Applied Drug Development for Personalized Medicine

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Precision Medicine Initiative

"Tonight I'm launching a new precision medicine initiative to bring us closer to curing diseases like cancer and diabetes. And to give us all access to the personalized information we need to keep ourselves and our families healthier"

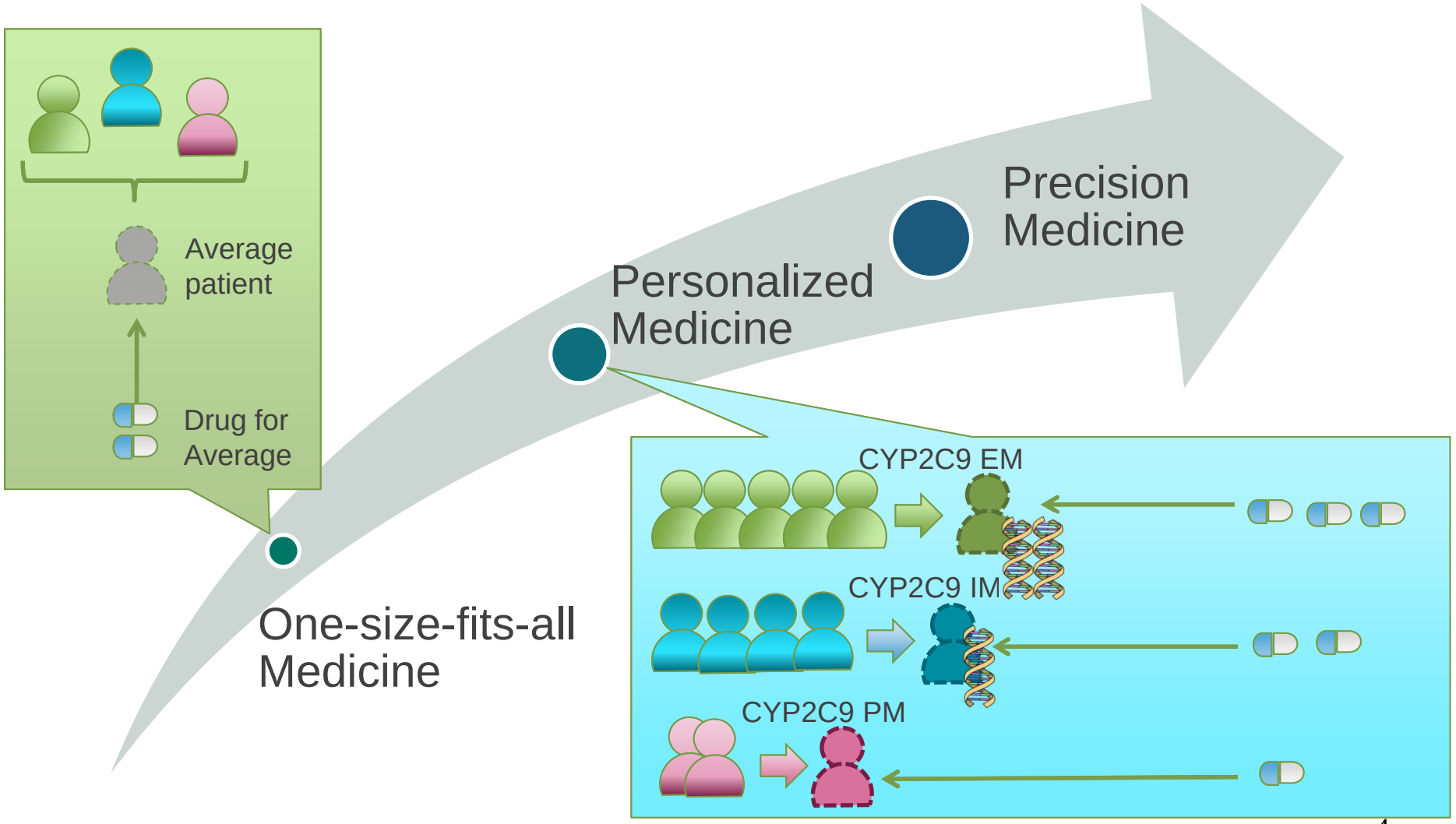
President Barack Obama

State of the Union Address | Jan 20, 2015

Personal Information for Medicine

Personal Information	Target	Example
DNA: Germline mutation	SNP, Copy number variations, Gene amplification, Fused gene, Mutation	UGT1A1 (Irinotecan) CYP2C9 (Warfarin)
DNA: Somatic mutation		EML4-ALK fusion gene (Crizotinib, Alectinib) BRAF (Vemurafenib) KRAS (Cetuximab, Panitumumab)
RNA	mRNA, miRNA, lincRNA, Splice variant	-
Protein	Membrane protein, Plasma protein, Nuclear protein	CCR4 (Mogamulizumab) HER2 (Trastuzumab) CD20 (Rrituximab) CD33 (Gemtuzumab Ozogamicin)
Metabolite	Metabolites profile	-
Epigenome	DNA Methylation, Transcription factor, Chromatin	DNMT (Azacitidine) HDAC (Vorinostat)

New Era of Personalized Medicine



JPMA Data Science Task Force 5

Objective

- Propose good development strategy and study design for personalized medicine in Japan

Task Force's Scope

- Investigate trend of the approved personalized medicine
  - Development stage in outside of Japan
  - Co-development of diagnostics
  - Study design and analysis method

JPMA Newsletter (Sep 2015)

JPMA NEWS LETTER

2015年9月号 No.169

Comment | 解説

さらなる個別化医療用医薬品の開発に向けて

医薬品評価委員会データサイエンス部会

土綿 慎一(推進委員)、山本 英晴(推進委員)、天野 靖浩、杉原 匡周、谷口 隆司、松本 喜彦、吉田 祐樹、淀 康秀

本稿では、これまでに開発された個別化医療に対応した医薬品(個別化医療用医薬品)に対する調査結果に基づき、タスクフォースからの提言を示します。

http://www.jpma.or.jp/about/issue/gratis/newsletter/html/2015/69m2-01.html

How to find out personalized medicines?

- Every drugs and candidates have potentials to become personalized medicine

How to identify personal information?

