

Role of biomarkers in the  
development of medicines  
An EU viewpoint

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# Using Biomarkers

- **Selection of products**
  - Toxicity
  - Efficacy in preclinical and early clinical trials
- **Selection of patients ( at risk for disease, responders)**
  - At risk for disease: to compare clinical events in M+ vs M- cohort of untreated patients, then to select patients likely to have more events, thus fewer patients in a clinical trial
  - Responders to a particular treatment: to compare clinical events in Tt A vs placebo (Tt B) in a cohort of M+ (or M-) patients, then to conclude about efficacy of a treatment in a particular subpopulation
- **Efficacy/Surrogate endpoints**
  - Shorter trials
  - Few regulatory constraints in phase II, more difficult in phase III

# Some statistics

- Briefing meetings: 20 meetings since 2003
- Scientific advices: from 2004 onwards, 15 products with a clear PgT/PgX content (2% requests), 13/15 in oncology (various TK inhibitors)
- Research the most active in the cancer field (pathways identified active in many cancer types)
- But my vision is (somewhat) biased...

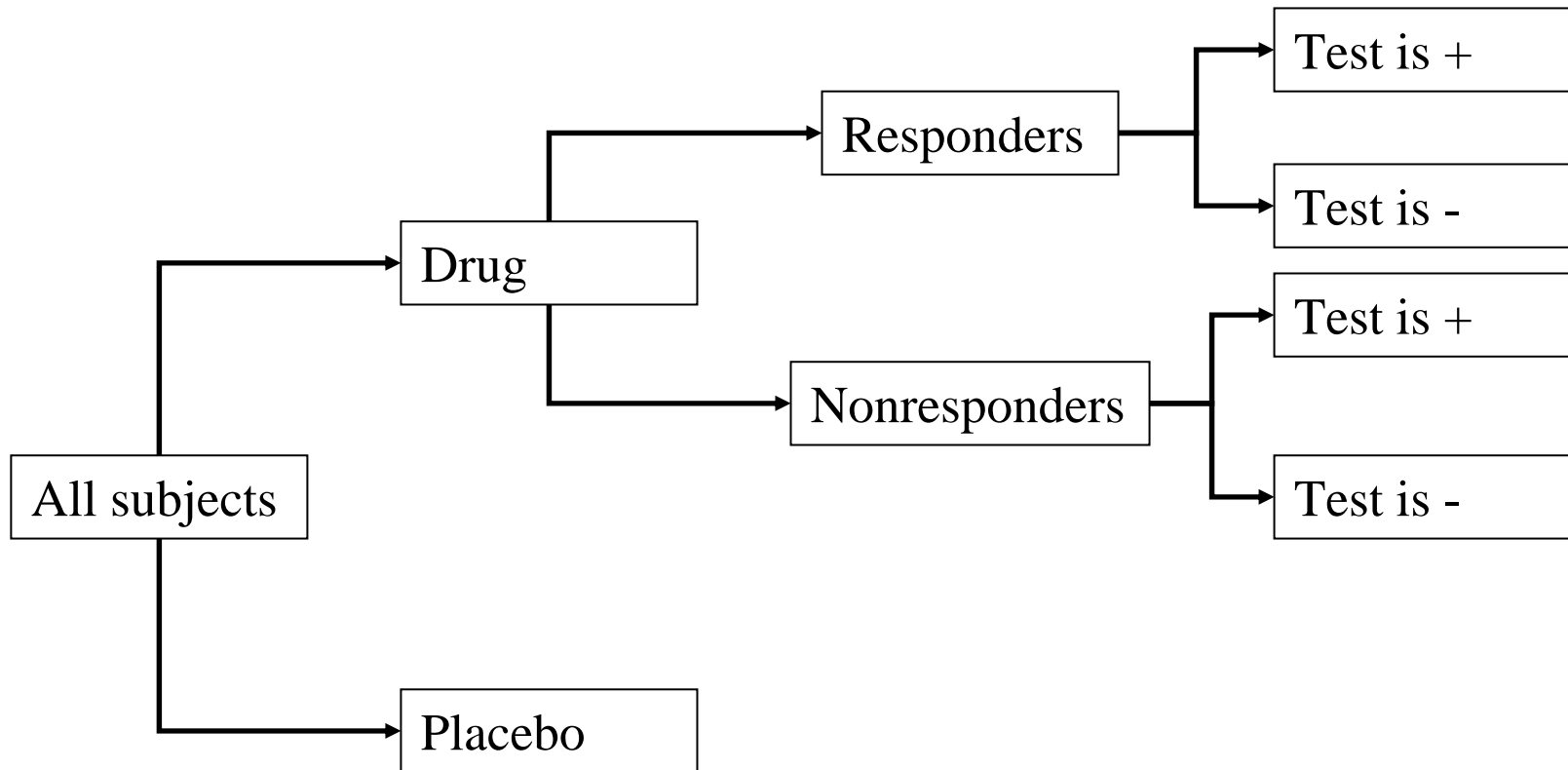
# Biomarkers to select a product

- Joint effort FDA/EMA Critical Path
- PSTC
- New procedure of qualification of biomarkers ongoing at EMA

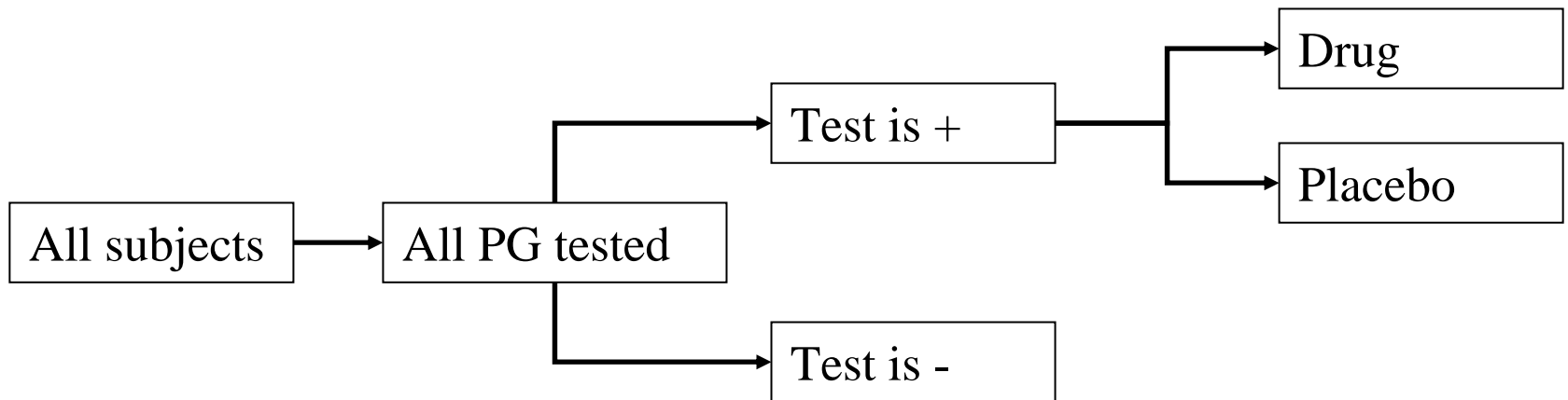
# **Biomarkers to select a population**

- Prospective, screened, no possible effect in (-) group
- Prospective, stratified, possible effect (and toxicity) in the (-) group
- Prospective, stratified, with explicit study of the unselected population
- Retrospective studies

