Baylor College of Medicine

Prognostic and Predictive Markers:

What's the difference? & Why should I care?

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Baylor College of Medicine

Houston, TX

Definition

A biomarker is a characteristic that is objectively measured as an indicator of:

- Normal biological processes,
- Pathogenic processes OR
- Pharmacological response to a therapeutic intervention.

Biomarkers Definitions Working Group (2001) Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther;69:89–95.

US FDA

- A **VALID** biomarker:
  - Is measured in an analytical test system with well established performance characteristics
  - Has a scientific framework or body of evidence as to physiologic, toxicologic, pharmacologic, or **clinical significance** of the test results
  - Is “Fit to purpose”, which is context specific
- **Clinically useful** biomarkers:
  - Address a specific setting
  - Are clinically actionable
  - Reliably estimate effect

http://www.fda.gov/cder/guidance/6400fnl.pdf
http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

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"What is the Purpose?"

• Risk or susceptibility?	MSI, Fam Hx, BRCA1
• Diagnosis?	PSA?
• **Prognosis?**	Stage, OncotypeDX?
• **Predictive of tx benefit?**	ER+,Her2+,KRAS-,BRAF, ALK
• PD/Dose adjustment?	CYP2D's, UGT1A1
• Disease progression?	CA125?, CTC?
• Surrogate endpoint?	Response?
• Early readout?	Fdg-PET?

Some of these pre-date current rules and are "Known" to be valid biomarkers by virtue of long experience supporting their use.

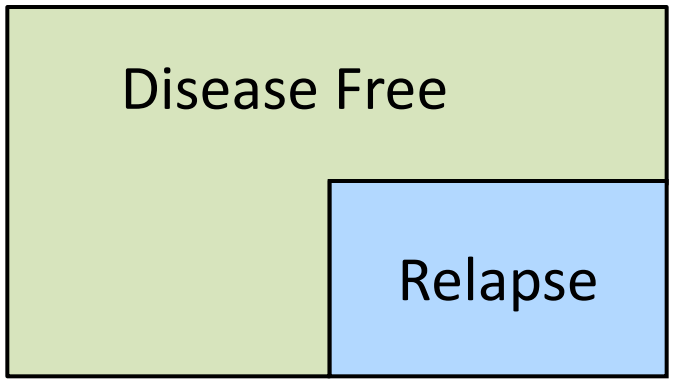
Importance of Purpose of Biomarker

Ex: Prognostic vs Predictive

Blue/Green Biomarker

Perfectly Predicts Long-term Outcome

Everyone got SRG & Systemic Adj. Tx



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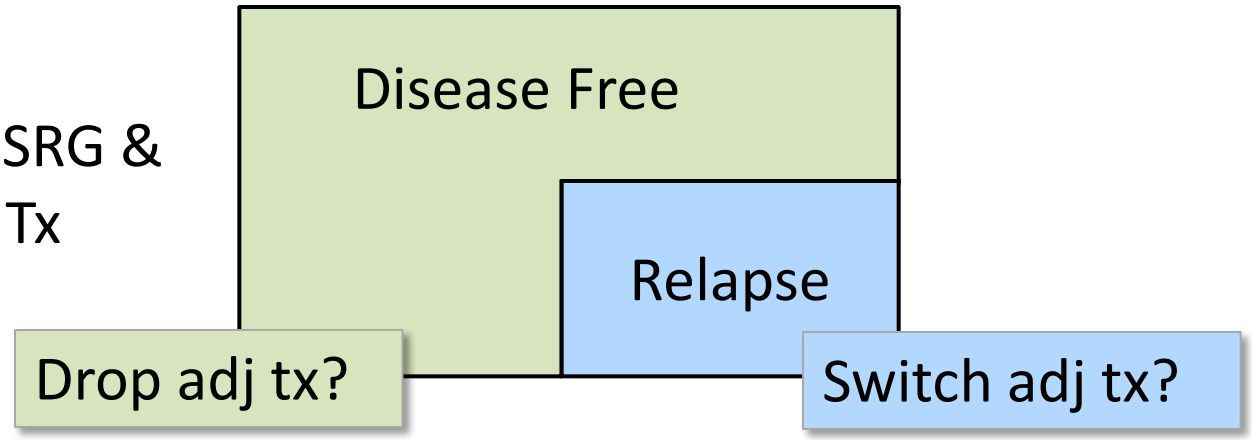

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Treatment Confuses the Issue

	Cured by SRG	Not Cured by SRG
Adj Tx Sensitive		
Adj Tx Resistant		

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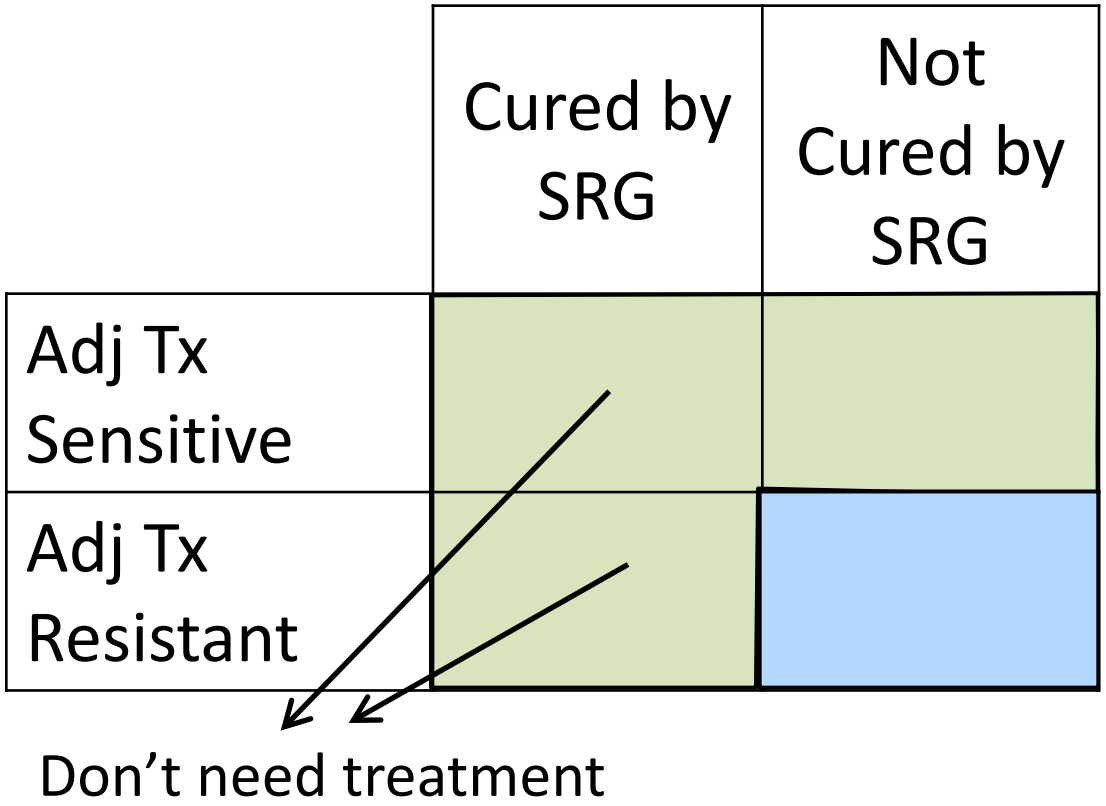