On target

PI could be identified by known mode of action

Examples

- Designed Medicine
- Antibody

Development was started by enrichment design

Off target

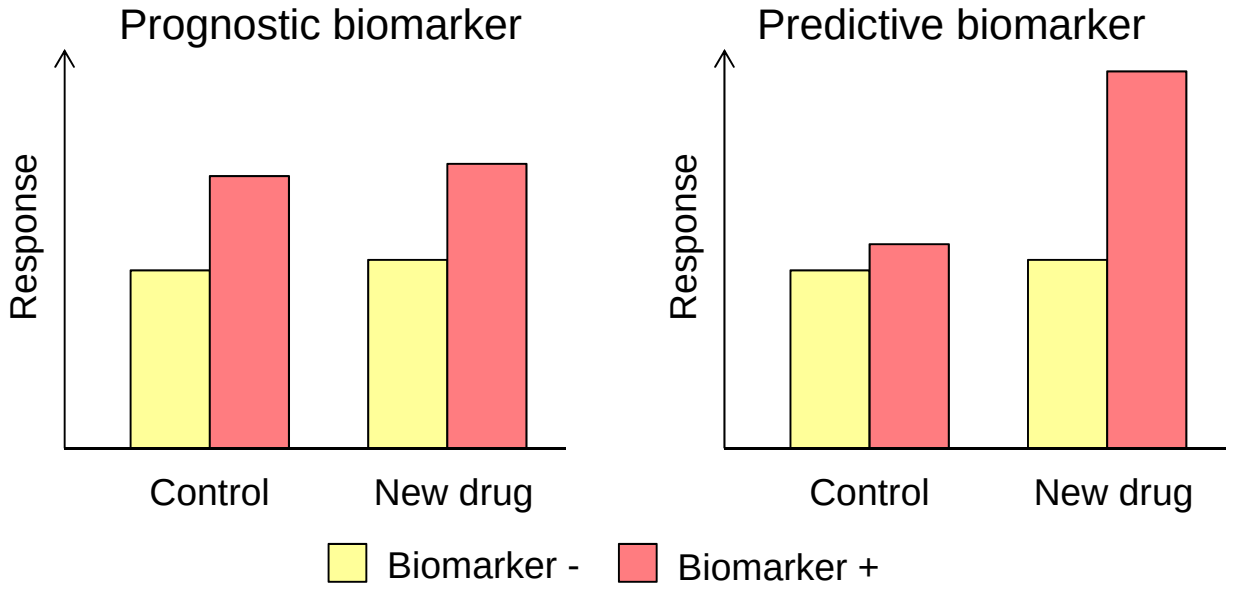
PI could not be identified by known information

- Retrospective review
- Newly found action / receptor / predictive biomarker

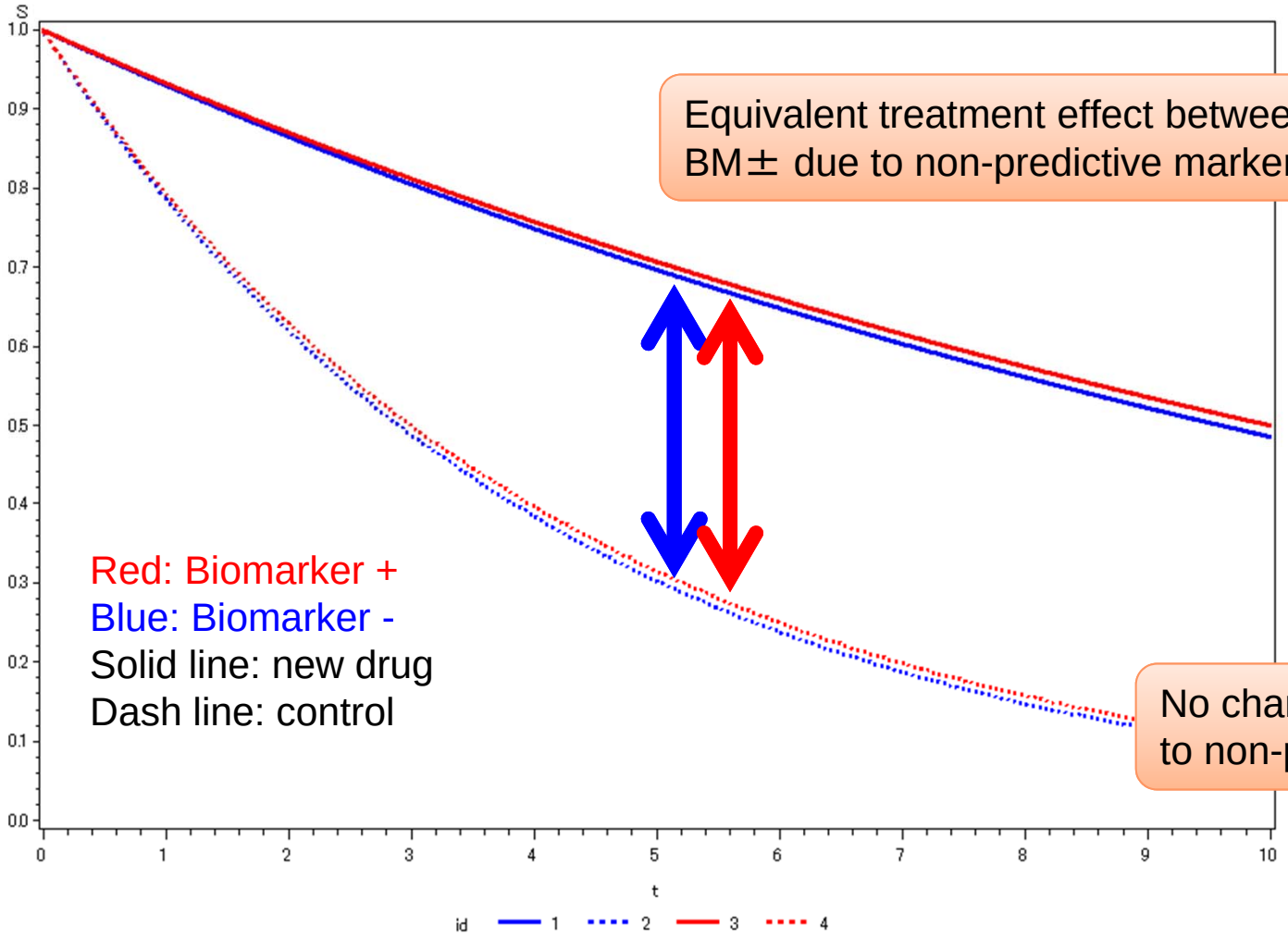
Development was not started by enrichment design

Types of biomarkers

- Prognostic biomarker
  - Provides information on the likely course of disease irrespective of treatment
- Predictive biomarker
  - Predicts the likely effect or lack of effect of a specific treatment



