Adaptive Design Information Asymmetry – Genomic Composite Biomarker in Drug Development*

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***The views presented are those of the authors and not necessarily of FDA**

Outline

- Conventional Randomized Trials
- Genomic Drug Trials (PG Trials)
- Adaptive Design Information Asymmetry
- Genomic Composite Biomarker (GCB)
- Development & Clinical Validation of GCB
- Design-Based Targeted Sub-Trial
- Concluding Remarks

Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*

A Study Adequate to Support Effectiveness Claims Should Reflect a Clear Prior Hypothesis Documented In The Protocol

*FDA Guidance for Industry, 1998

Conventional Clinical Trial

A clearly stated primary hypothesis, e.g.,

T is superior to C adjusting for covariate Z

In randomization-based approach, the covariate effect is balanced in probability

When there is suspicion that T effect may differ between strata, e.g., Male vs. Female, White vs. Black, T*Z interaction maybe explored

$$\text{logit}\,(Y|X_T) = \pi + \tau X_T + \zeta X_Z + \eta X_{TZ}$$

Genomic Drug Trial (GDT or PG Trials)*

Clinical trials employing (high or medium) throughput) genomic technology to identify molecular signals including transcription, SNP or proteomic profiling in complex biological mixtures for use as genomic biomarkers of disease, of drug exposure/drug disposition, or of drug response including efficacy and toxicity

Wang (2004, Proceedings of the Biopharmaceutical Section, ASA)

Information Asymmetry

- **Hypothesis testing characteristics of Ph-III trials should not change as a result of the availability of new genomic technologies**

- **Information Asymmetry: When the treatment effect is inappropriately described in the sense of being diluted by the studied phenotypic patient population, what is likely to change is how to utilize differential genomic effect to select from or to stratify the heterogeneous patient population to be included**

Experience in RCTs Using Genomic/SNP Biomarkers

Genomic/SNP Biomarker

Efficacy:

- **Her2/Neu 3+ (Herceptin)**
- **EGFR+ (Tarceva)**

Safety:

- **HLA B57 allele (Abacavir)**
- **CYP2D6 variant (Strattera)**

None of these are prospectively defined

Wang (2005, ICSA Applied Statistics Symposium)

Example #1: overall pts

	P	T	OR (95%CI)	p-value
Overall (S + S')	32.1%	28.8%	0.86 (0.76, 0.97)	0.009
Subgroup S	42.5%	24.9%	0.45 (0.29, 0.70)	0.0002
Subgroup S'	31.2%	29.1%	0.90 (0.80, 1.02)	0.096

% of patients: 8%:92% (S:S')

Subgroup effect? Differences in response to treatment. Generally treated with skepticism, retrospective subset, exploratory, explanatory

What we are not used to see in design-based

Targeted Sub-Trial vs.

Overall Trial:

Molecularly targeted Sub-Trial

e.g., patients are classified as presence or absence of a Genomic Composite Biomarker (GCB) - a classifier described by a set of DNA genomic biomarkers that is expressed by a prediction algorithm (e.g., SVM, CERP) with a pre-specified cutoff value, say, C

GCB +: if patient's risk (prediction) score $\geq C$
GCB -: if a patient's risk score $< C$

Wang (2005, ICSA, Annual DIA, JSM); Wang, Chen (2005)

Example#2: Prospectively Stated a Priori Hypothesis on GCB+ Pts

	P	T	OR (95%CI)	p-value
Overall (S + S')	19.4%	19.7%	1.02 (0.89, 1.18)	0.499
Sub-Trial in S	27.1%	17.3%	0.56 (0.34, 0.93)	0.0001
Sub-Trial in S'	18.8%	19.9%	1.78 (0.55, 2.04)	0.350

% of patients: 8%:92% (S:S')

Usual notion without pre-specification: An effect in Sub-Trial Only ? Probably a spurious finding!

Note, it's the only pre-specified sub-trial of interest

Critical Path Research

Why high failure rate in Ph-3 trials?

