Utilisation of Biomarkers in Drug Development

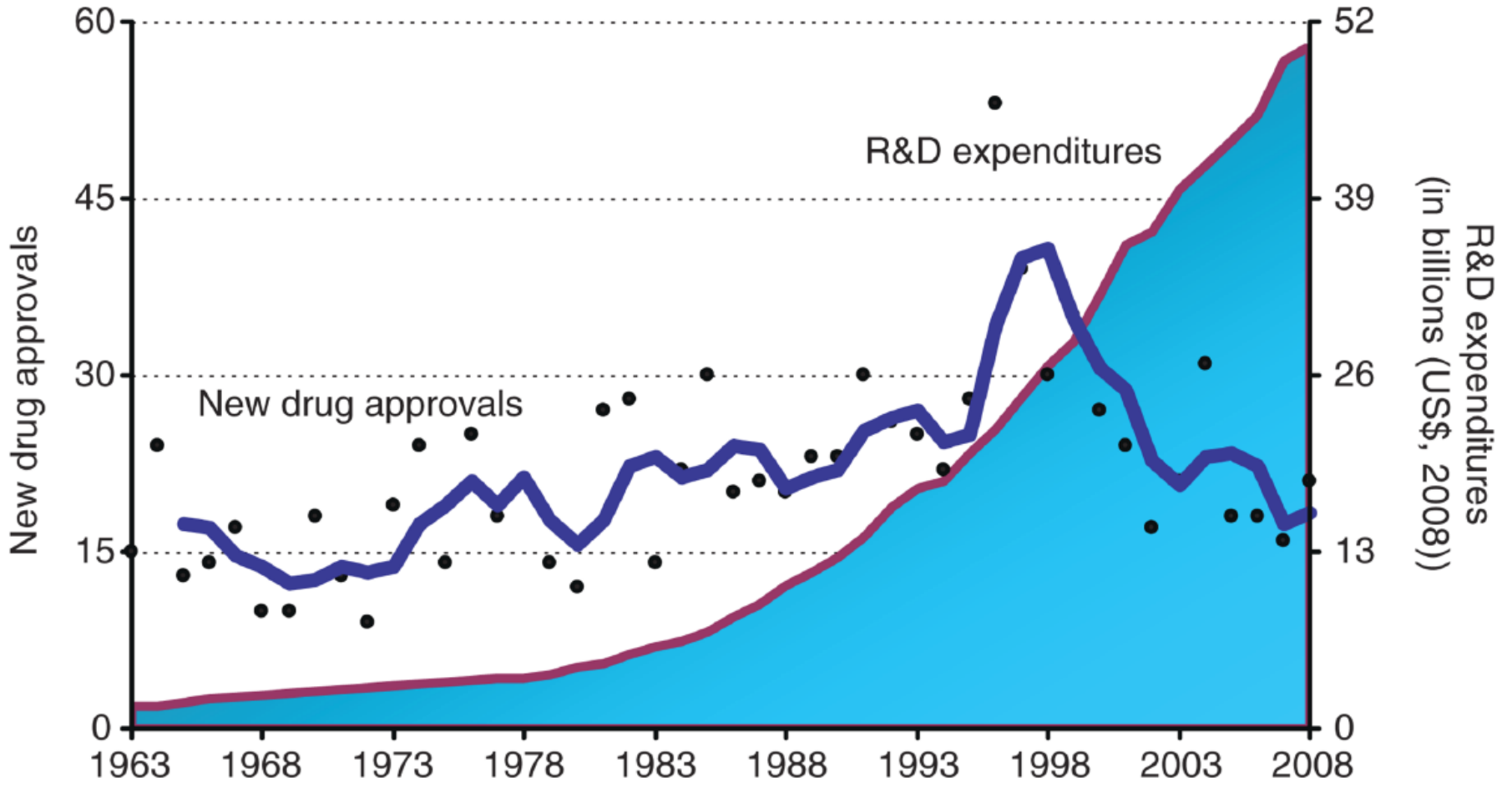
Akihiro Hirakawa, Ph.D.