Non-prognostic and non-predictive

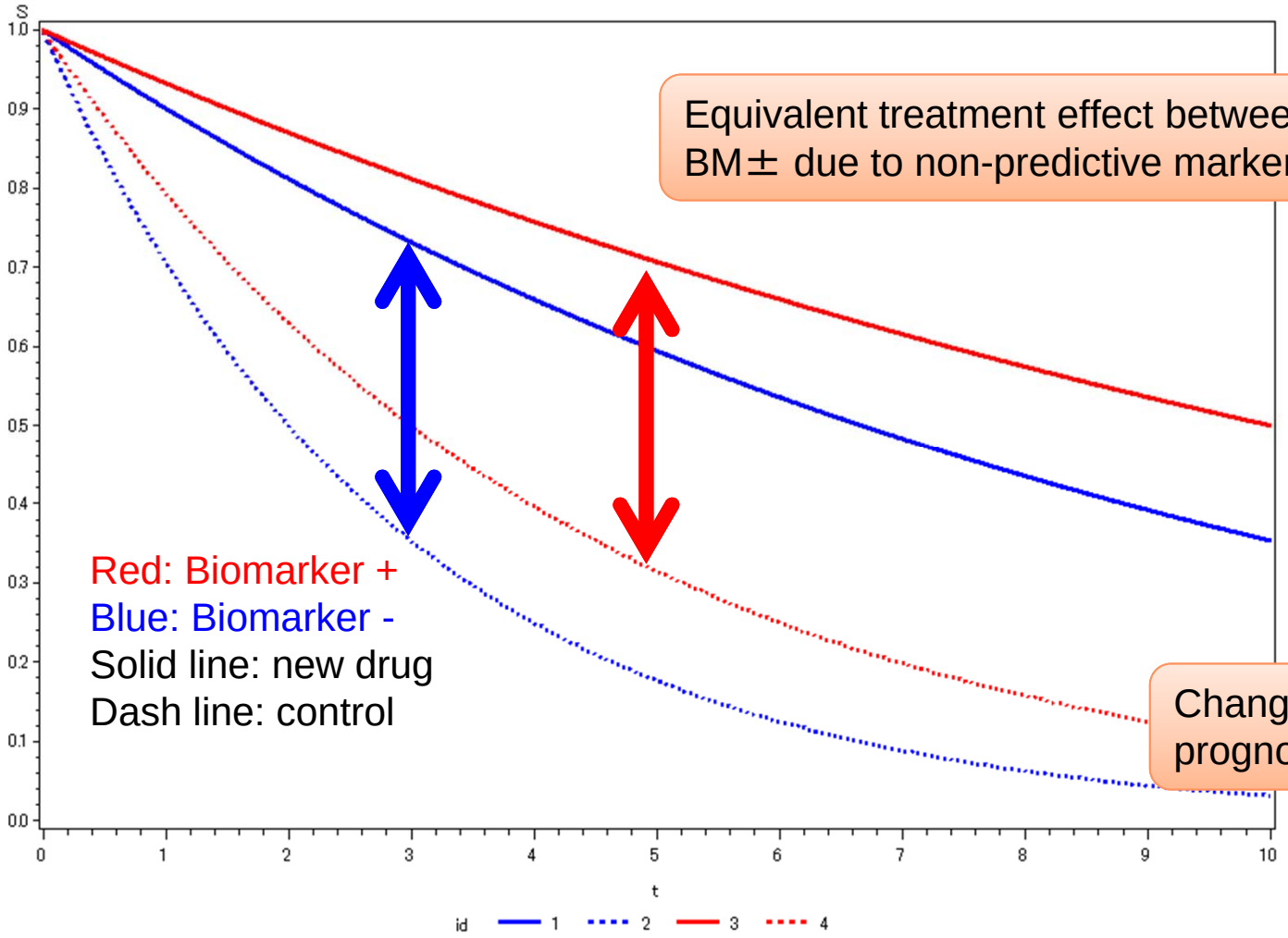


Equivalent treatment effect between BM± due to non-predictive marker

Red: Biomarker +
Blue: Biomarker -
Solid line: new drug
Dash line: control

No change in prognosis due to non-prognostic marker

Prognostic and non-predictive



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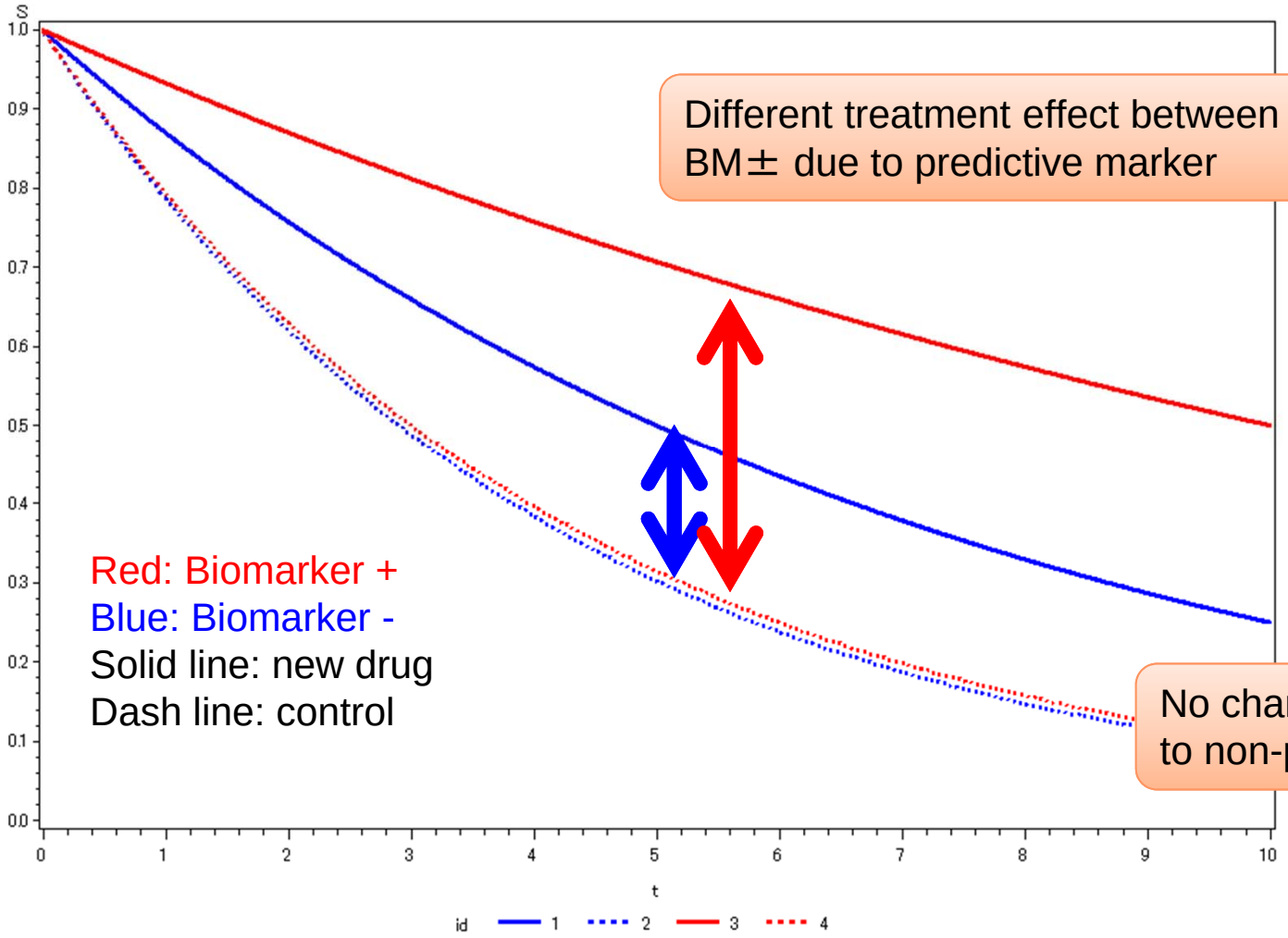
Change in prognosis due to prognostic marker