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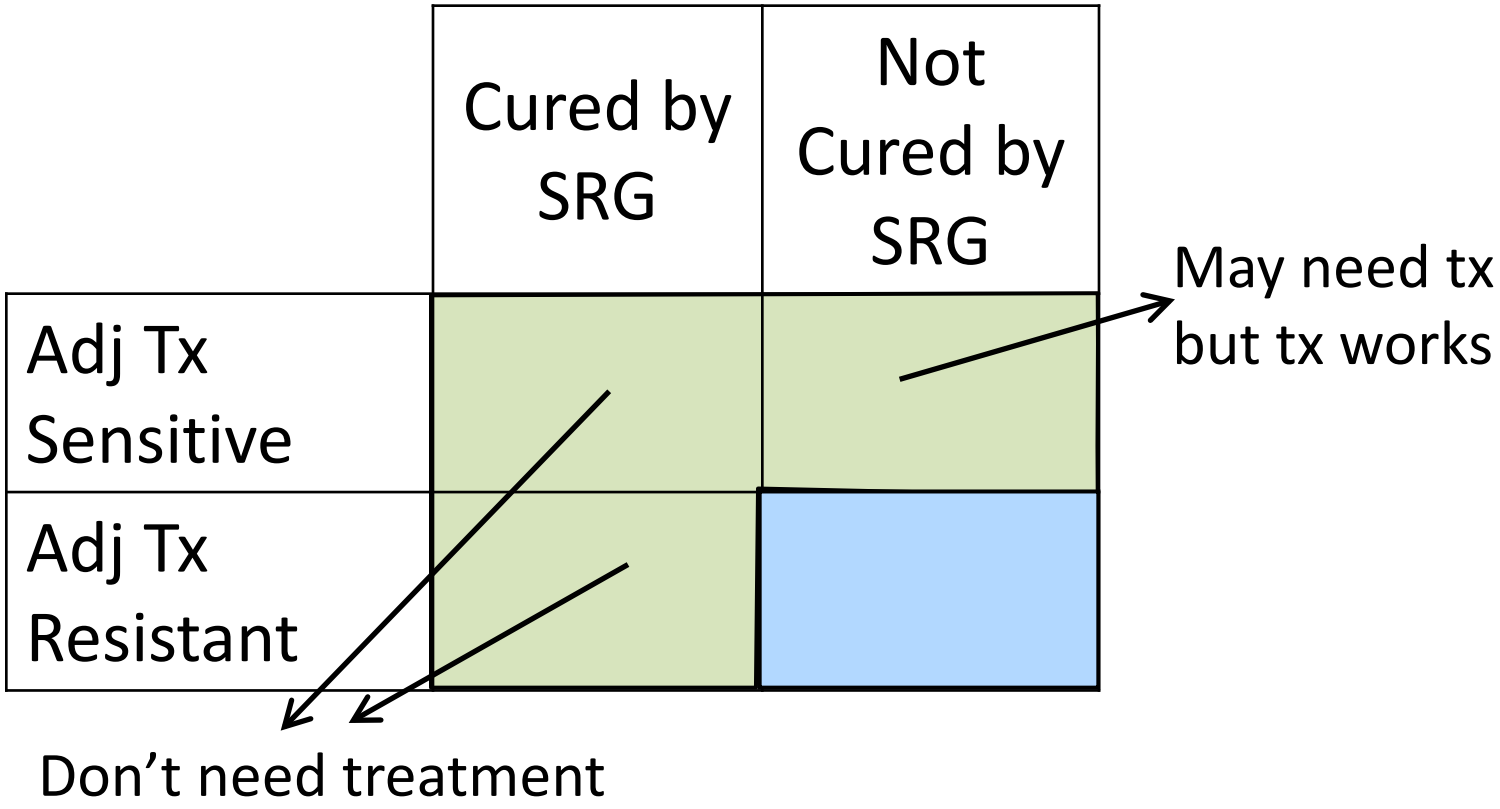

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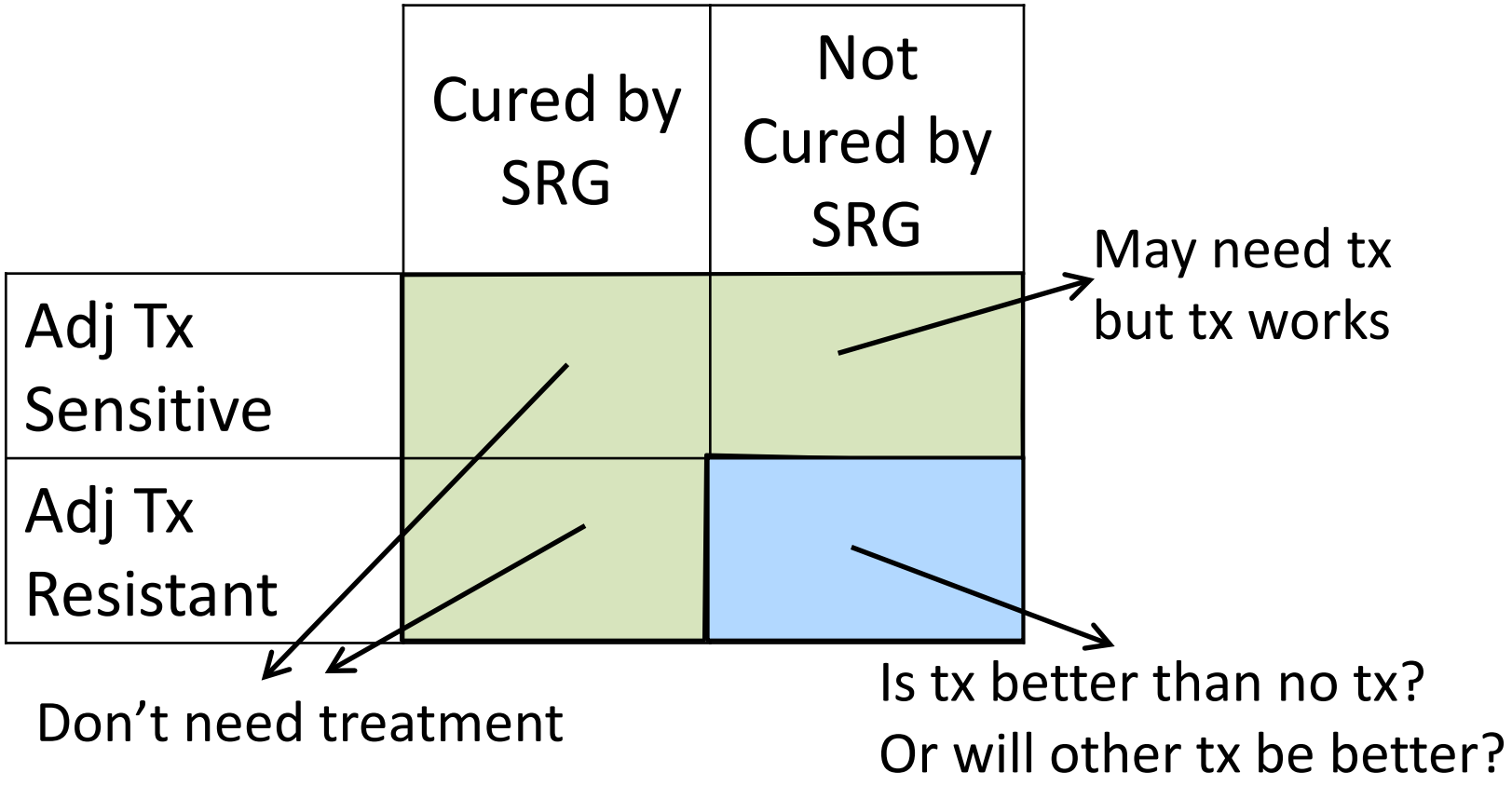

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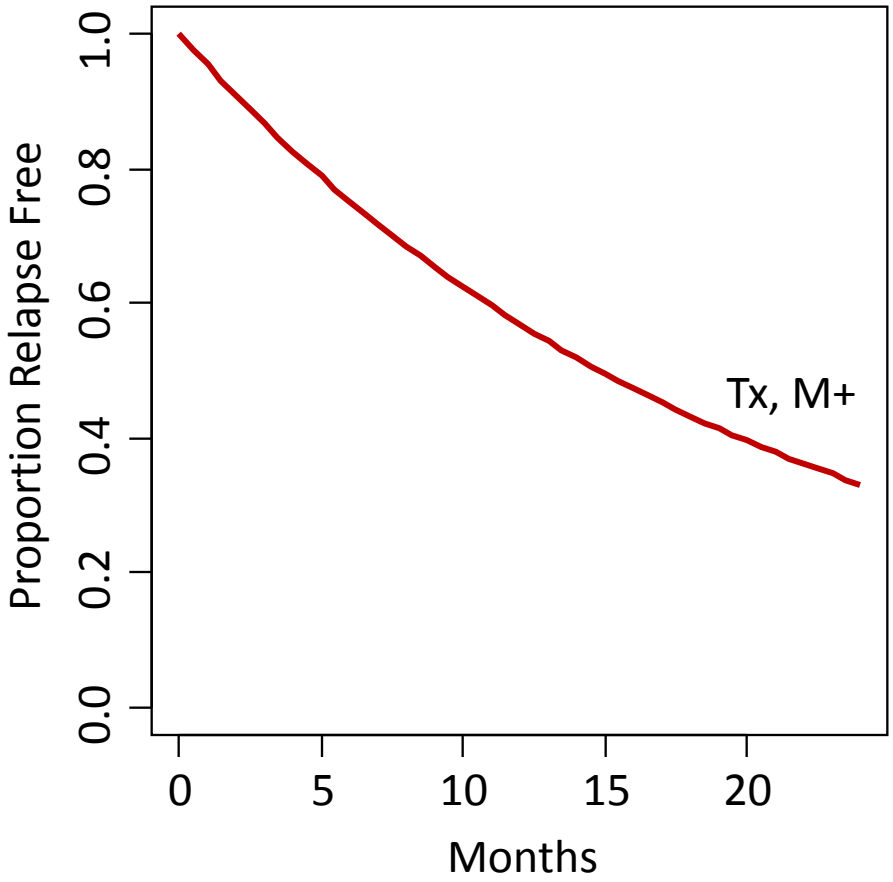
Are these studies helpful?