Treatment effect

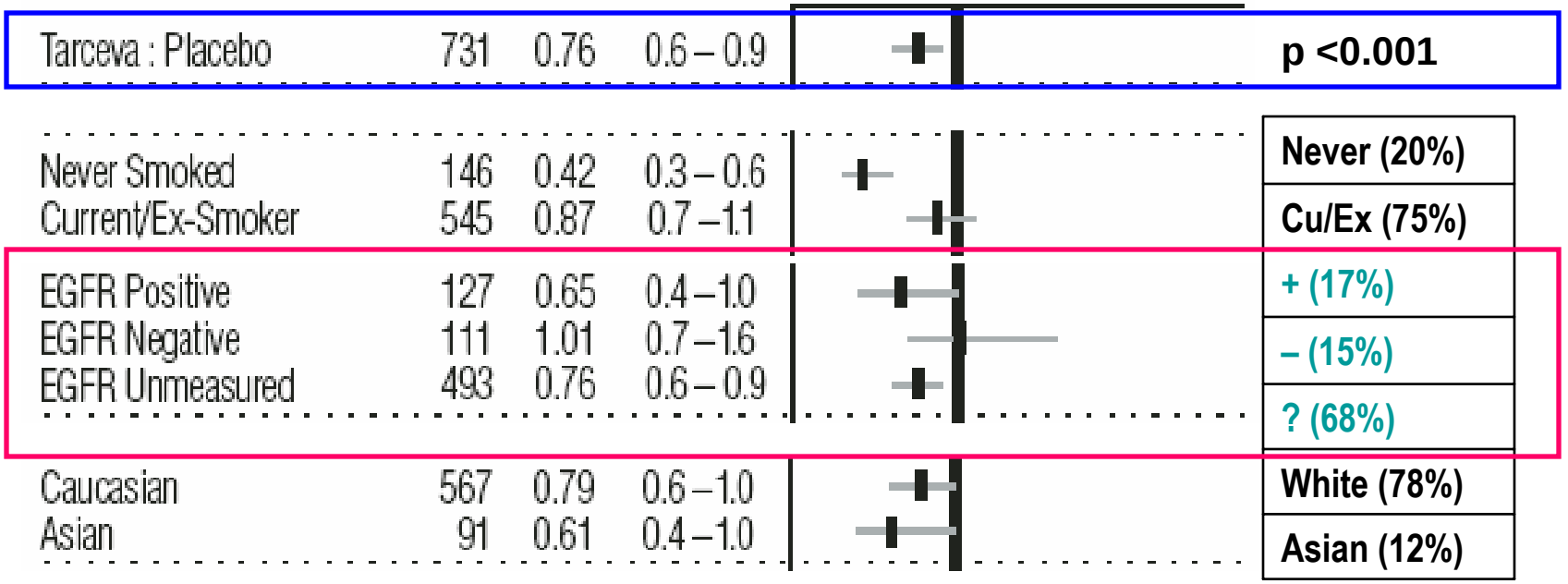
- **not shown in overall patients (Ex#2)**
  - **? Underpowered study**
  - **? Observational subgroup**
  - **? Molecularly heterogeneous patient populations**
- **shown in pts w/ GCB+ only (Ex#2)**

&Pharmacogenomic (therapeutic) sub-trial?

Wang (2005, ICSA, JSM)

Example #1: post-hoc subgroup

Figure 2: Survival Hazard Ratio (HR) (Tarceva : Placebo) in Subgroups According to Pretreatment Characteristics