Non-prognostic and predictive



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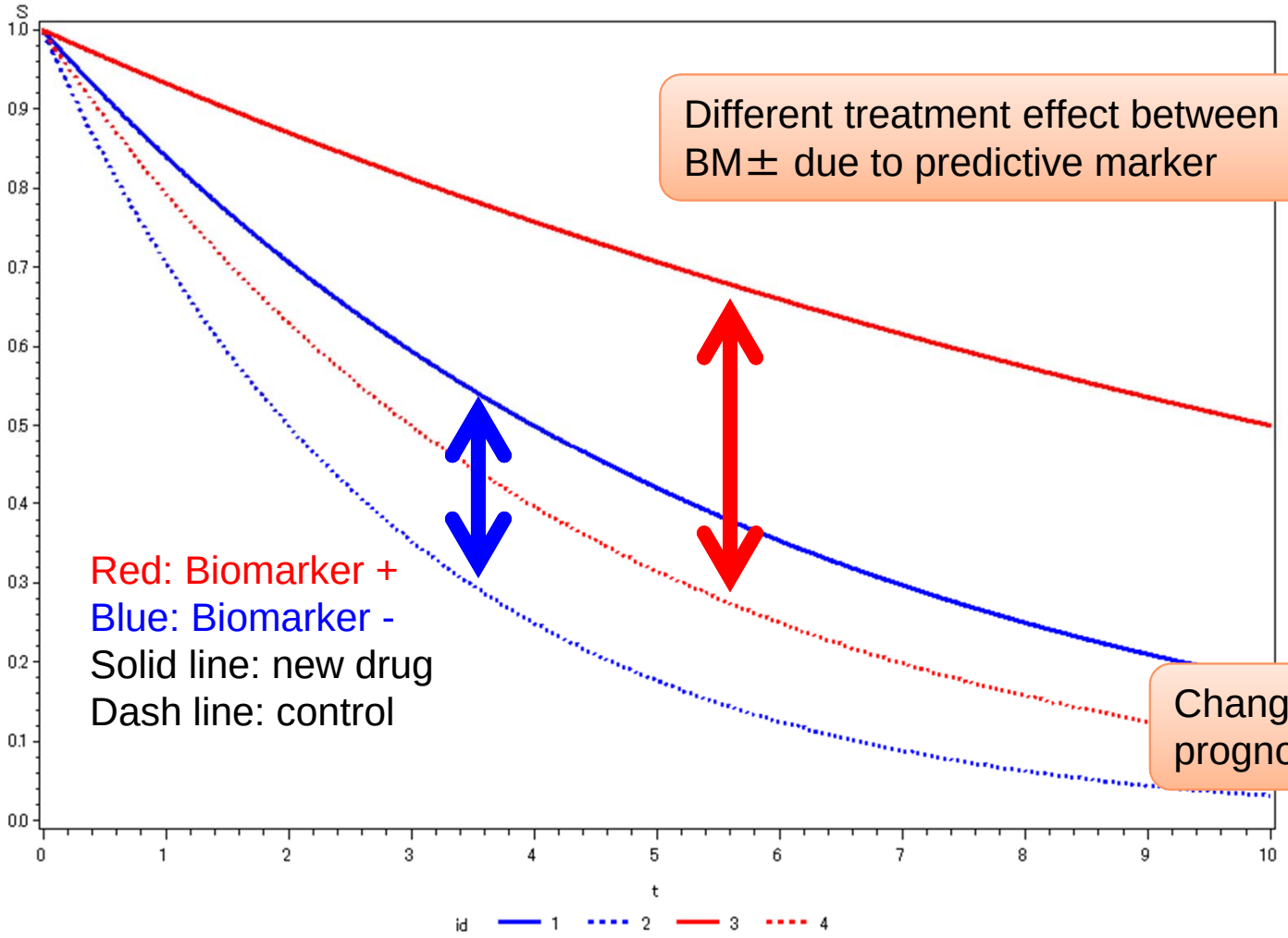

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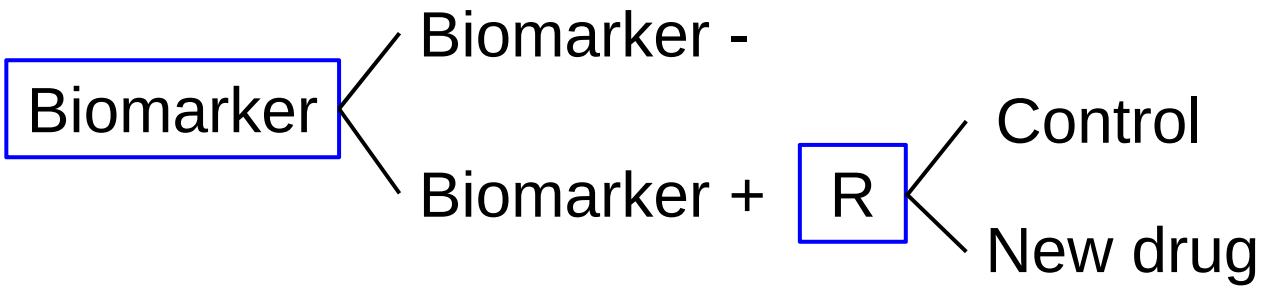
Change in prognosis due to prognostic marker

Enrichment design



- This design is appropriate for cases where there is a strong biological basis for believing that biomarker-negative patients will not benefit from the new drug.

Biomarker-negative patients

Technical Guidance on Development of In Vitro Companion Diagnostics and Corresponding Therapeutic Products (Dec, 2013. Japan)

2.1.1. Handling of biomarker-negative patients in early development phase of molecular targeted drugs, etc.

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Therefore, it is important to establish a development strategy for a therapeutic product which reflects the necessity of analyzing biomarker-negative patients from early development phase. For instance, in clinical trials in early development phase, such as exploratory dose-response studies, both biomarker-positive and negative patients should be included in principle.

The guidance encourages to obtain some information on the marker-negative population to assess the predictive performance and the validity of the clinical cut-off.