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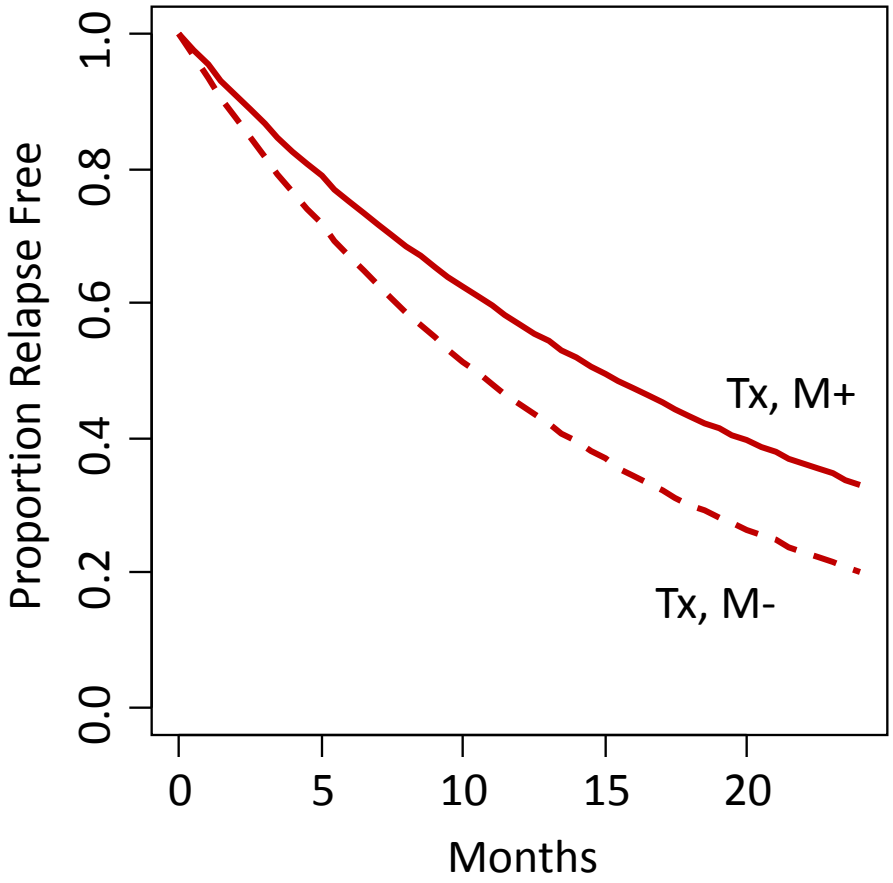

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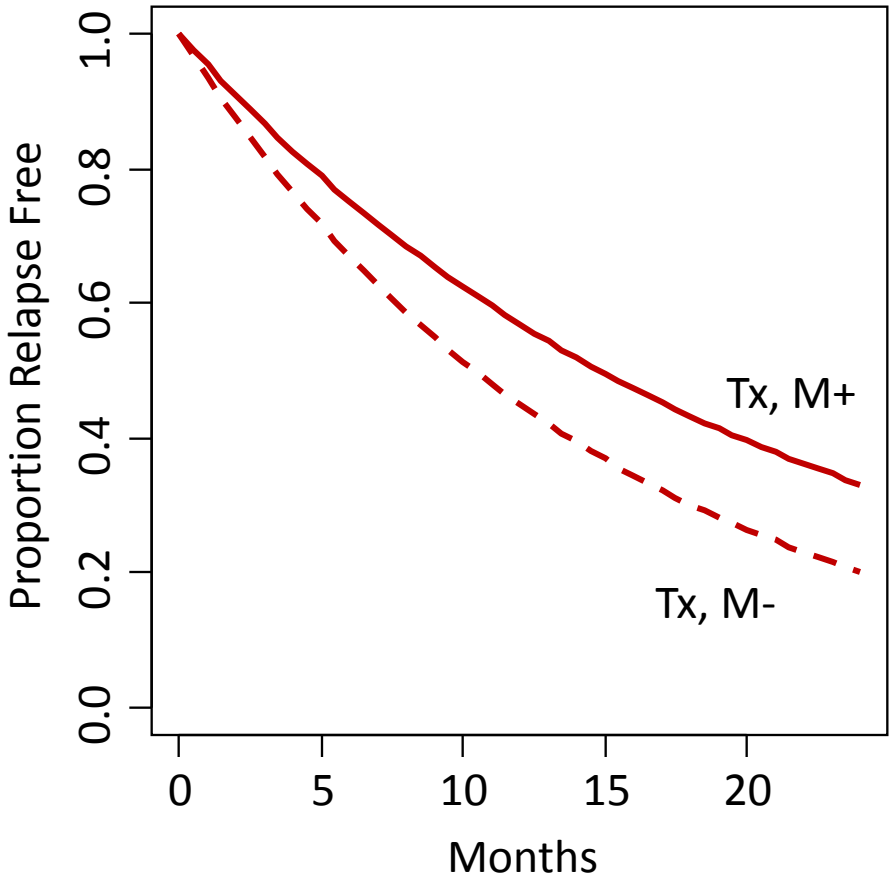

Ex: retrospective study of biomarker in resected, tamoxifen treated cases

Might be prognostic, need control.

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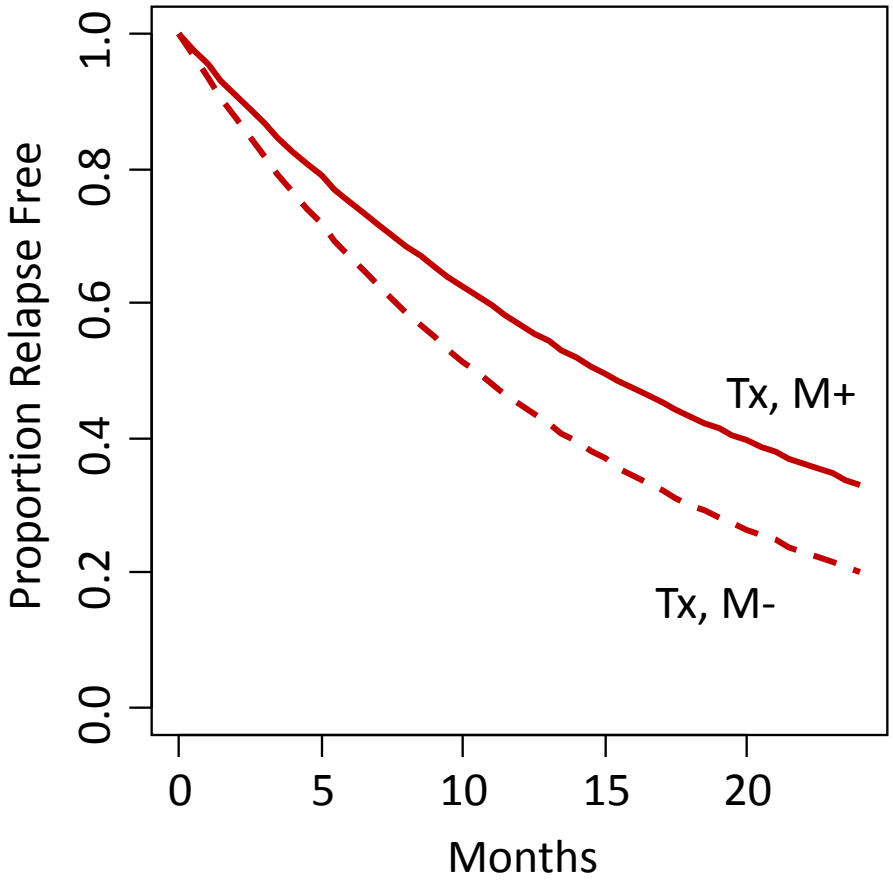