Extracted from Tarceva Package Insert

How to objectively and statistically consider a

Targeted Sub-Trial vs. Overall Trial

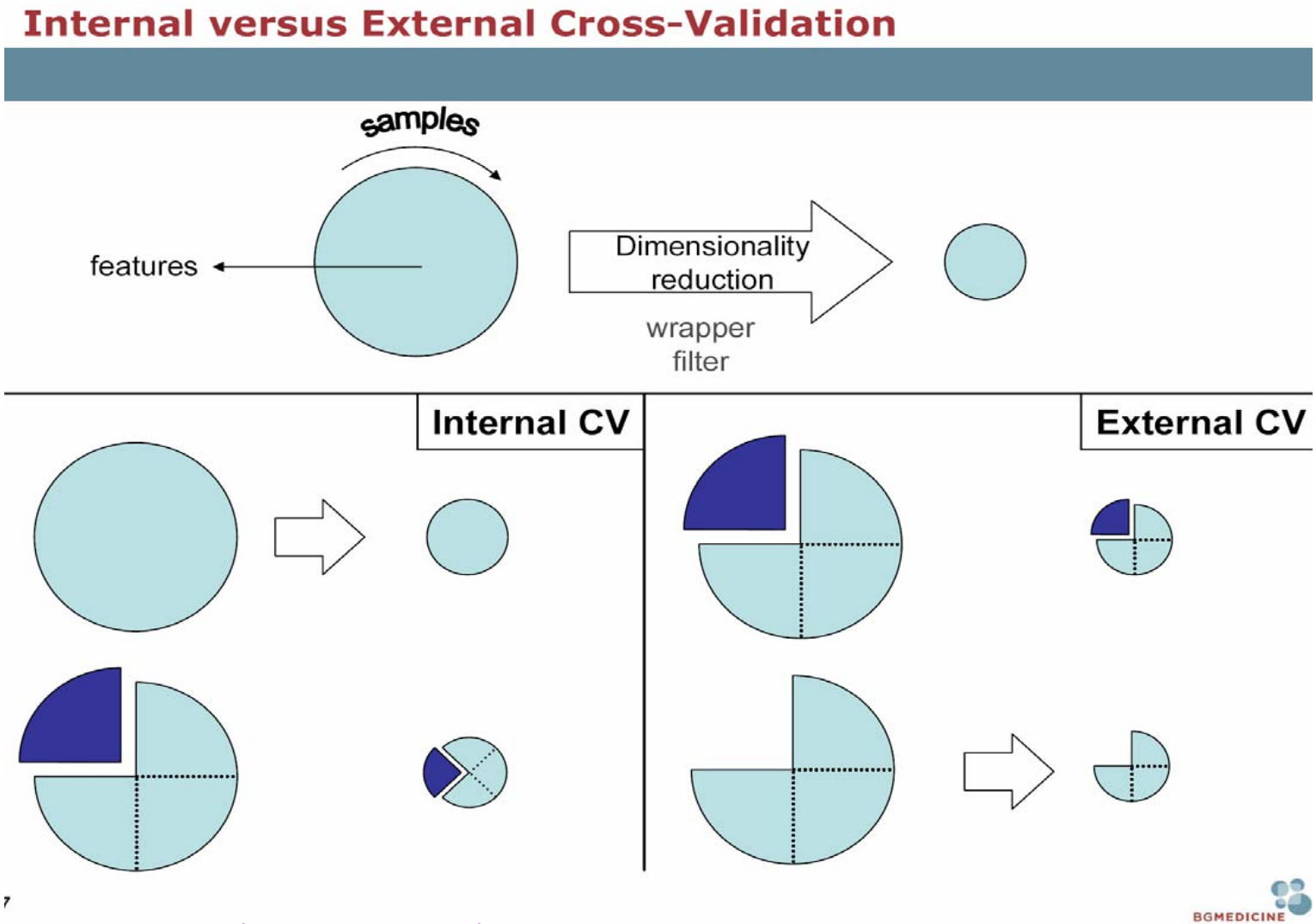
Prospective GCB Classifier

- **Three components**
  - ➢ **Genes/SNPs selection**
  - ➢ **Statistical prediction algorithm**
  - ➢ **Performance assessment of GCB's clinical prediction**

- **The aggregated information from the genes/SNPs set that together gives the most accurate therapeutic prediction (training, testing, performance) ➔ GCB**
- **GCB development might be concurrent, but, external to RCT**