Biostatistics and Bioinformatics Section

Center for Advanced Medicine and Clinical Research

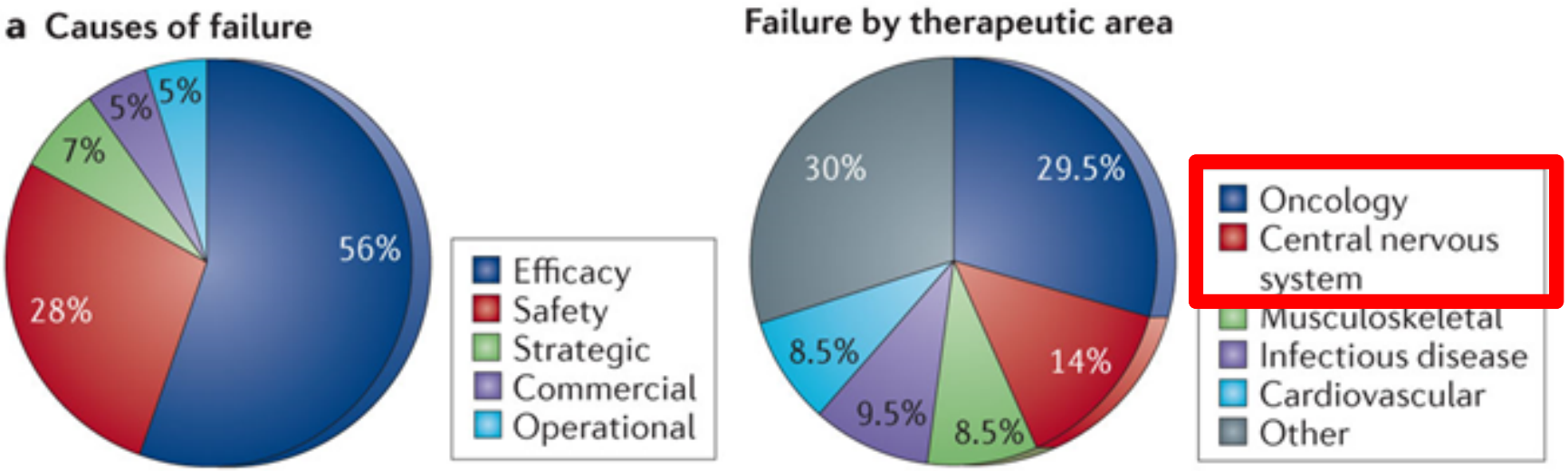
Nagoya University Hospital

Research and Development Trend



Kaitin. 2010 Clin Pharmacol Ther

Research and Development Trend



Arrowsmith J, Miller P. 2013 Nat Rev Drug Discov

Outline

- Overview of biomarker utilization in oncology and for the central nervous system (CNS)

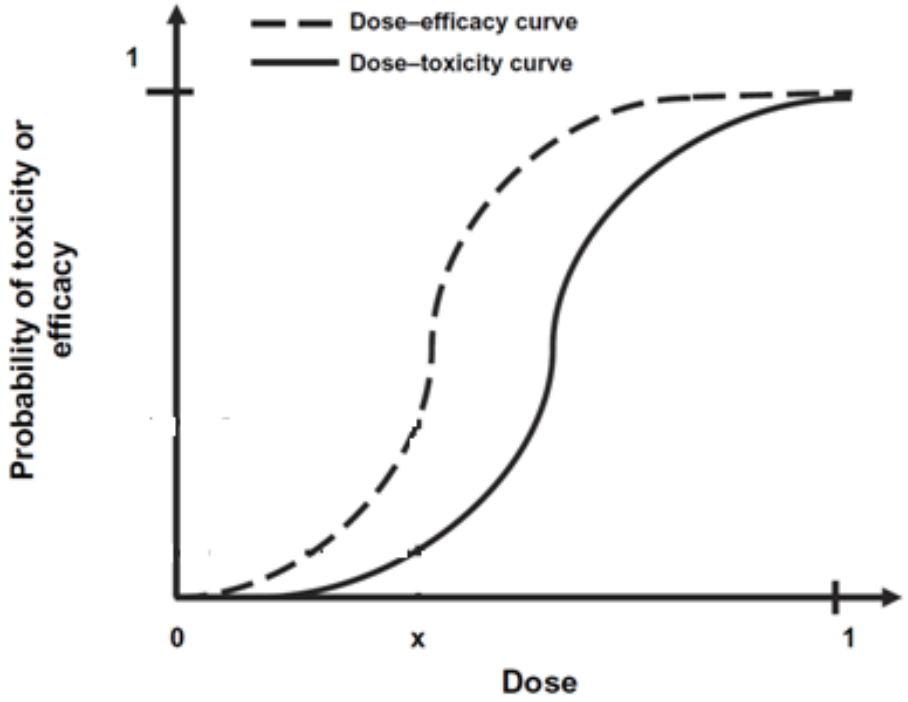
- Oncology
  - Phase I trial: from MTD to BOD
  - Phase II trial: Basket trials
  - Phase III trial: All comer or enriched
- CNS
  - Role of biomarkers