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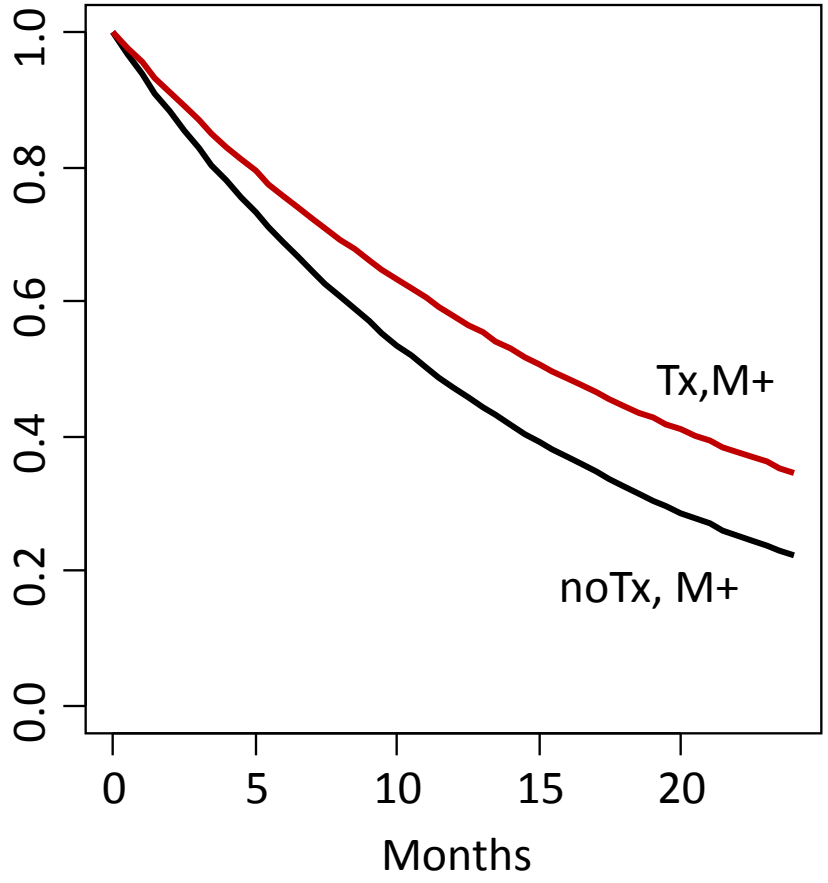
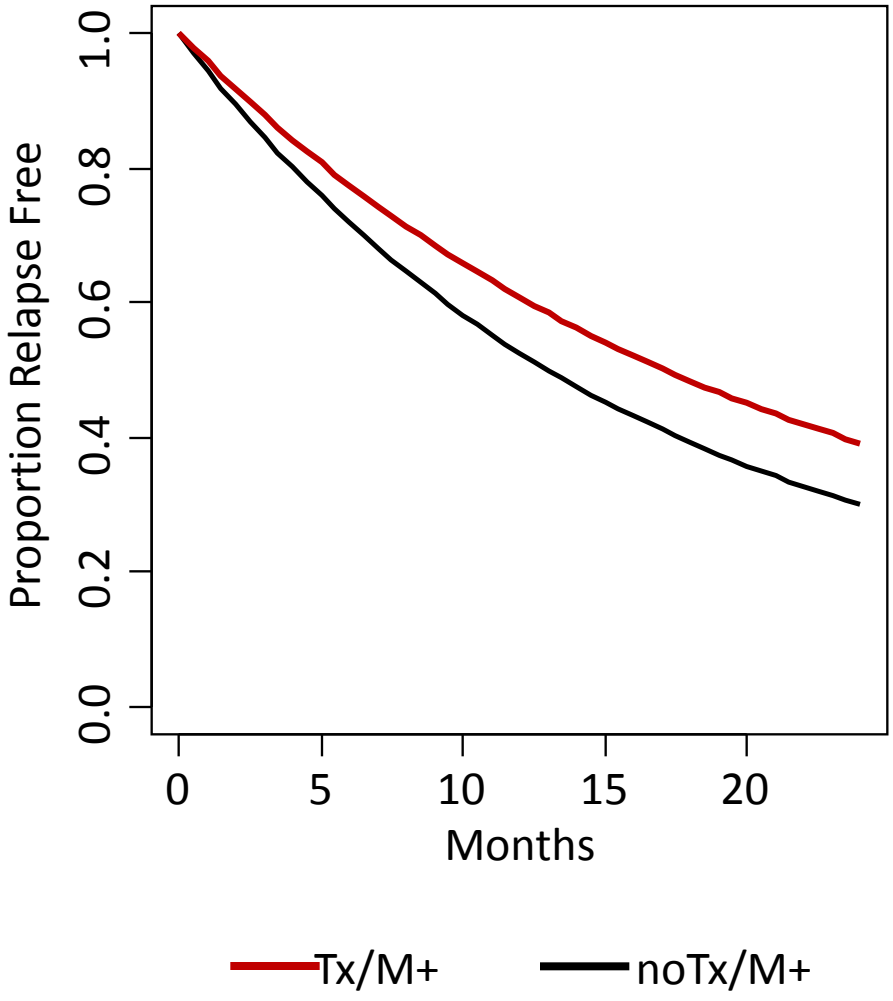