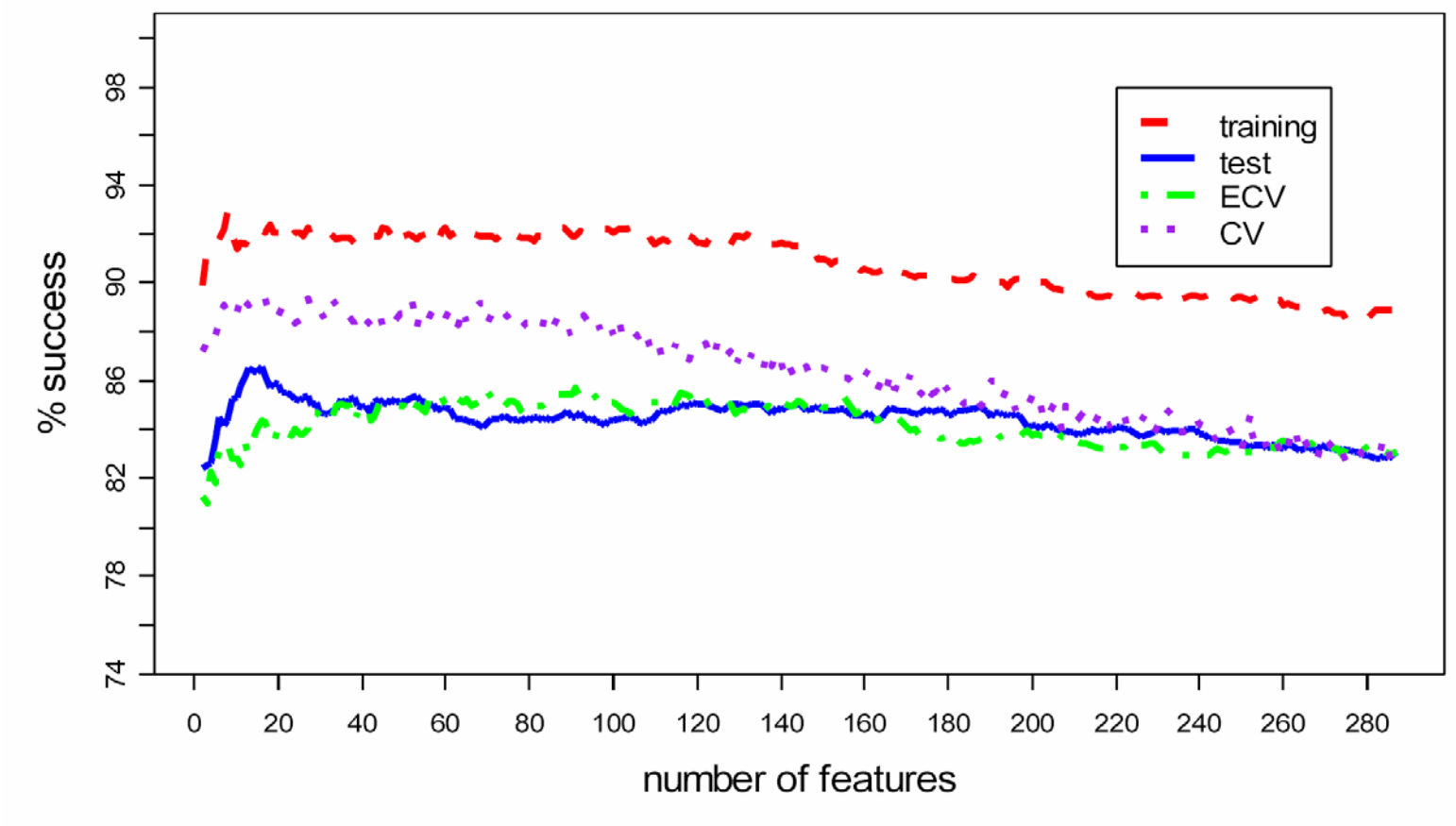
Wang (2005, ICSA); Wang, Chen (2005)