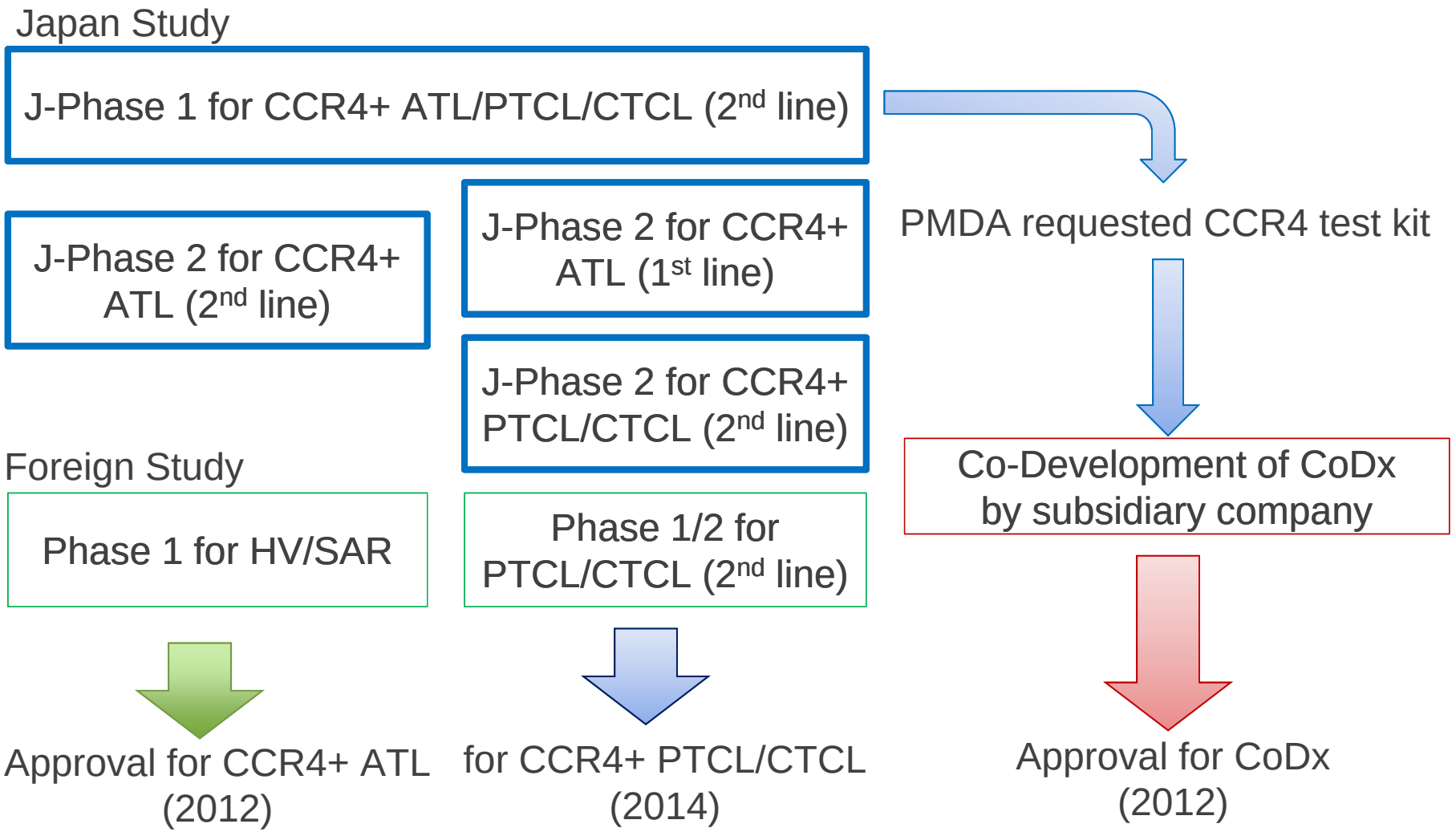
Major Personalized Medicines in Japan

- On Target Development
  - Cetuximab
  - Vemurafenib
  - Mogamulizumab
  - Alectinib

Enrich design was applied for all Japanese studies

- Off Target Development
  - Panitumumab
  - Celecoxib

Case Study: Mogamulizumab (On target)



Case Study: Panitumumab (Off target)

Foreign Study

Phase 3 Mono for EGFR+ metastatic colon/rectal cancer

PFS in wild-type *KRAS* > mutation by retrospective analysis

Discussion with FDA/EMEA

Phase 3 Combi for metastatic colon/rectal cancer (1st line)

Update study design (*KRAS* wild vs mutation)
Target (900) was increased to 1150

Global study (Japan)

G-Phase 3 Combi for metastatic colon/rectal cancer (2nd line)

Update analysis plan after enrollment closed

Start Development by Enrichment Design

Advantage

- ✓ Selecting patient expected good response
  - – Decreasing required number of patients
- ✓ Avoiding high risk and/or low benefit patient
  - – Avoiding serious adverse reaction
  - – Reinforcing clinical evidence

Disadvantage

- ✓ Opportunity lost to obtain information for excluded patients
  - – Appropriateness of threshold
- ✓ Necessity of method for assessing personal data
  - – Co-development of CoDx

Potential issues

- On target

  Started by enrich design may make difficult to change strategy
  - Does pre-clinical data support enrichment?
  - Is it for avoiding adverse effects?
  - Is threshold appropriate?

- Off target

  Difficulty to discover predictive biomarker
  - Lots of candidates: SNPs and biomarkers
  - Multiple factors
  - Multiple routes of action
  - Noise of personal data
  - Multiplicity issues for statistical analysis

Predictive Biomarkers in Clinical Trials

- Predictive biomarkers are typically initially identified by retrospective analyses of existing patient series (off target).
  - Retrospective analyses may be sufficient to identify and validate them to a degree that enables them to be incorporated into trial design and clinical practice.

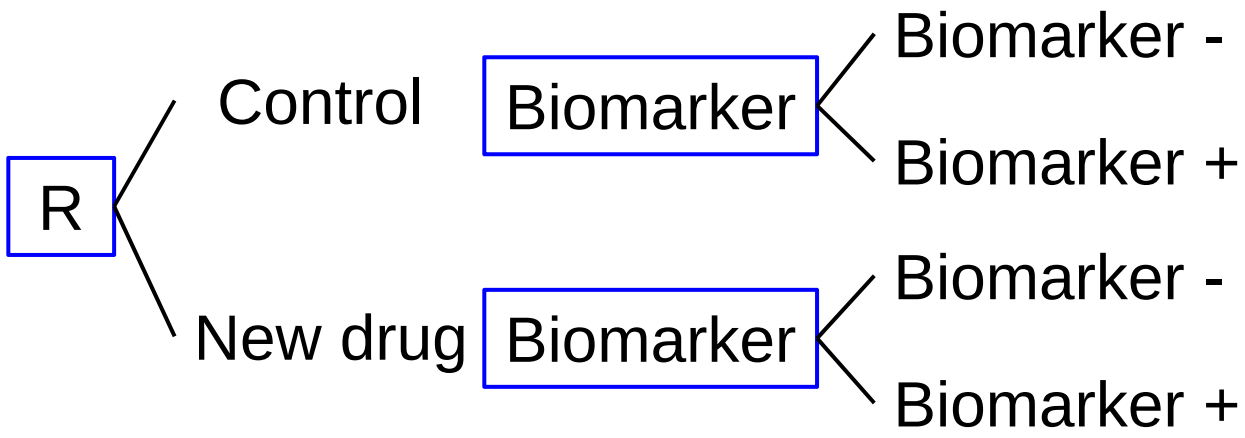
- Prospective clinical trials are required to obtain definitive evidence of a predictive biomarker for clinical use.

Prospective validation of predictive biomarkers

- Clinical trial designs for prospective validation
  - Randomized all design
  - Biomarker-stratified design (Interaction design)
  - Biomarker-strategy design with standard control
  - Biomarker-strategy design with randomized control
  - Adaptive parallel design
  - Tandem two-stage design
  - Adaptive designs