Ex: prospective study of GFR inhibitor vs placebo in GFR+ cases only

Might miss effect in GFR-

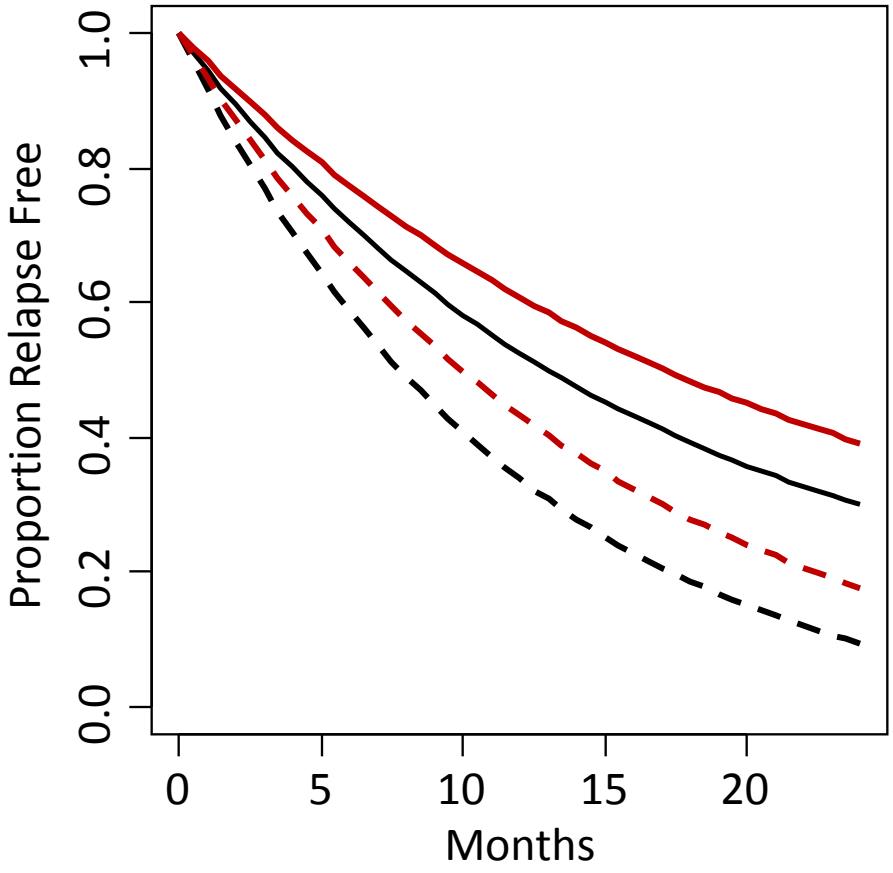
Extreme Possibilities



Extreme Possibilities

Prognostic, but NOT Predictive

Treatment Benefits Everyone Equally



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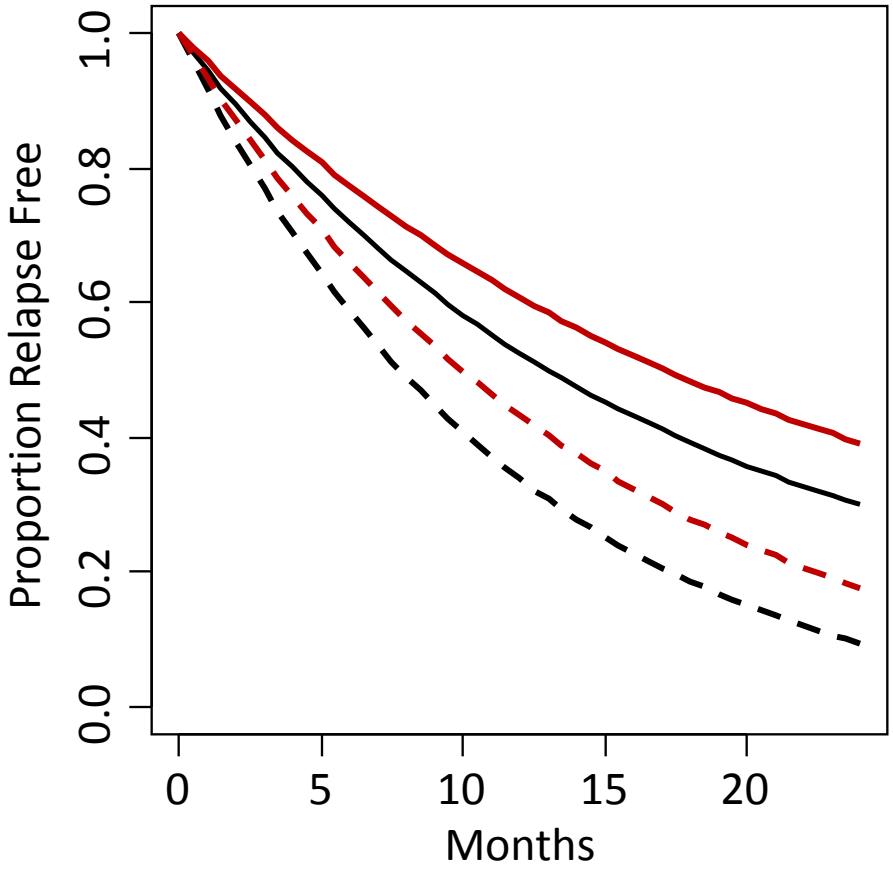
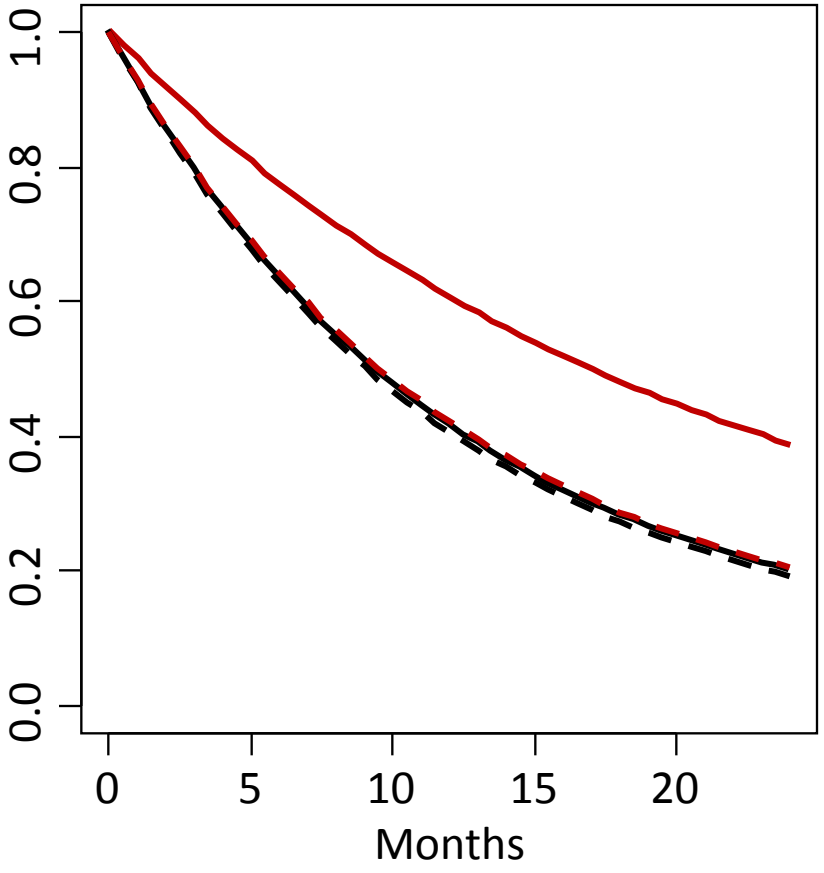


Predictive, but NOT Prognostic

Treatment Benefits only Marker +

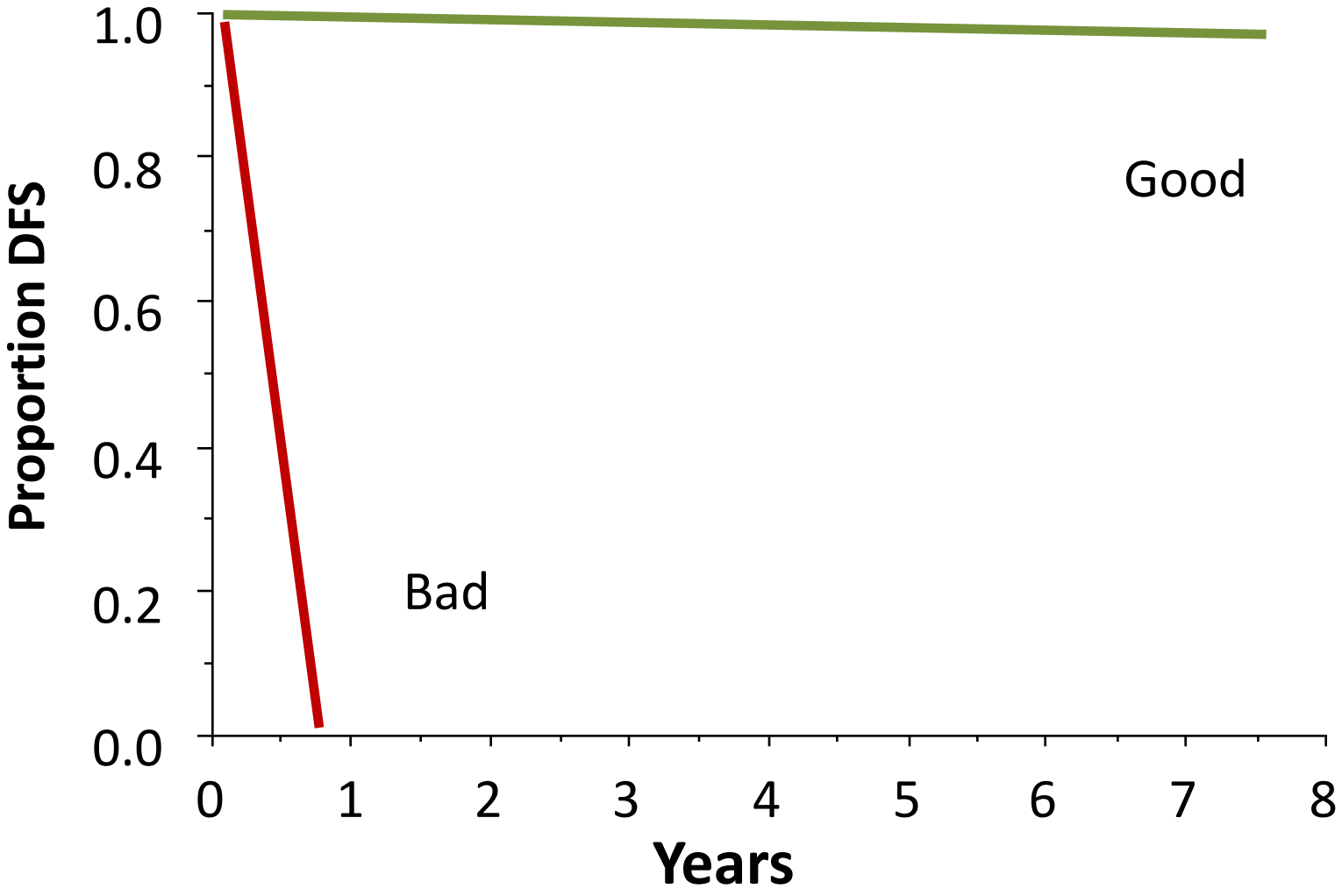


Tx/M+ noTx/M+ Tx/M- noTx/M-

Prognostic vs Predictive Biomarkers

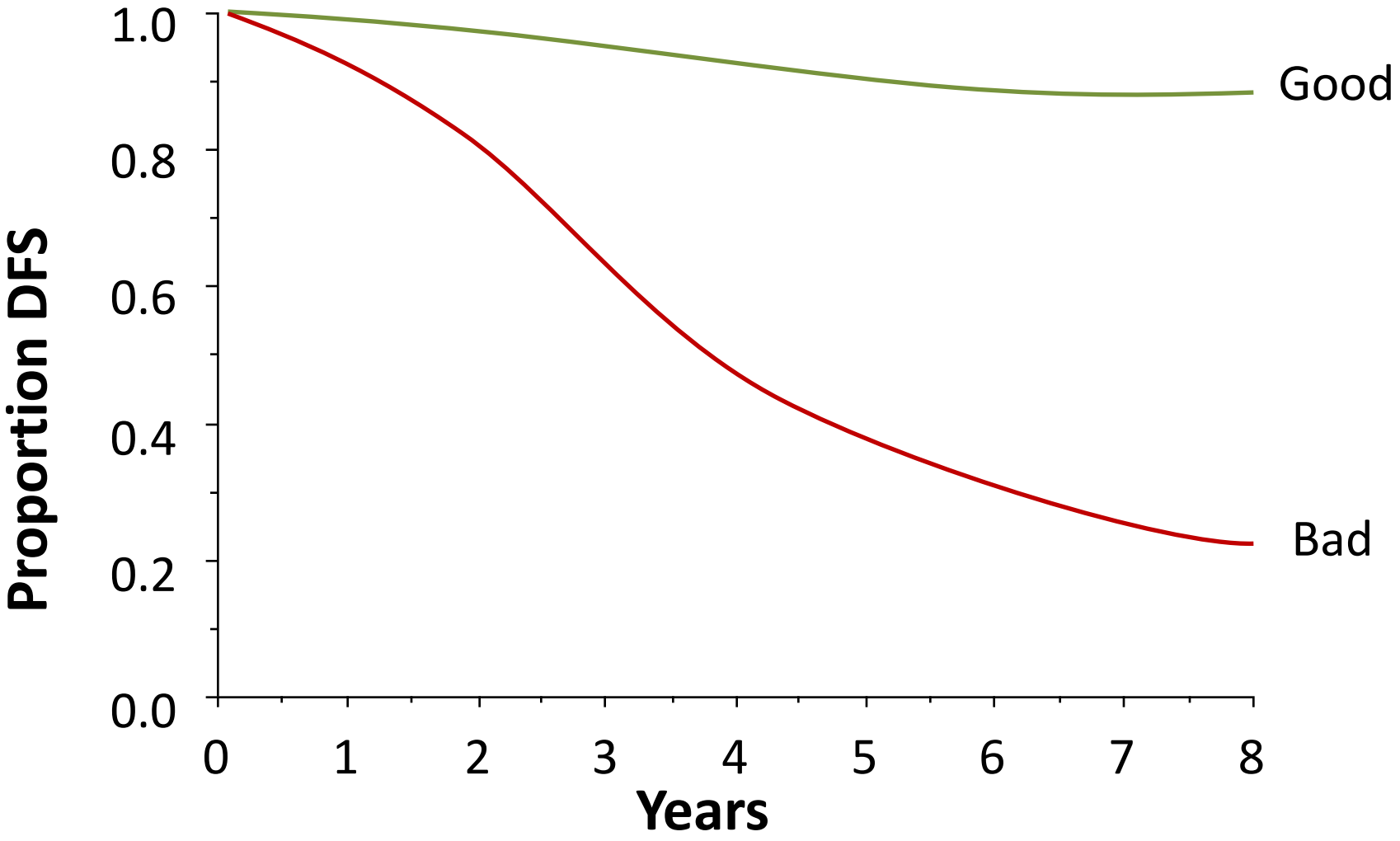
- Prognostic marker – natural history of disease, independent of treatment
  - Might indicate need for further treatment, but not WHICH treatment
- Predictive marker – benefit from specific treatment; helps to select particular treatment over another
- How good does the marker have to be?
  - What is “actionable”?