Validation Issues



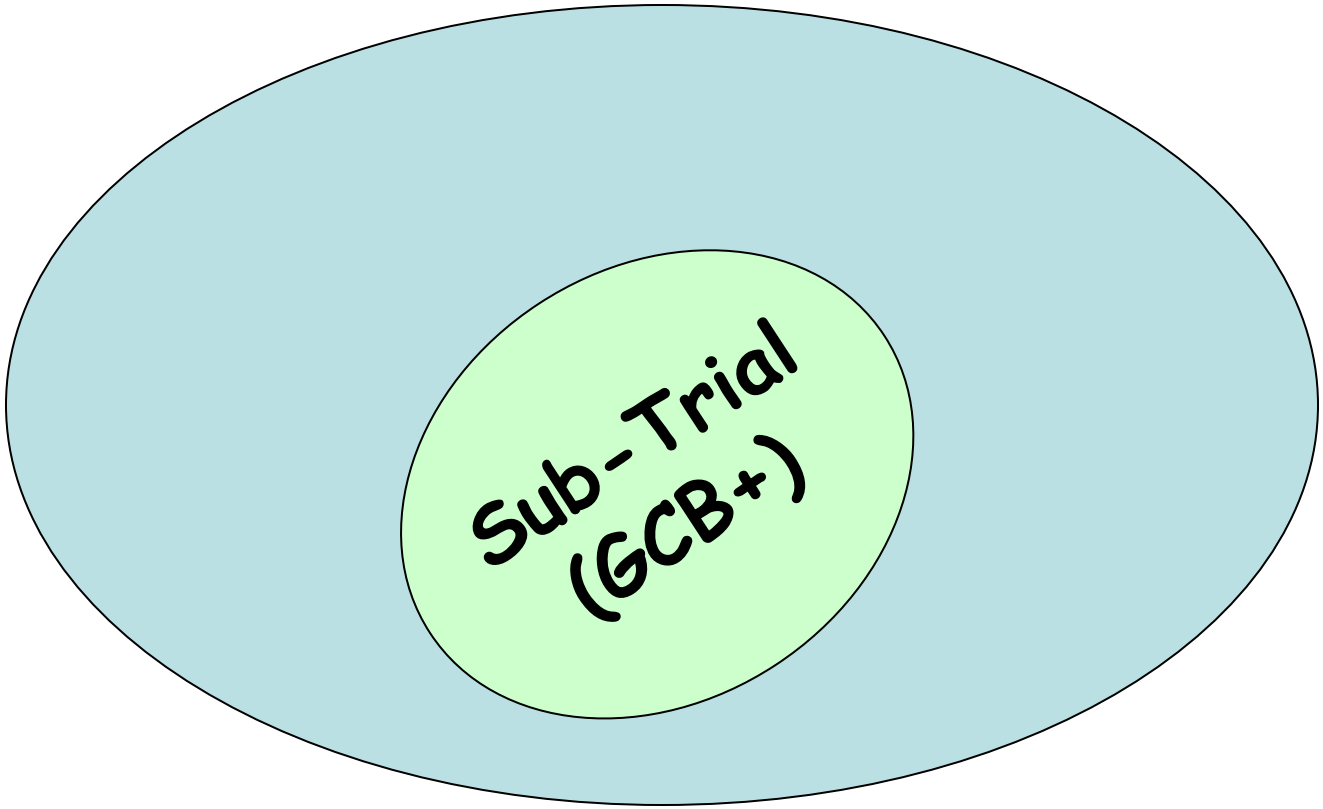
Damian D. (2005, JSM)

Results – K Nearest Neighbors (for K = 5)



Damian D. (2005, JSM – consider training: 36 mice; test: 53 mice)

A Prospective GCB+ SubTrial



Sub-Trial is correlated with All-Trial

Wang, Hung (2005, JSM)

Adaptive α-Allocation Strategy

Define Sub-Trial, say, molecularly targeted, a priori

Aim: To identify an overall effect or a sub-trial effect

Overall Type I Error Rate:

$$pr\{Z_N > z_{\alpha_1} \text{ or } Z_M > z_{\alpha_2} \mid H_0 : \Delta = 0 \text{ and } \Delta_S = 0\}$$
$$= 1 - pr\{Z_N \le z_{\alpha_1} \text{ and } Z_M \le z_{\alpha_2} \mid H_0 : \Delta = 0 \text{ and } \Delta_S = 0\}$$

Wang (2005, ICSA); Wang, Hung (2005, JSM)

Strategy – con't

Under H_0,

$$\begin{pmatrix} Z_N \\ Z_M \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 1 & \sqrt{M/N} \\ sym & 1 \end{pmatrix} \right).$$