Phase I Trials

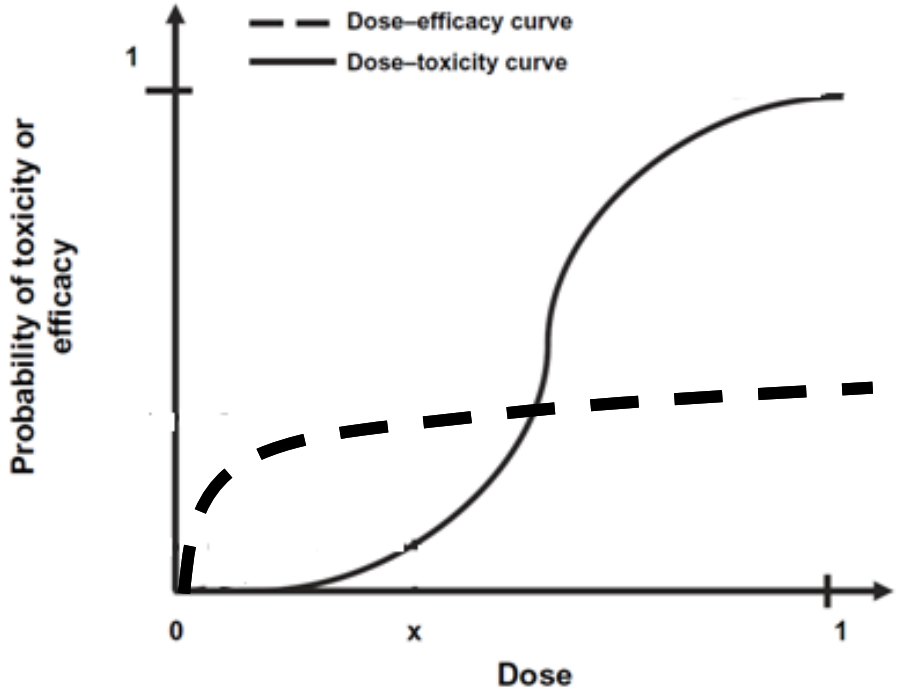
From Maximum Tolerated Dose (MTD) to Biologically Optimal Dose (BOD)

Cytotoxic agents

- Normally, toxicity and efficacy increase monotonically with dose escalation
- Dose-finding design based solely on toxicity



Molecularly target agents (MTAs)



- Some MTAs may exhibit non-monotonic efficacies in relation to the dosage efficacy

A dose-finding method that incorporates the efficacy outcome is required.

A biomarker can be used to attain the desired efficacy outcome in phase I dose-finding trials

Limitations in the use of biomarkers

1. In rare instances, a biomarker is identified during the early clinical development stage
2. Need to determine the cut-off value of the biomarker used
3. Heterogeneity of patients enrolled in phase I trial (e.g., tumor type and drugs/regimens previously administered)
4. Assay validation

Phase II Trial

Utilisation of Basket trials for New Drug Application

CAMCR

Current approval policy in PMDA

- Indication for each cancer type
  - CoDx: one-maker, one-test, one-drug

- A confirmatory phase III trial should be mandatory for every cancer type
- However, the basket trial included several tumor types that can be treated using one drug can be possibly utilized in NDA or supplementary NDA in Japan

Clinical data package in oncology

Between April 2004 to March 2014, 103 applications were reviewed by the PMDA.