Ideal Prognostic Biomarker



“Actionable” Prognostic Biomarker?

Statistical vs Clinical Significance



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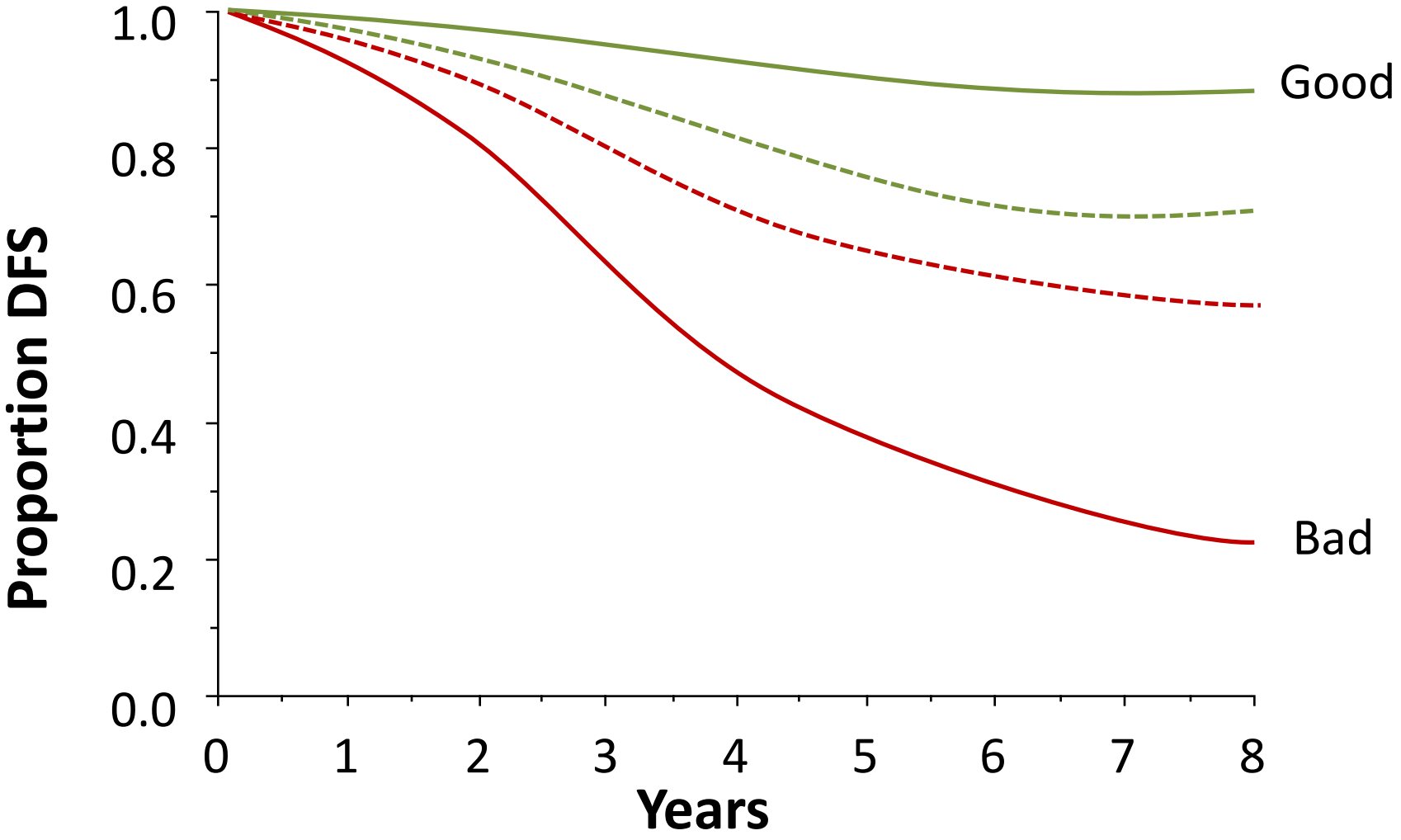
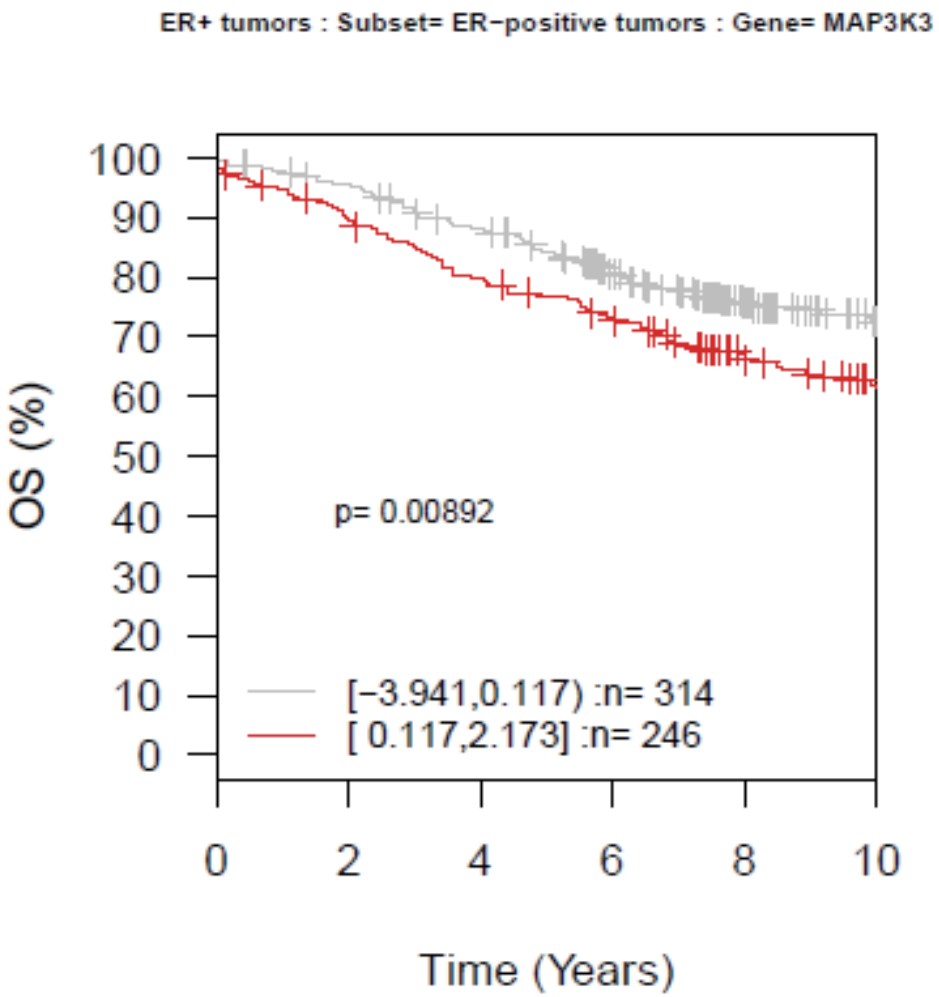


How often have you seen this?