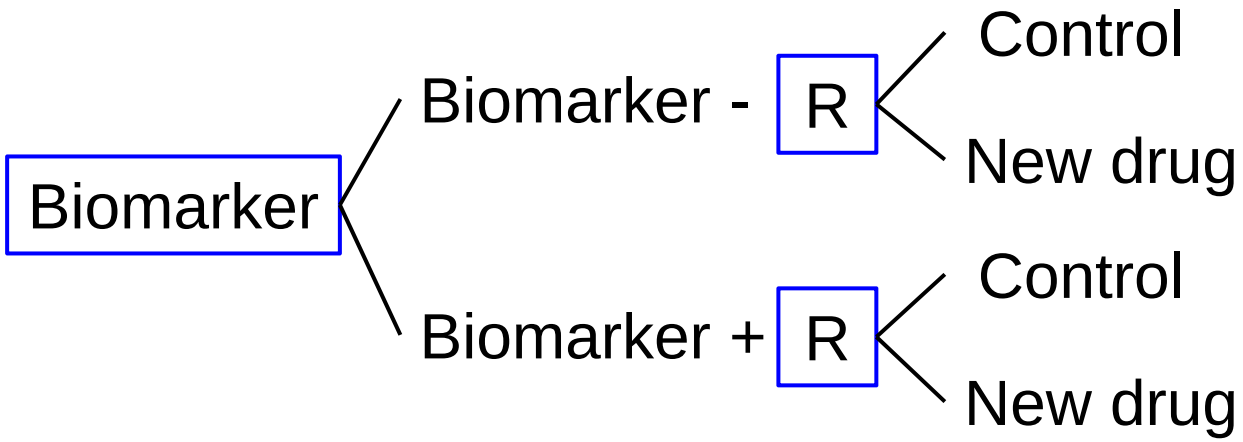
Buyse et al., Expert Rev Mol Diagn 2011

Randomize-all design



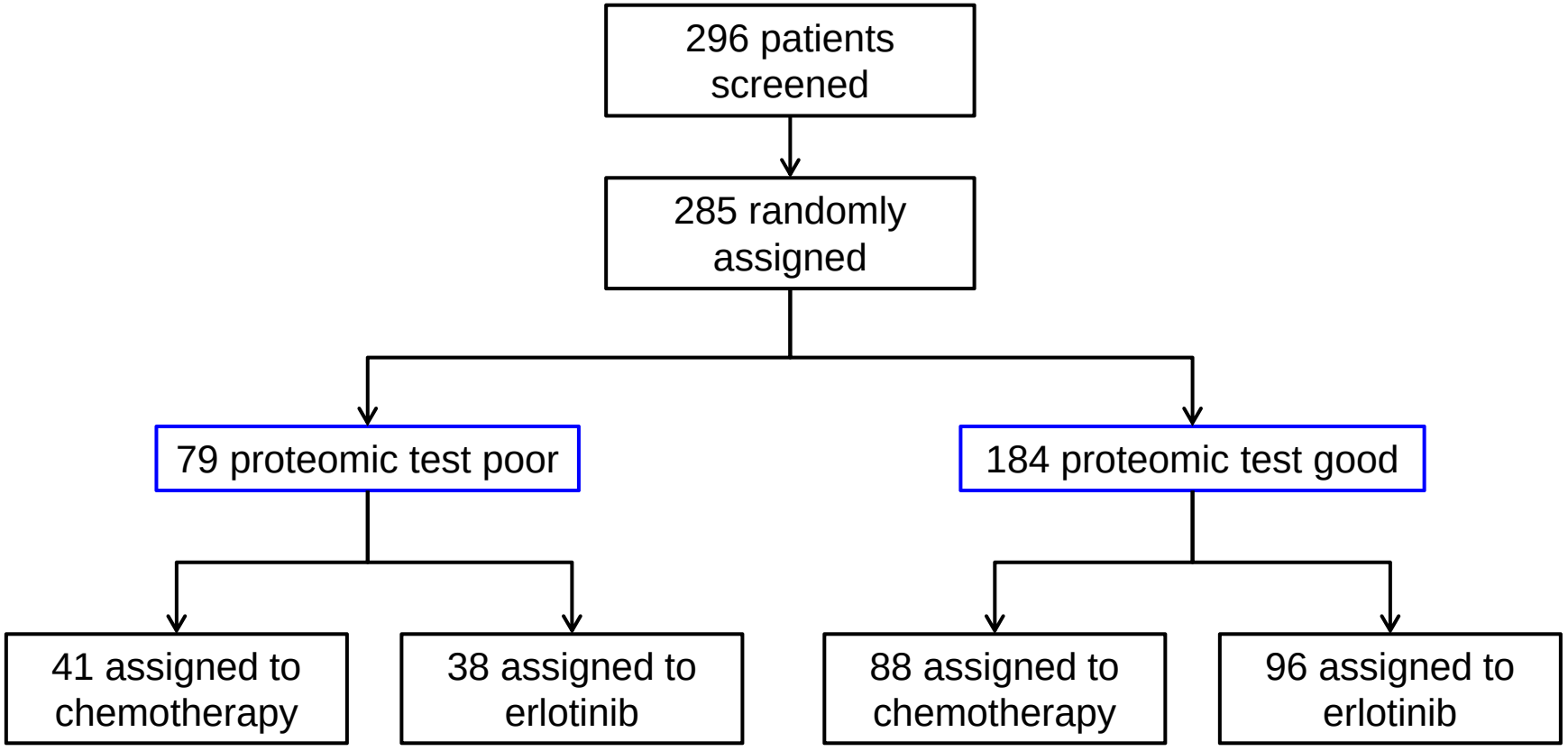
- If no compelling biological or clinical trial data for biomarker-negative patients, it is generally appropriate to include all patients.

Biomarker-stratified (interaction) design



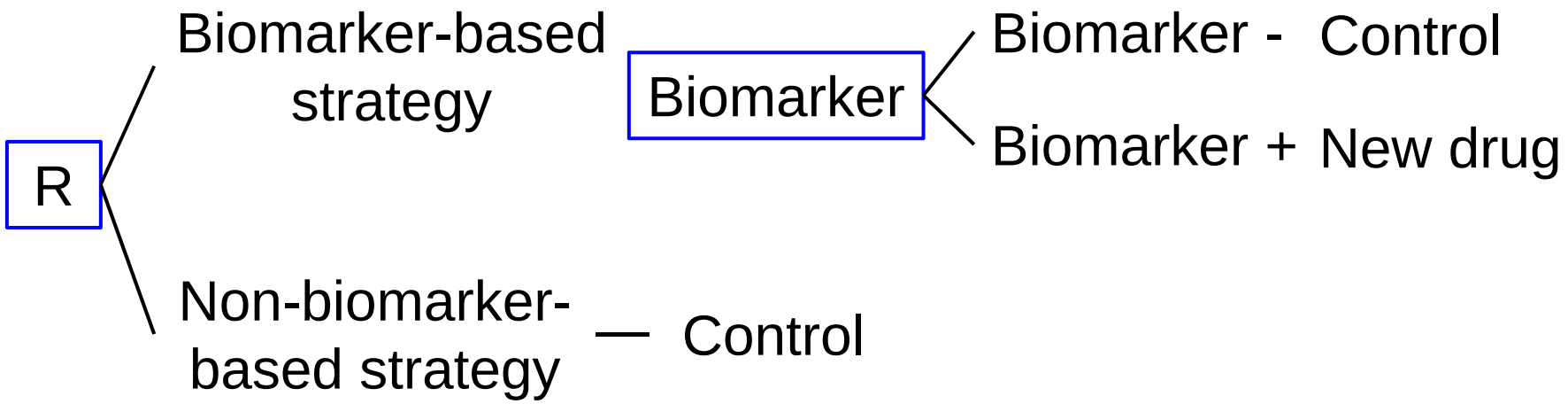
- If the biomarker is available prior to initiating the trial, it is desirable (though by no means essential) to stratify the patients by their biomarker status and then randomize them.
- The benefits of stratification are balancing treatment groups with respect to biomarker status, while also making sure that the biomarker status is known for all patients.