	Phase III		Phase II		Phase I	Total
Type	Global	Overseas	Overseas	Domestic	Domestic	
1	○				○	10
2	○				×	14
3	×	○		○	○	24
4	×	○		○	×	14
5	×	○		×	○	7
6	×	×	○	○		4
7	×	×	○	×	○	5
8	×	×	×	○		25

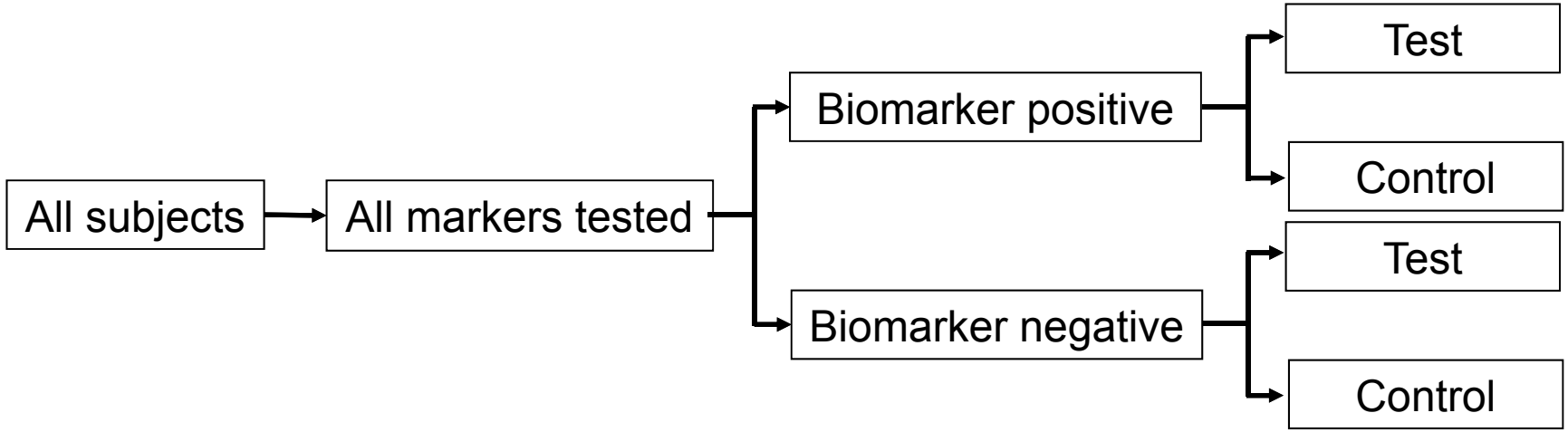
平川ら. (2015) 抗悪性腫瘍薬の臨床データパッケージ分析からみる今後の課題. 医薬品医療機器ﾚｷﾞｭﾗﾄﾘｰｻｲｴﾝｽ; 46: 714-720.

Phase III Trial

All comer or enriched?

