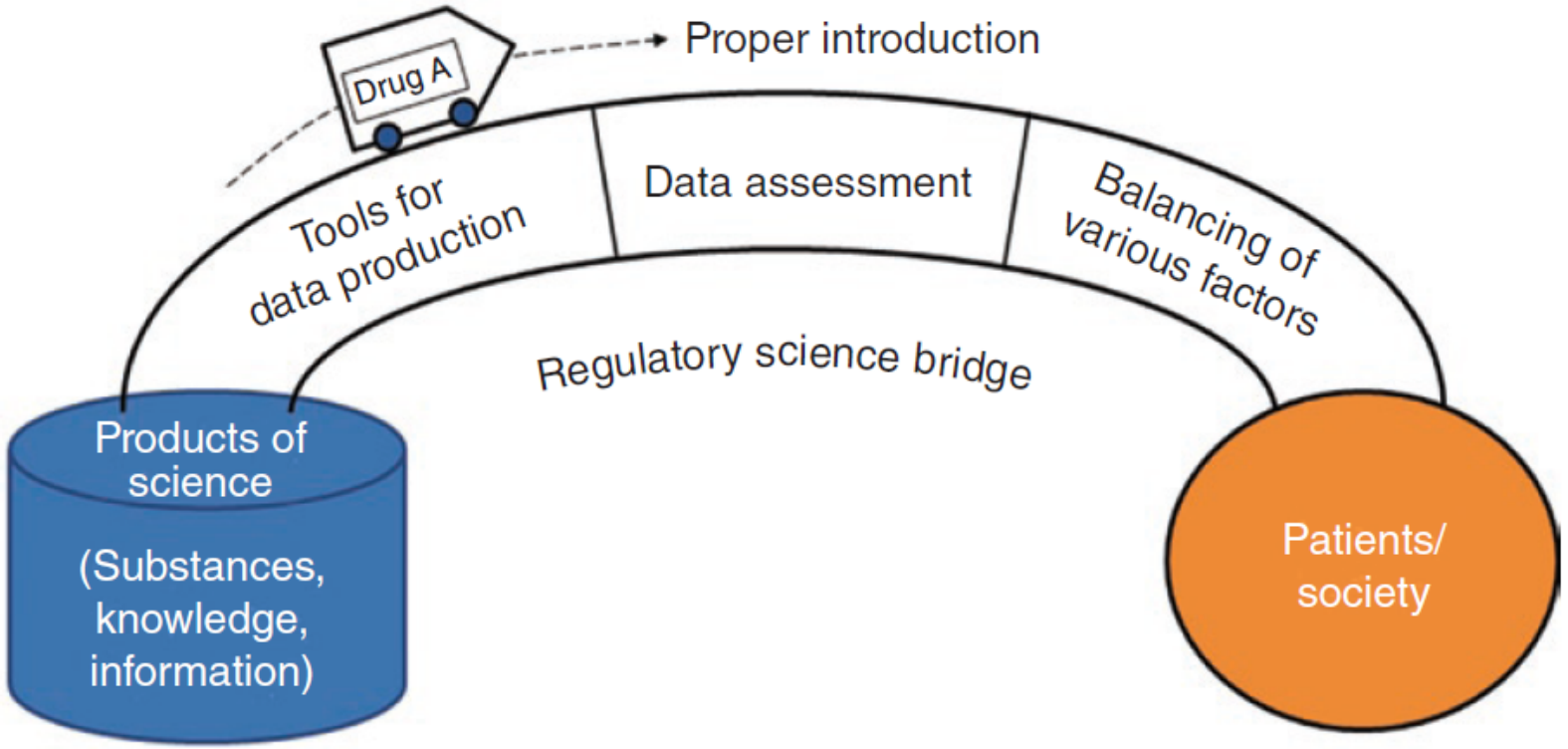
- How to describe PGx information/data relating to ethnicities?
- Include more data in a stratified population in terms of race, nationality, and/or ethnicities?

Expanding PMDA Scientific Consultations



Revised from Figure by Ichimaru K et al, *Clin Pharmacol Therapeut*, 88: 454-457, 2010

Advancing Regulatory Science



Stronger & More Complete Regulatory Science Bridge will help us for the future drug developments

Tominaga T et al, Clin Pharmacol Ther, 90: 29-31, 2011

- *SMART* Global -

- Sharing data/experiences/knowledge globally
- Managing projects/issues globally
- Advancing regulatory science globally
- Respect for other idea/views globally
- Transparent process globally

WORKING TOGETHER FOR PATIENTS

Information

- **PMDA HOMEPAGE (English)**
  http://www.pmda.go.jp/english/index.html
- **E-mail:**
  uyama-yoshiaki@pmda.go.jp

Thank you for your attention