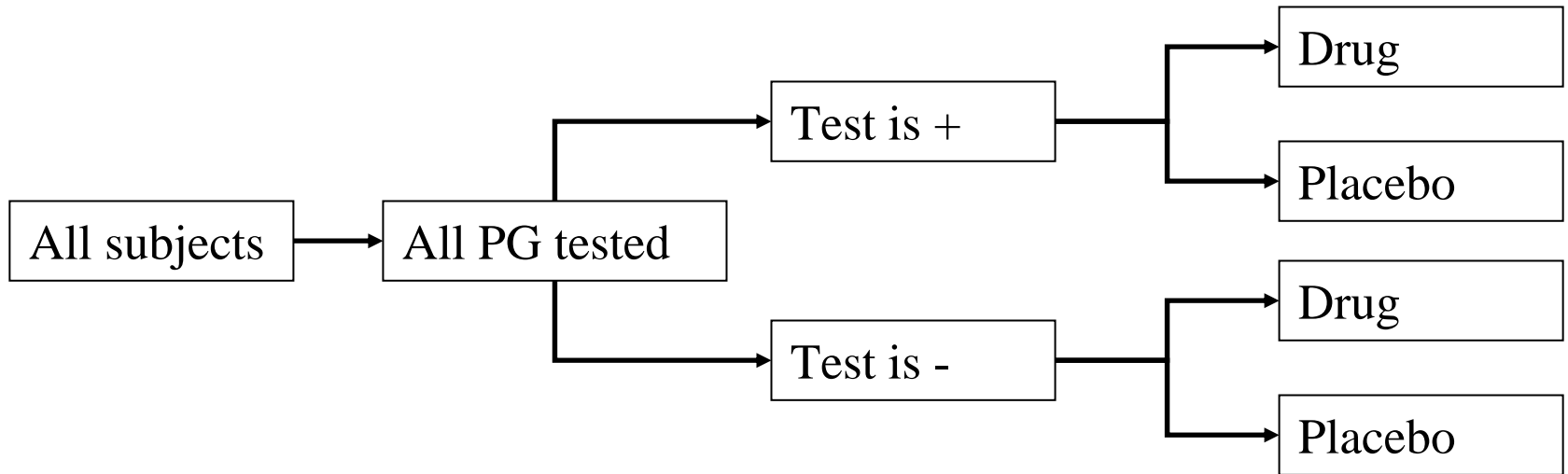
# Retrospective (Ph II)