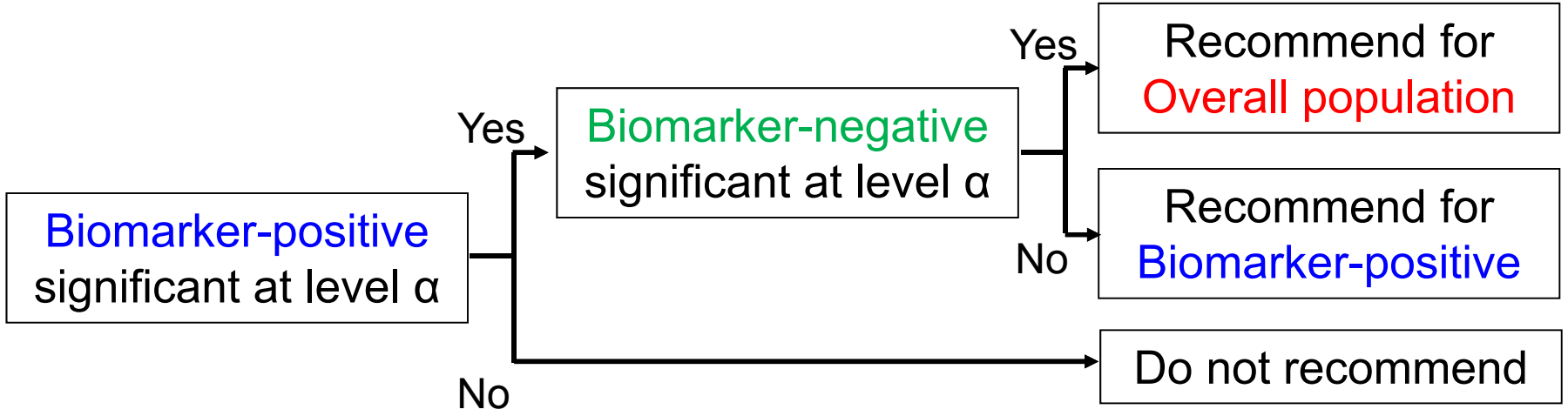
All-comers design

In this design, it was necessary to prospectively plan to conduct the subset analysis based on the biomarker with a control of the study-wise type I error rate.

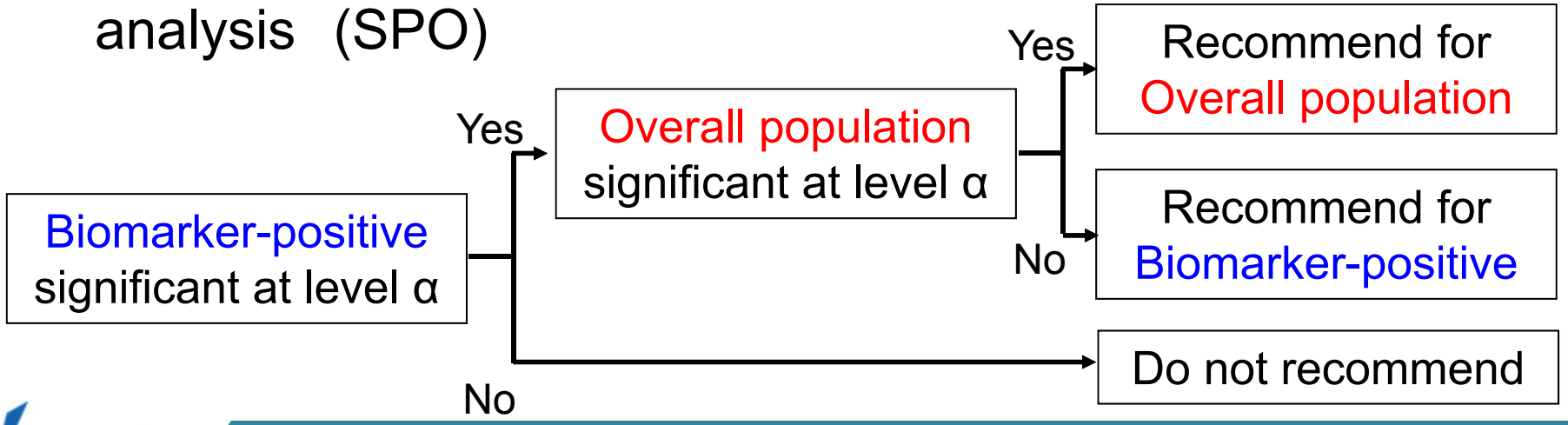


Analysis plans in the all-comers design (1)

- Sequential subgroup-specific analysis (SPN)