Wang (2005, ICSA); Wang, Hung (2005, JSM)

$$pr_{H_0}\{\sqrt{t}Z_M + \sqrt{1-t}Z_{N-M} \le z_{\alpha_1}, Z_M \le z_{\alpha_2}\}$$

$$= pr_{H_0}\left\{Z_{N-M} \le \frac{z_{\alpha_1} - \sqrt{t}Z_M}{\sqrt{1-t}}, Z_M \le z_{\alpha_2}\right\}$$

$$= E\left\{pr_{H_0}\left(Z_{N-M} \le \frac{z_{\alpha_1} - \sqrt{t}Z_M}{\sqrt{1-t}}\right) I_{\left(Z_M \le z_{\alpha_2}\right)}\right\}$$

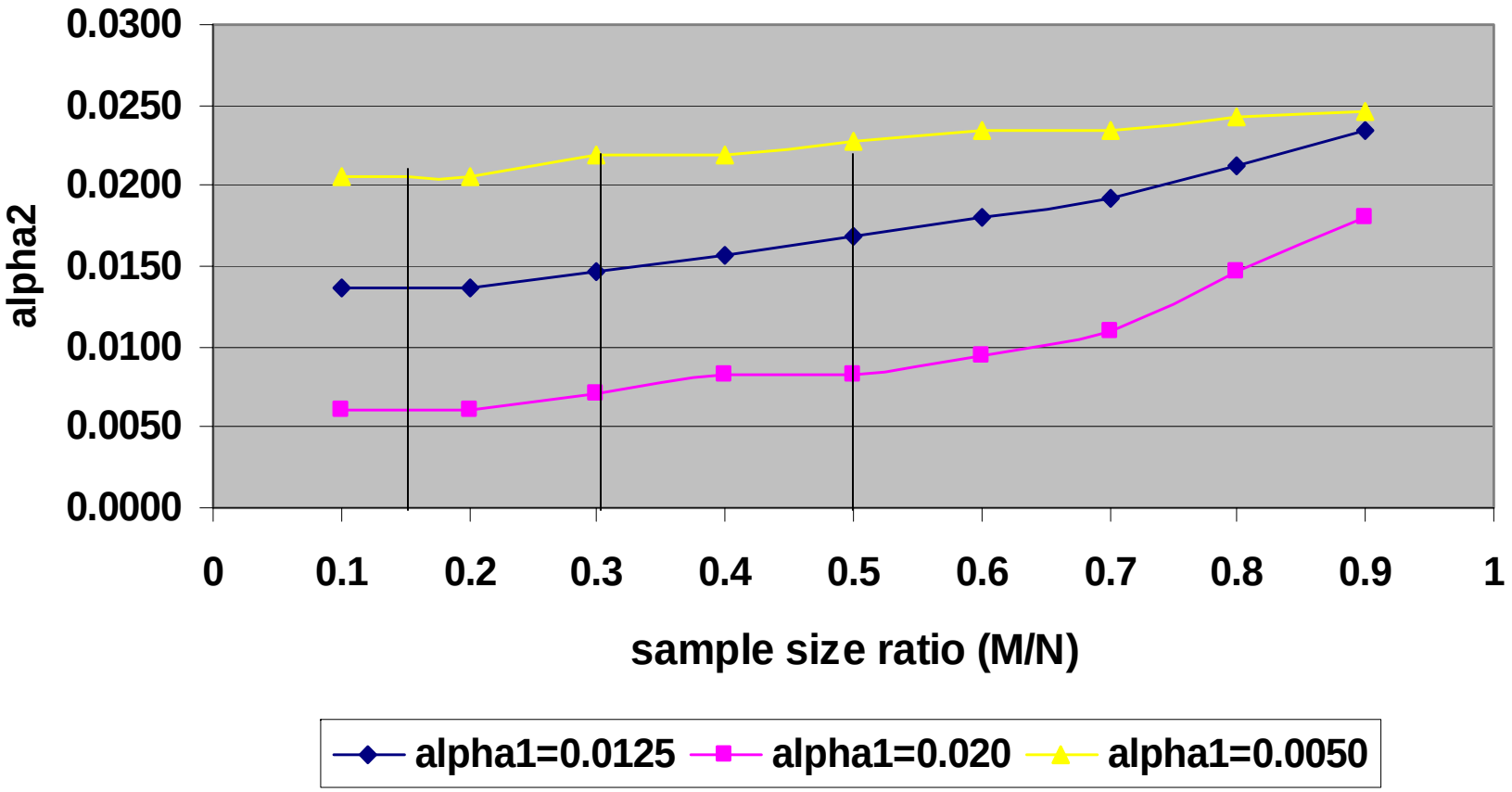
$$= \int_{-\infty}^{z_{\alpha_2}} \Phi\left(\frac{z_{\alpha_1} - \sqrt{t}z}{\sqrt{1-t}}\right)\phi(z)\,dz$$