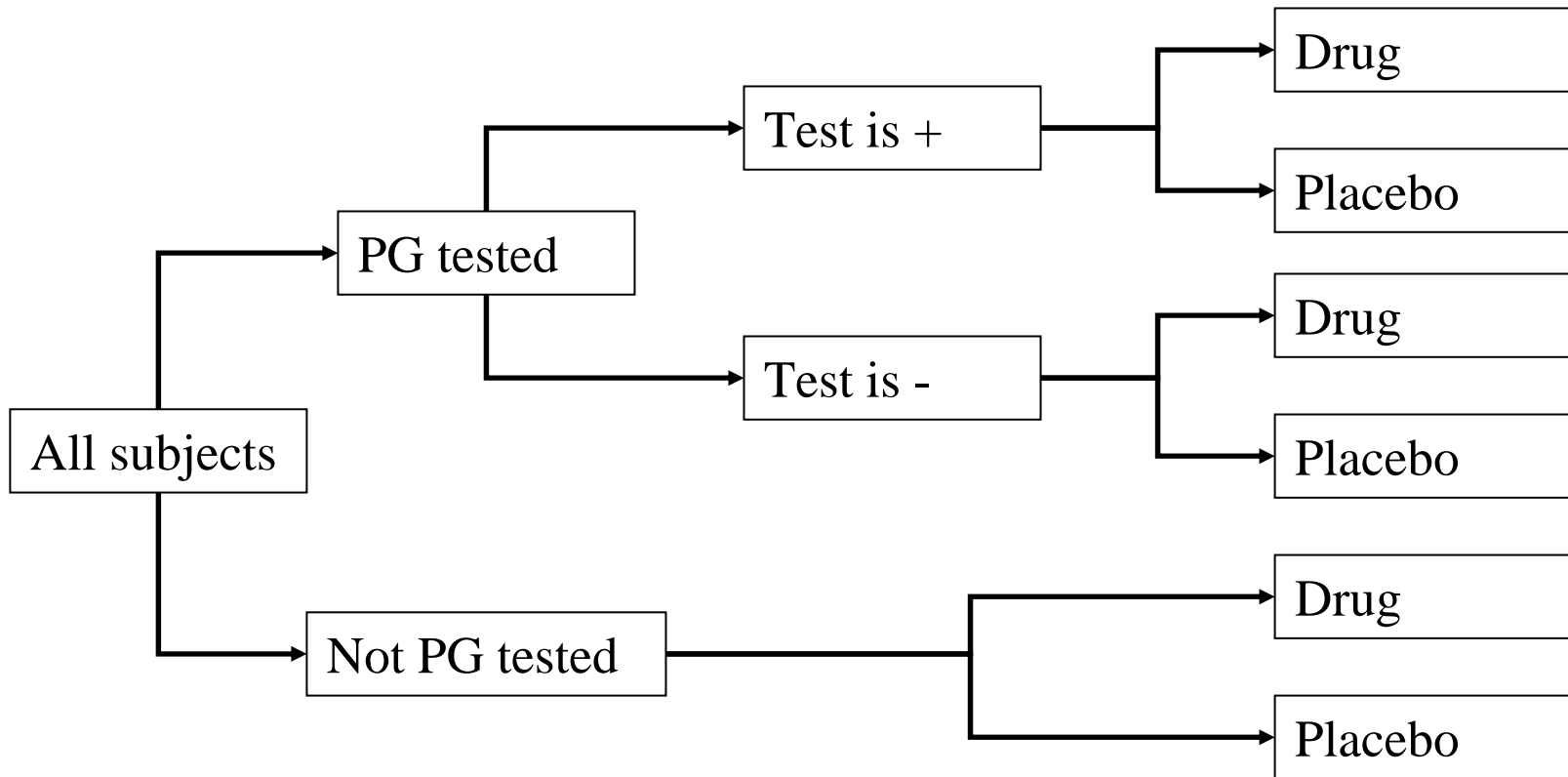
# Prospective, screened - no possible effect in (-) group (Ph III)



**Prospective, stratified, where there is possible effect in the (-) group and/or where toxicity in the (-) group needs to be evaluated (Ph III)**



# Prospective, stratified, provides explicit study of the unselected population (Ph III)



# Biomarker as a surrogate

- A biomarker that is intended to substitute for a clinical endpoint. Should predict clinical benefit based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.
- How to validate a surrogate endpoint ? We need some form of correlation between biomarker and clinical outcome in epidemiologic and therapeutic intervention studies (usually lacking)

# Biomarkers as a surrogate

- **Either these biomarkers are not fully validated...:**

Help company in Phase I and II

In general not sufficient as primary endpoint in pivotal studies

“Conditional” approval if:

- Unmet medical need, serious disease, no satisfactory alternative
- Benefit/Risk balance positive, based on (reasonably) likely surrogate endpoint, pending further studies

# Biomarkers as a surrogate

- **...Or these biomarkers are fully validated:**

Effect on surrogate predicts the desired clinical benefit

“Full” approval

Few examples: blood pressure, LDL cholesterol, viral load, A1C (but rosiglitazone, torcetrapib cases recently in CV field.)

# Conclusion

- Qualification of BM is an important issue (BM fit and valid for an intended use in a specific context)
- Analytical part is paramount..
- Rest dependent on clinical use
  - BM as a « generic » pharmacodynamic marker: work of the PSTC
  - BM to select a population (towards « personalized » medicines): pathways in oncology, development based on « enrichment » studies, not too difficult if we have a good drug....