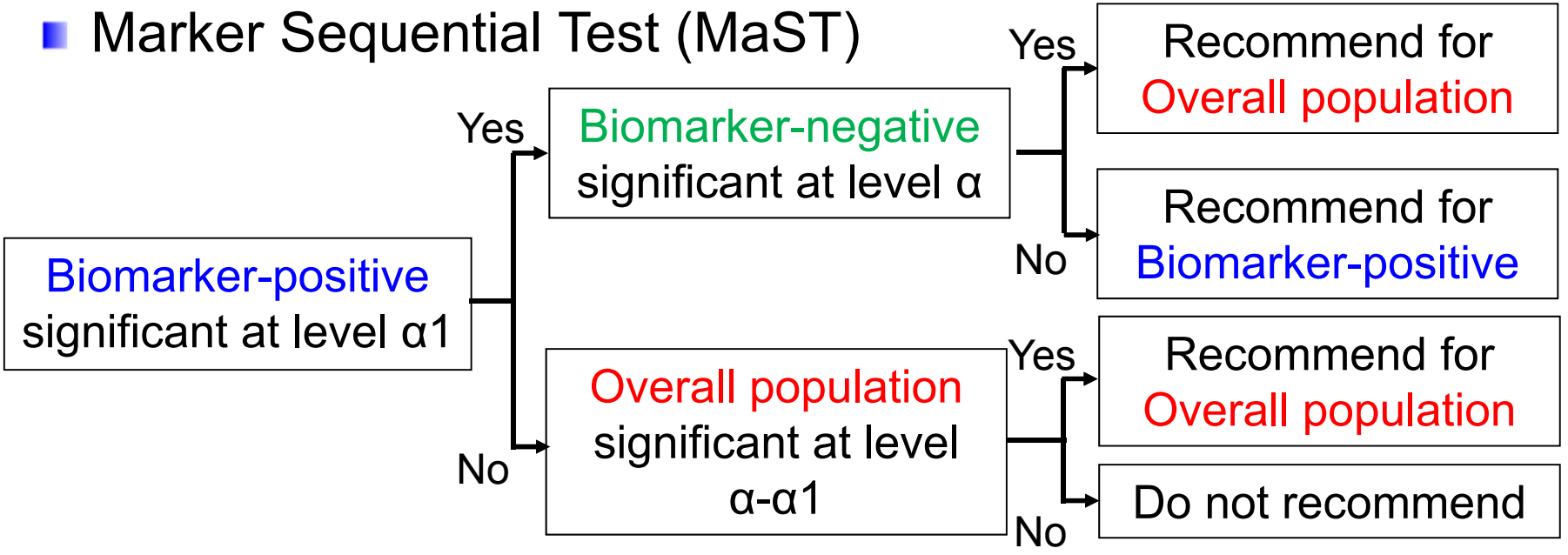


- Sequential biomarker-positive and overall population analysis (SPO)

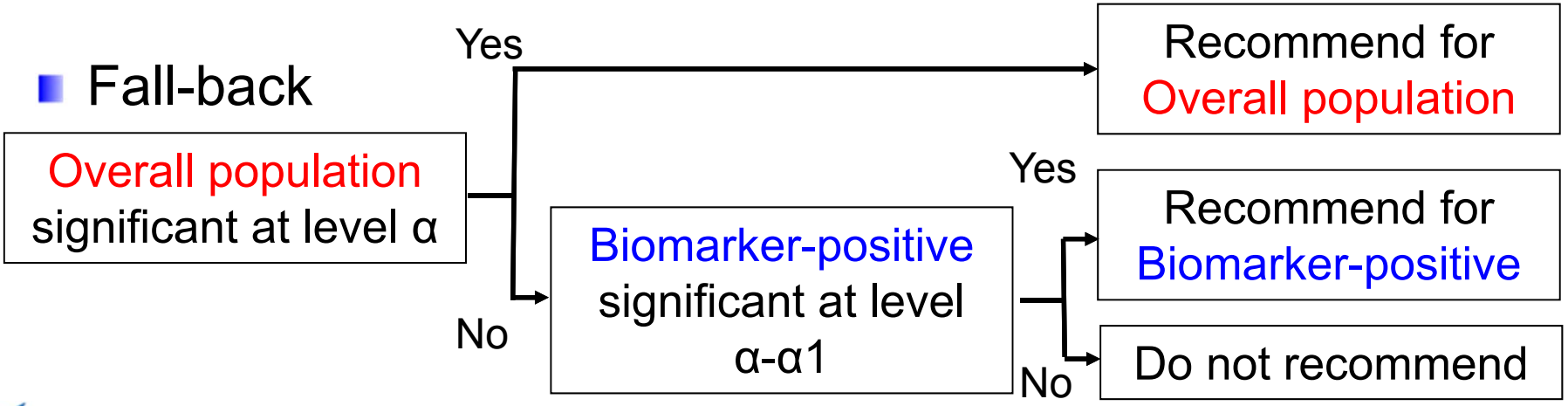


Analysis plans in all-comers design (2)

- Marker Sequential Test (MaST)