Case Study: PROSE study in NSCLC



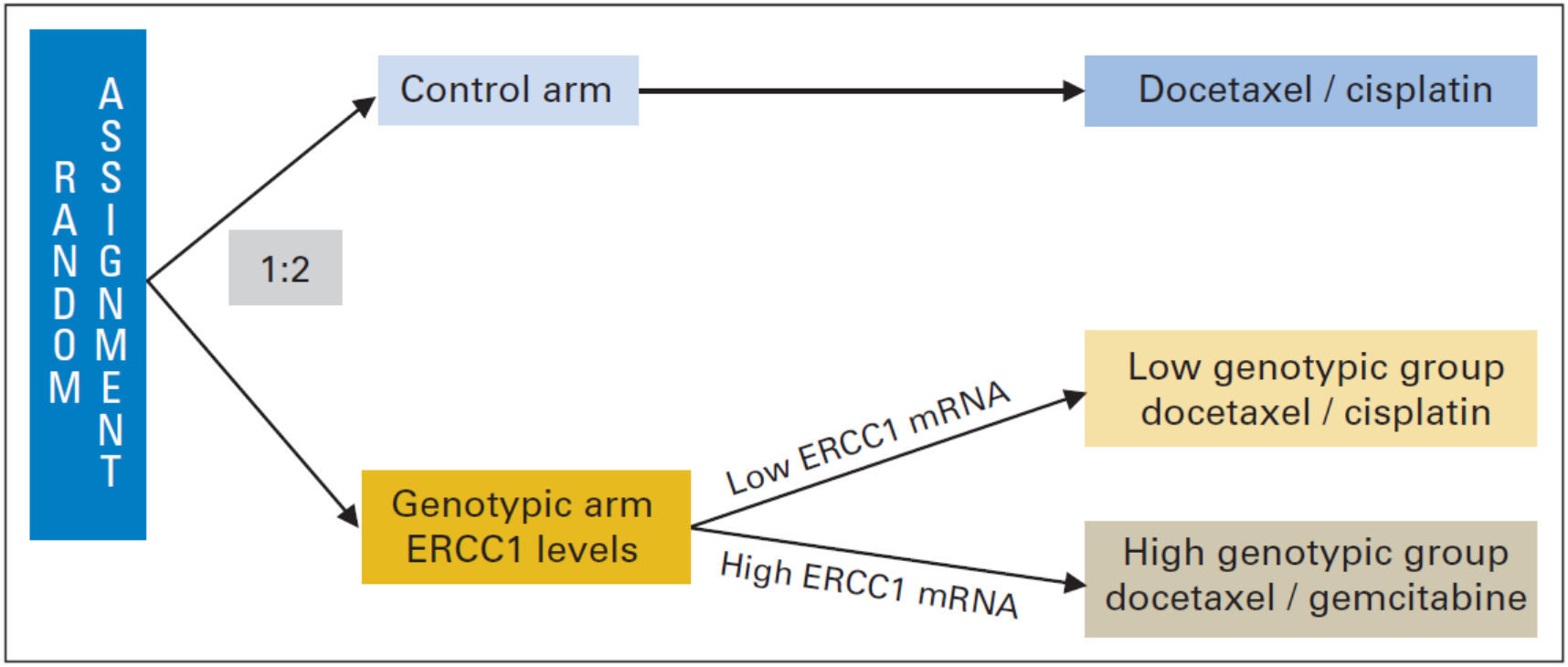
Gregorc et al., Lancet Oncol 2014

Biomarker-strategy design



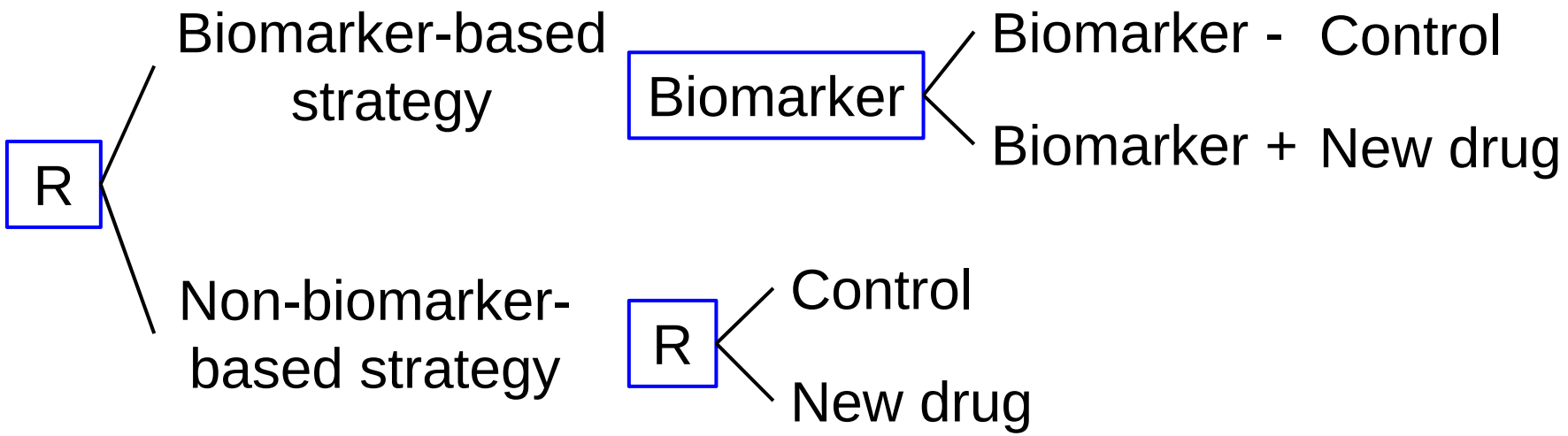
- Two strategies with and without use of the biomarker in determining treatment are compared.
- There are two main concerns as follows:
  1. When the prevalence of a positive biomarker is low, the difference between the two randomized arms is expected to be small
  2. Even if a difference was observed between the randomized arms, it could be due to a better efficacy of the experimental arm, regardless of the biomarker status