$$= 1-\alpha$$

Given α_1 and *t=M/N*, solve for α_2

Wang (2005, ICSA); Wang, Hung (2005, JSM)

Figure 1. Subtrial alpha-level ($\alpha 2$) required to maintain overall type I error at 1-sided 0.025



Wang (2005, ICSA); Wang, Hung (2005, JSM)

Finding – Fig. 1

Given M/N, α_1 and α_2 are inversely related

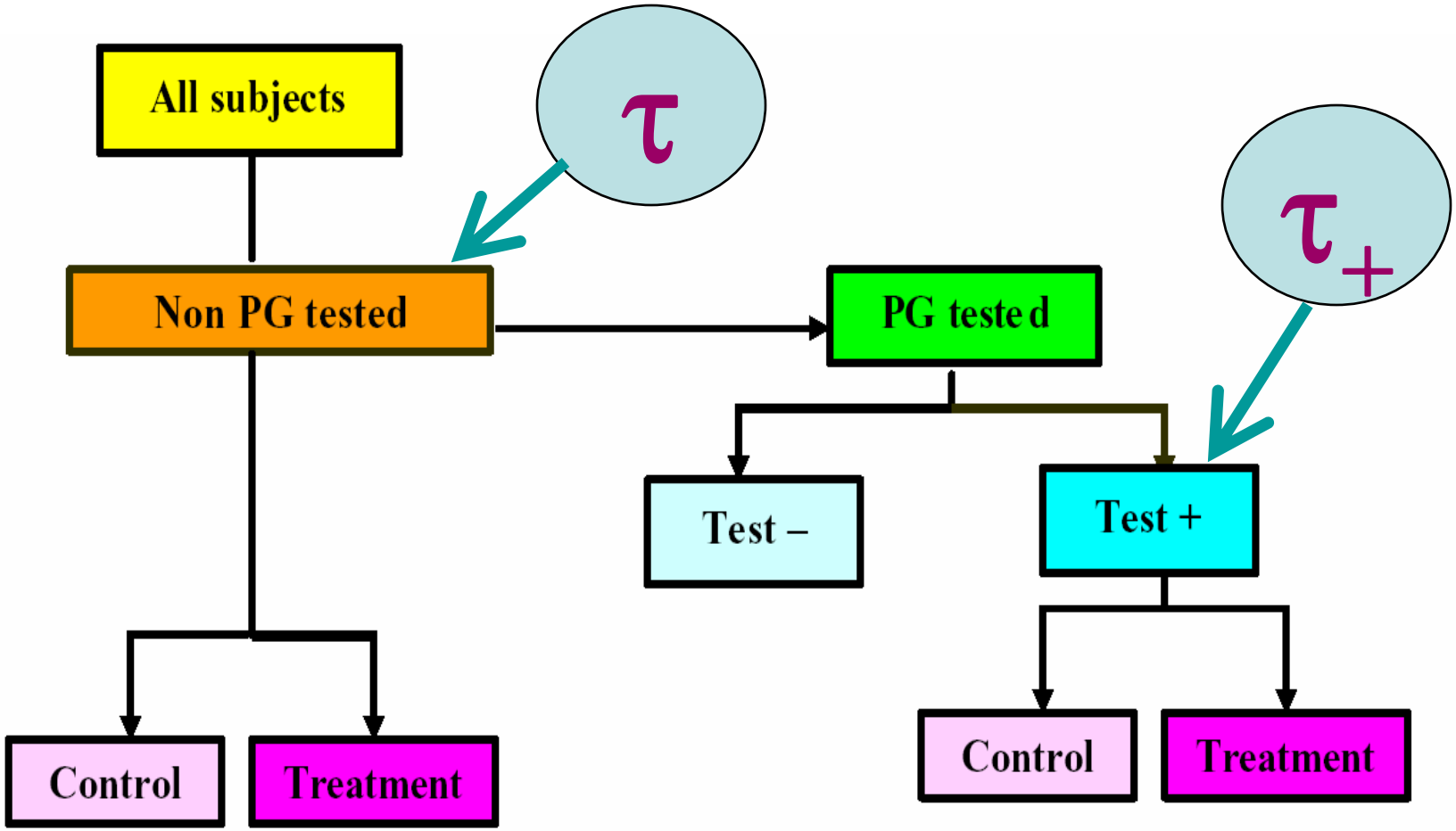
Given α_1, as M/N ↑ ➔ the allowable α_2 ↑
Although $\alpha = 0.025$, $\alpha_1 + \alpha_2 > \alpha$