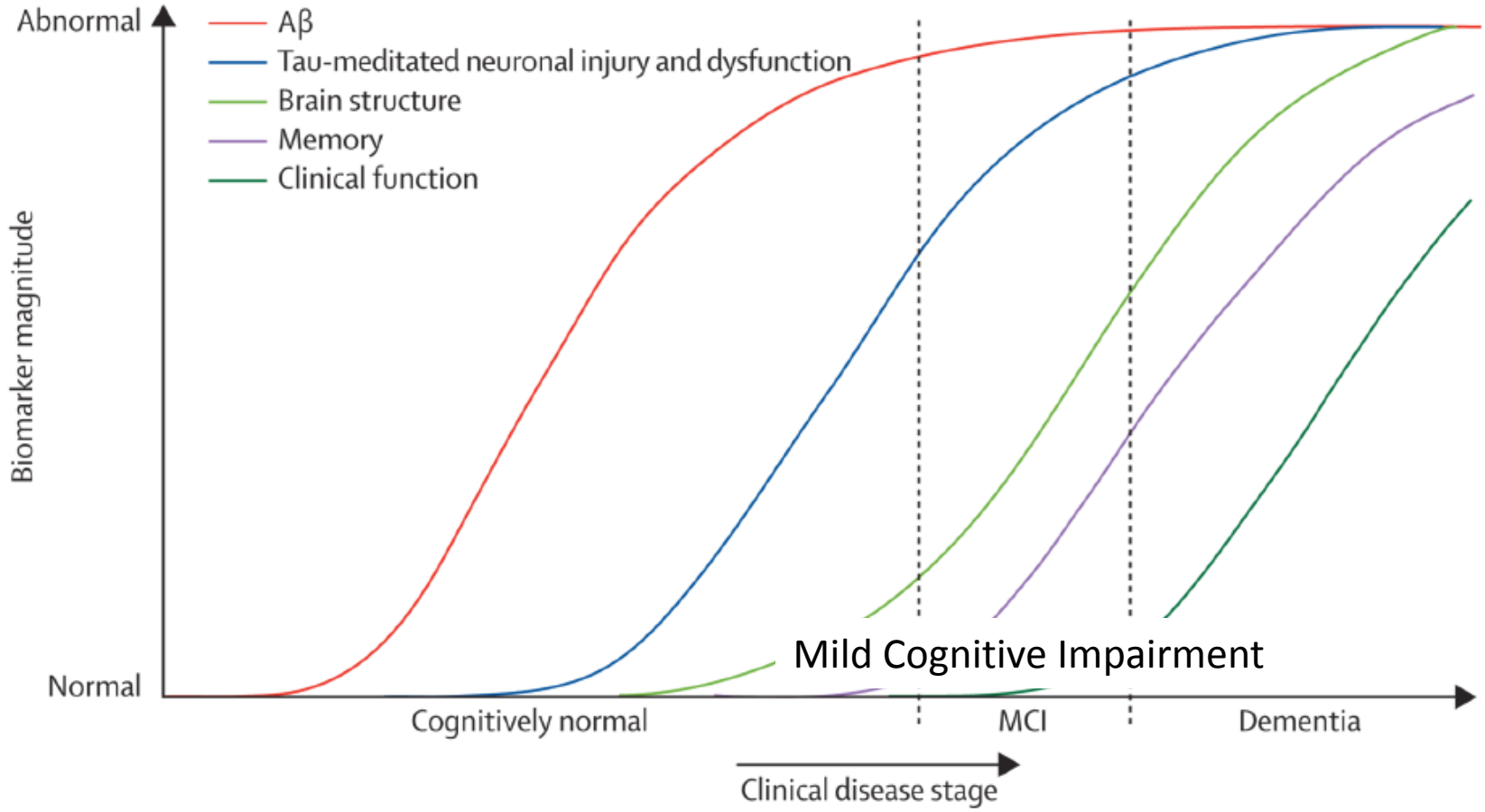


- Fall-back



Role of biomarkers in CNS

Alzheimer's disease



Jack et al. Lancet Neurol. 2010

Role of biomarkers in CNS

- No reliable evidence indicates association between changes in biomarkers and clinical benefits
  - Difficult to use as surrogate endpoint
  - Secondary endpoint
- Examine the preclinical and prodromal stages of the disease

Summary

- Oncology
  - Biomarker to determine BOD in phase I dose-finding trials in phase I trials
  - Basket trial in phase II trials for NDA (or sNDA) in Japan
  - Biomarker-based trial designs in Phase III trials

- CNS
  - Utilisation at the preclinical and prodromal stages