Case Study: GILT study in NSCLC



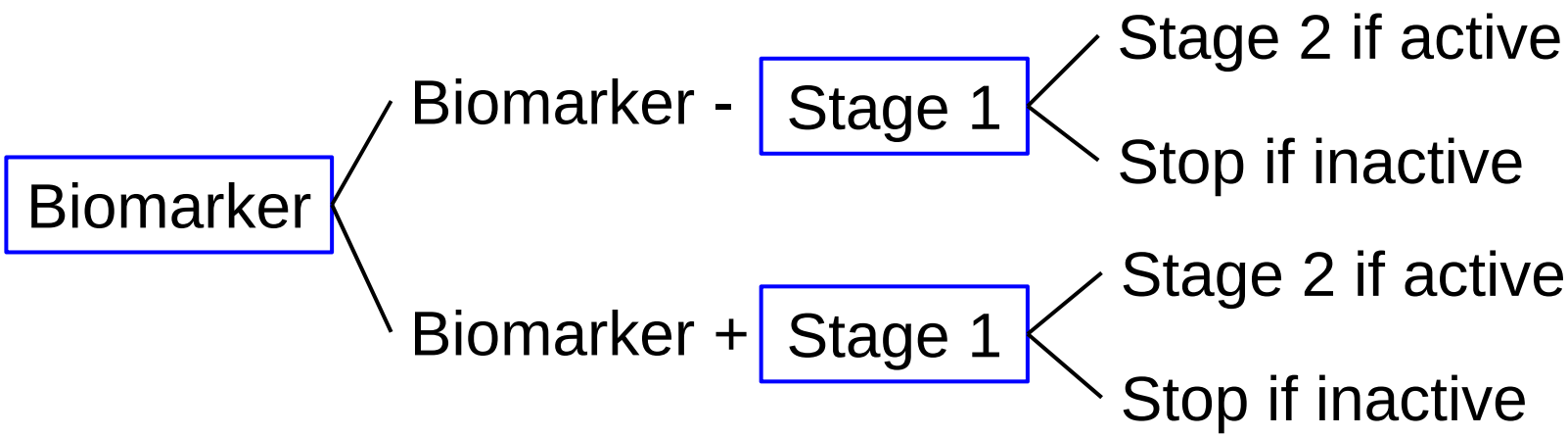
Cobo et al., J Clin Oncol 2007

Biomarker-strategy design with randomized control



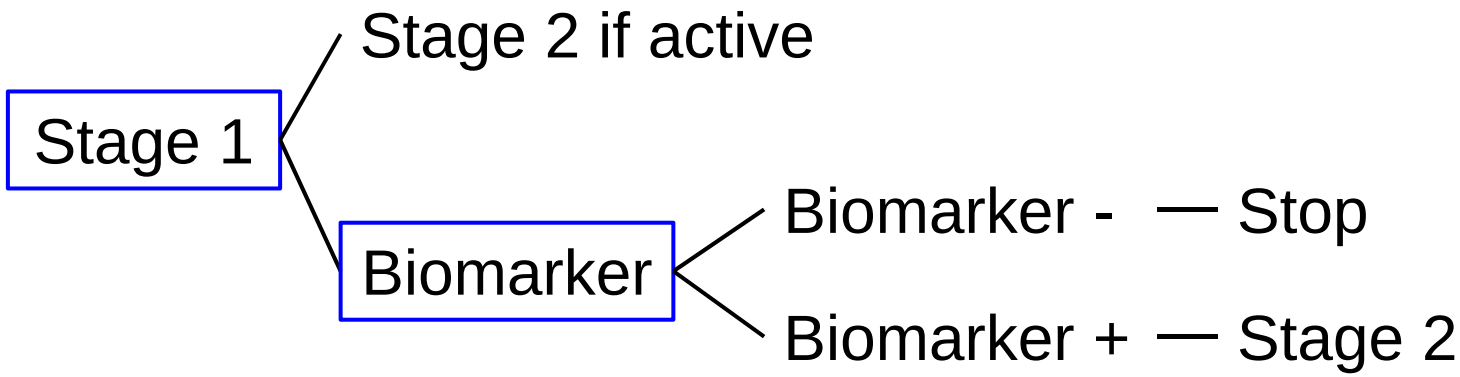
- The biomarker-strategy design is modified in the non-strategy arm
  - This addresses the second concern of biomarker-strategy design

Adaptive parallel design



- Both biomarker groups are tested in parallel at the first stage
- After the first stage, the trial may continue in all patients or only in the biomarker-positive group (expected to benefit more from treatment)

Tandem two-stage design



- All patients are tested in the first stage
  - If enough clinical responses are observed, the study proceeds to the second stage in the overall population.
  - If observed clinical responses are insufficient, the study accrues only biomarker-positive patients (expected to benefit more from treatment)

Adaptive designs

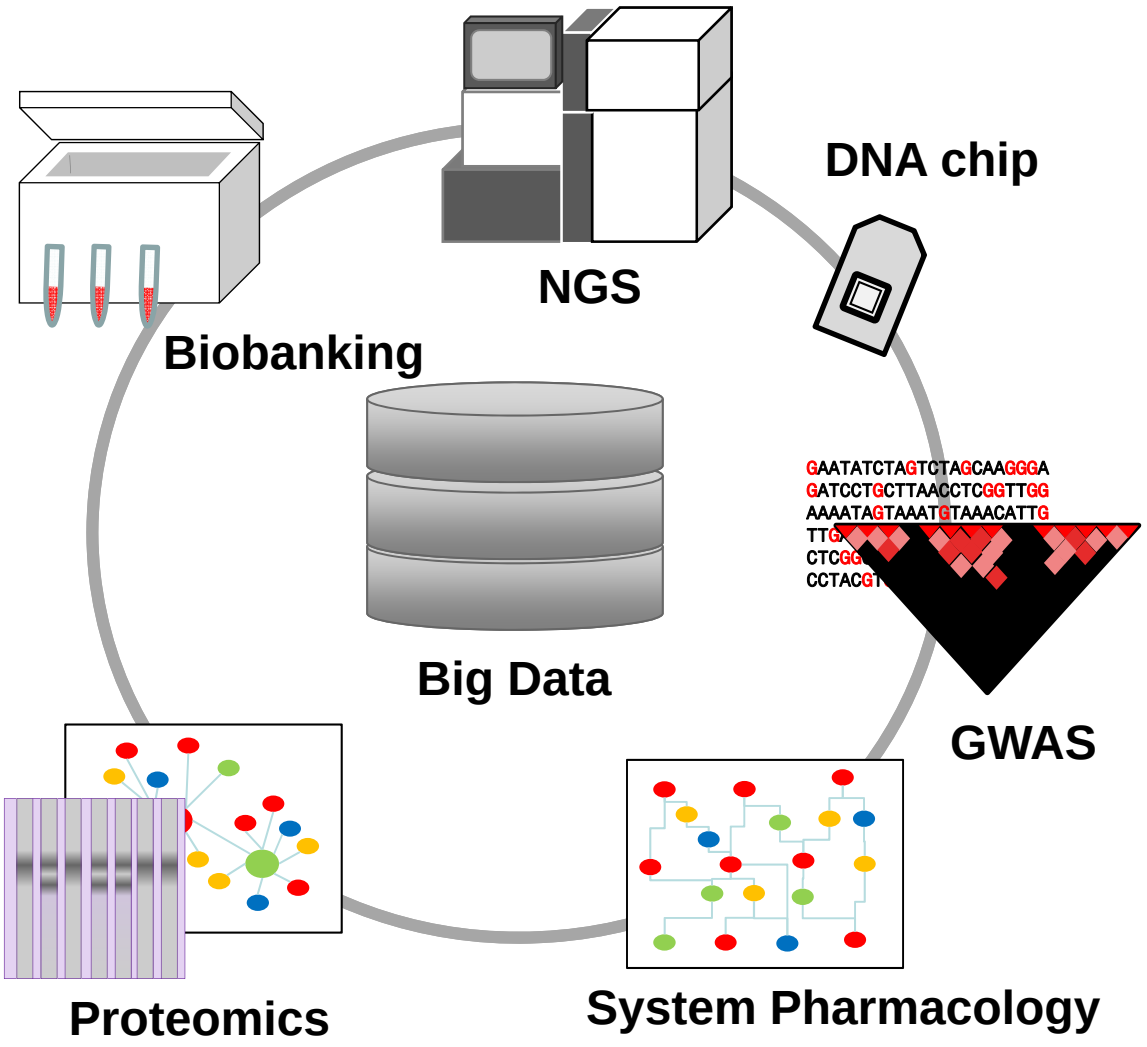
- Adaptive enrichment design
  - Starting the trial in the entire patient population, and then stopping accrual in the non-responsive subgroup based on the results of interim analyses (Brannath et al., Stat Med 2009; Jenkins et al., Pharm Stat 2011; Mehta et al., Stat Med 2014)

- Other adaptive design
  - Starting the trial only in the targeted subgroup in the first stage and allow the trial either to be terminated owing to futility after stage 1 or to start recruitment of the entire patient population in stage 2 (Liu et al., Clin Trials 2010)

Proposal from Data Science Task Force 5

- Taking actions to identify a predictive factor and its threshold at an early stage of development
  - Understand the value of a predictive factor and begin biomarker research as early as possible
  - Collect information about biomarkers from retrospective research (e.g., Biobanking)
  - Plan first-in-human study to research the predictive factor and/or determine the threshold, when there is no ethical issues.

Technologies for biomarker discovery



Cost-Effectiveness of Personalization

- Points to consider
  - Efficacy and safety in target and non-target populations
  - Opportunity loss for non-target population
    - Acceptance of try and error
    - Period to decision making (evaluation of efficacy)
  - Ratio of target population
  - Accuracy of biomarker test
  - Cost of biomarker test (includes CoDx development)

Acknowledgement

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