M/N	15%	30%	50%
$\alpha 1 = 0.0200$	0.0060	0.0070	0.0080
$\alpha 1 = 0.0125$	0.0138	0.0148	0.0171
$\alpha 1 = 0.0050$	0.0205	0.0218	0.0228

Wang, Hung (2005, JSM)

Adaptive Design Information Asymmetry

Molecularly untargeted → Targeted*



* Wang (2005, ICSA, JSM)

Prospective Adaptive Design

Evaluate overall T effect with a single pre-planned GCB+ sub-trial T-effect

- **Possibly two hypotheses to be tested**
- **Sample size based on overall T effect**
- **One trial with 2-hypotheses each tested at reduced level to ensure chance of a false positive finding in the trial is limited to 5%**

*** Simon, Wang (2005, under review)**

Prospective Adaptive Design

Evaluate overall T effect with a single pre-planned GCB+ sub-trial T-effect requiring the overall T-effect showing non-inferiority before investigating the pre-specified genomic GCB+ subtrial

- **NI design due to ethical consideration**
- **GCB+ subtrial testing – a straightforward step-down approach**

Adaptive α-Allocation Strategy

- Account for correlation structure of 2-hypotheses
- Implicit in sub-trial relationship to overall patients

  ➔Reflects in multiplicity of 2-hypotheses

Question of pertinent interest:

Is there an explicit effect via drug intervention in prospectively defined sub-trial?

➢pre-specified sub-trial to be considered is often molecularly defined with pathophysiological or pharmacological interpretation

Wang (2005, ICSA)

Sub-Trial Power

- With $\alpha 1 = 0.020$
  $\delta_S = 2\delta$, Sub-Trial power 90%, if M/N ≥ 0.30
  $\delta_S = 3\delta$, Sub-Trial power 90%, if M/N ≥ 0.17
- With $\alpha 1 = 0.005$
  $\delta_S = 2\delta$, Sub-Trial power 90%, if M/N ≥ 0.20
  $\delta_S = 3\delta$, Sub-Trial power 90%, if M/N ≥ 0.09

Wang, Hung (2005, JSM)

Concluding Remarks

Overall patient population may consist of genomically heterogeneous patient subgroups, although they are phenotypically similar

Required subgroup analysis w/o formal statistical decision

Age, Race, Gender

When these subgroups are separately studied, it can be considered as a form of enrichment: e.g.,

- **By age: pediatric (or geriatric) trials (to extend the label)**
- **By race: trial studied only in self-identified Black (e.g., Bidil, limit the label to the studied population) based on prior evidence and pre-specified criteria**

Concluding Remarks

To formally test if treatment-effect is mainly explained by subpopulation in the Sub-Trial:

- **Define the Sub-Trial hypothesis a priori, in addition to overall hypothesis: DESIRE to target either the overall effect or the Sub-Trial effect, while controlling the overall type I error rate, specification of an (adaptive) α-allocation strategy is required, sub-trial power followed**

- **Alternatively, one can study the enriched Sub-Trial if factors for enrichments have been thoroughly investigated**

Contributors

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