"We analyzed publically available breast cancer data to evaluate the effect of MAP3K3 on outcome. MAP3K3 is an important new prognostic biomarker."



http://co.bmc.lu.se/gobo/gsa.pl

Pros:

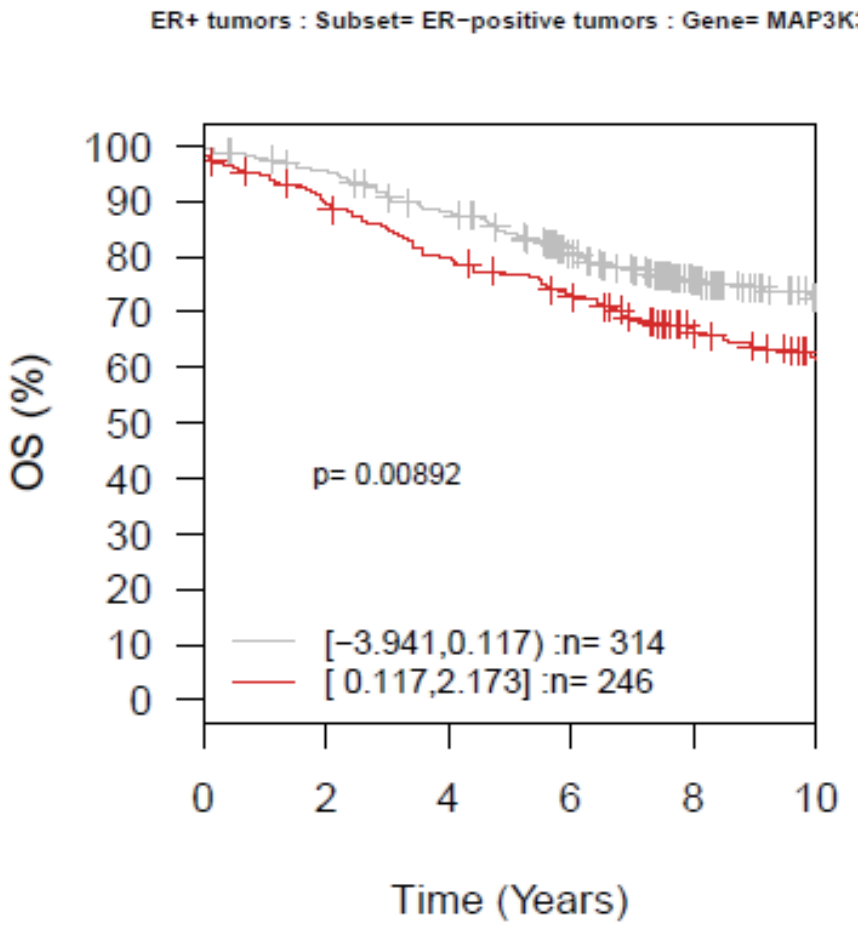
- Cheap and easy
- Many tools available to wet lab investigators
- Can provide clues for further study

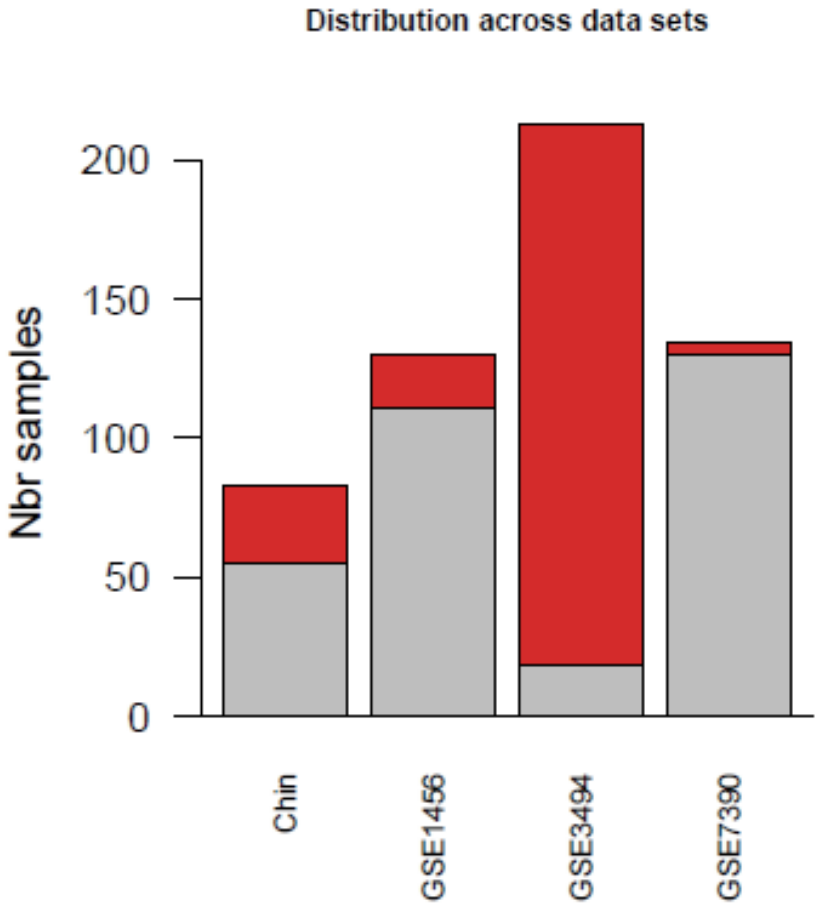
Cons:

- Many tools available to wet lab investigators
- Statistically significant, BUT is it clinically significant?
- Same "flawed" datasets have been re-analyzed 100's of times
- Important sources of confounding often totally ignored
  - Batch effects in assay
  - Differences in selection or clinical characteristics (i.e. stage, subtype)
  - Mixtures of treatments, etc

How often have you seen this?

Analysis of Publically Available Data: MAP3K3





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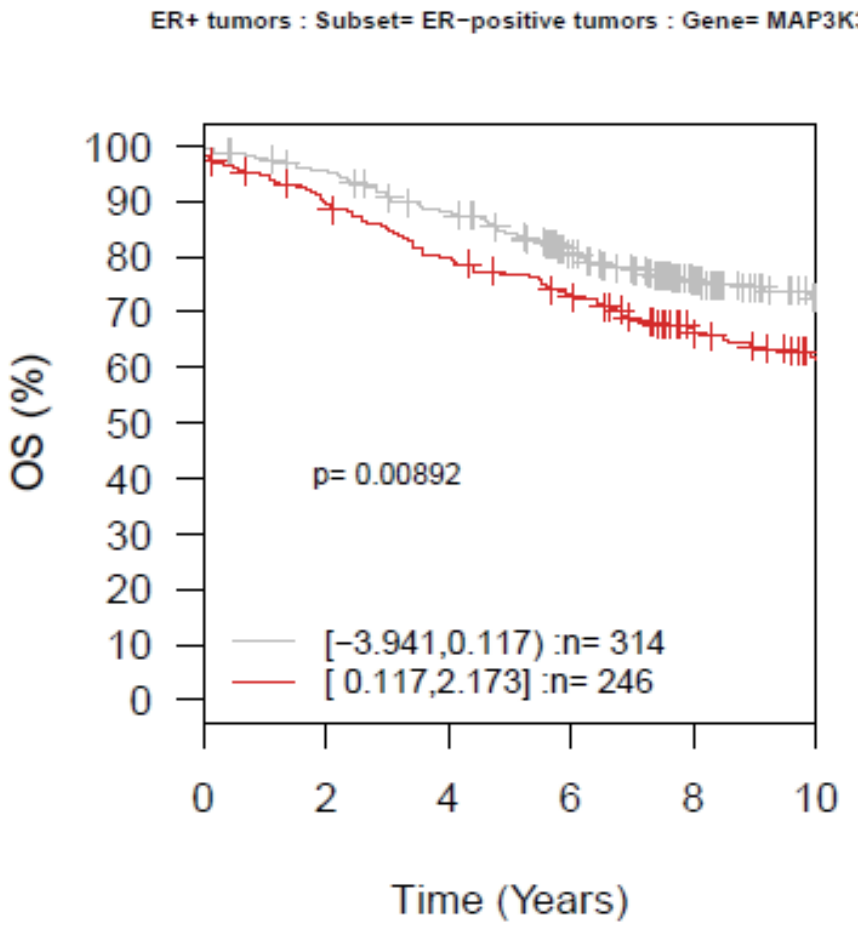

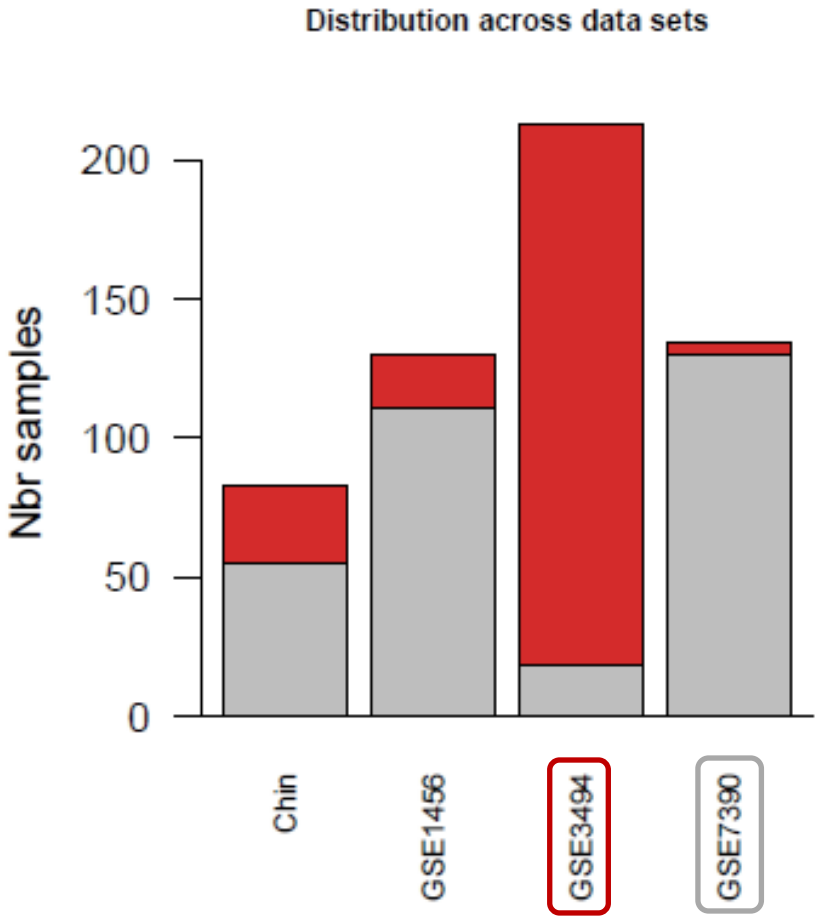

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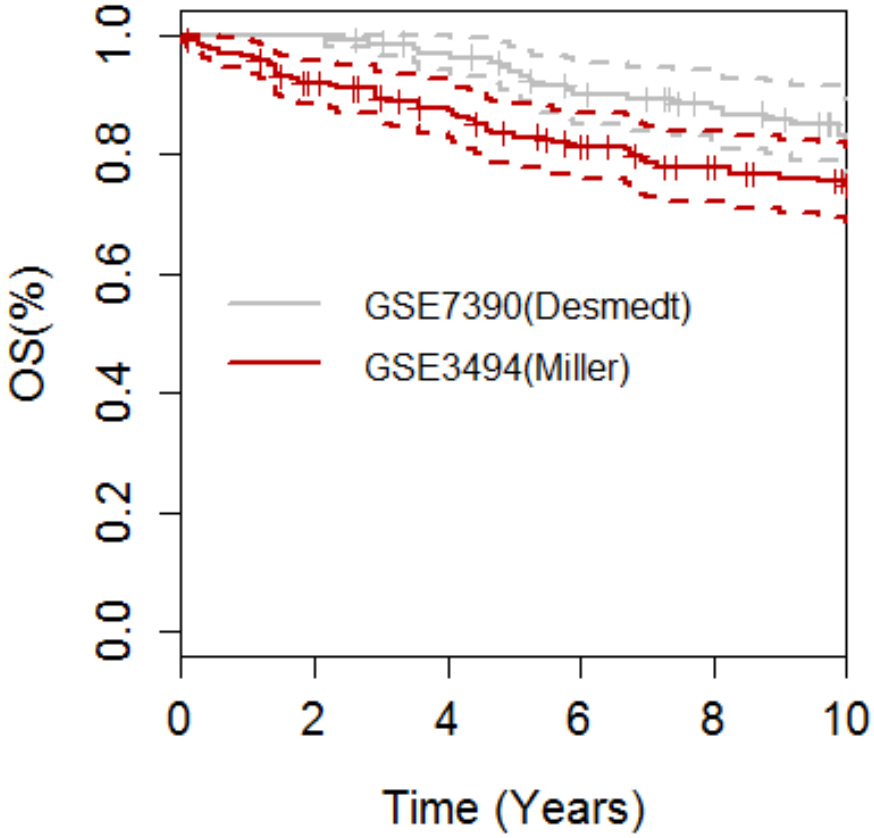
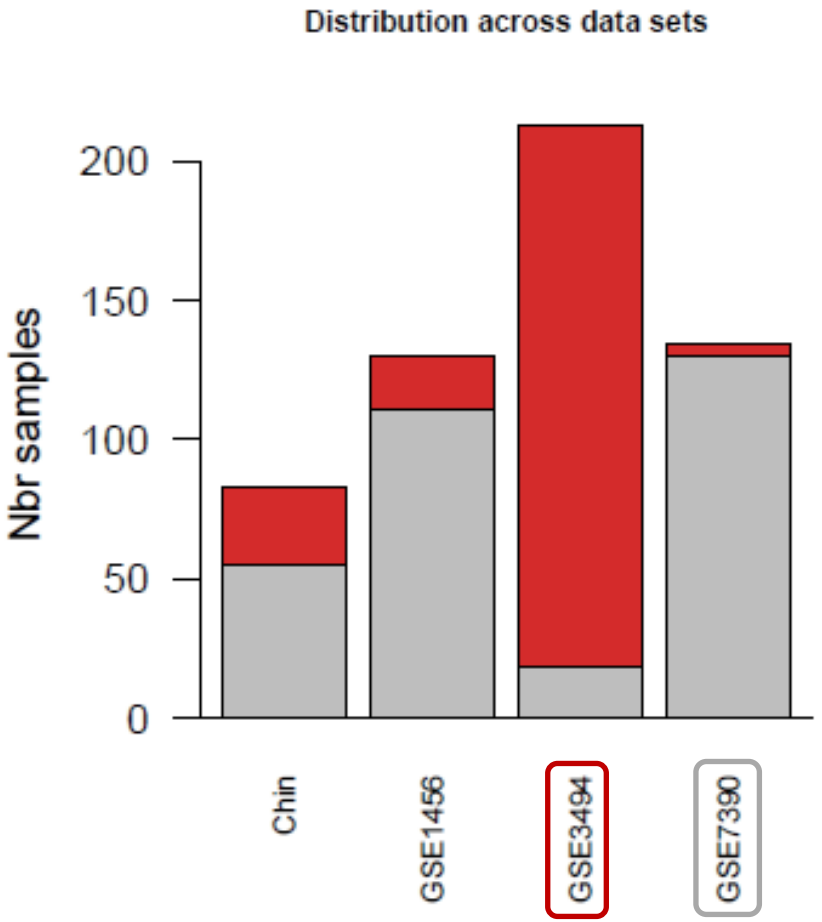
Is this really prognostic?





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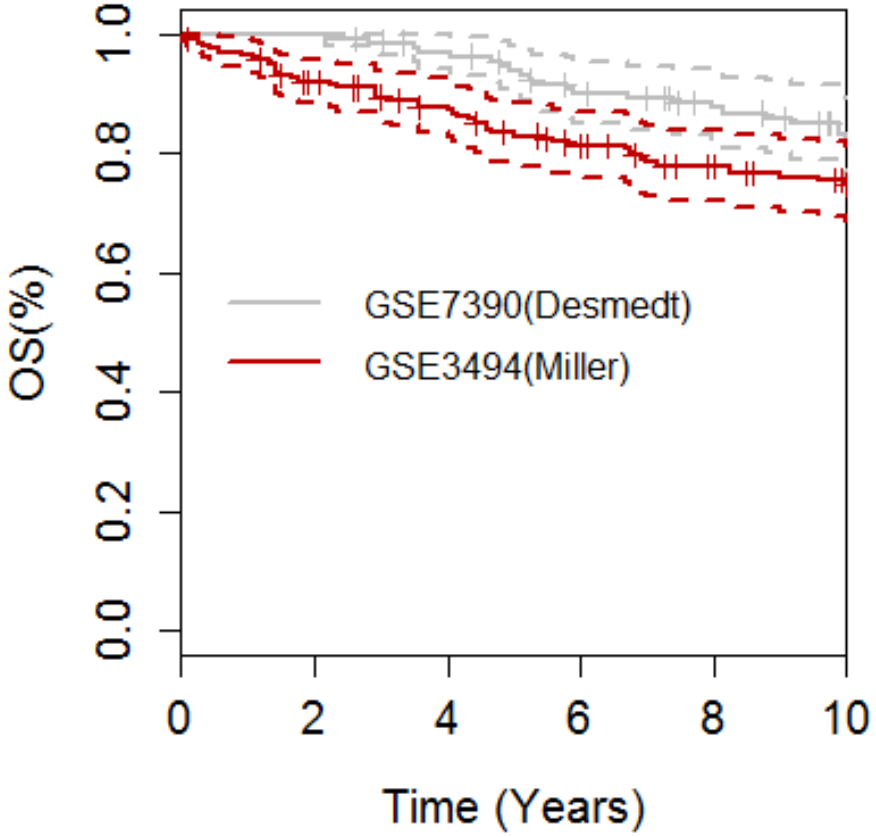

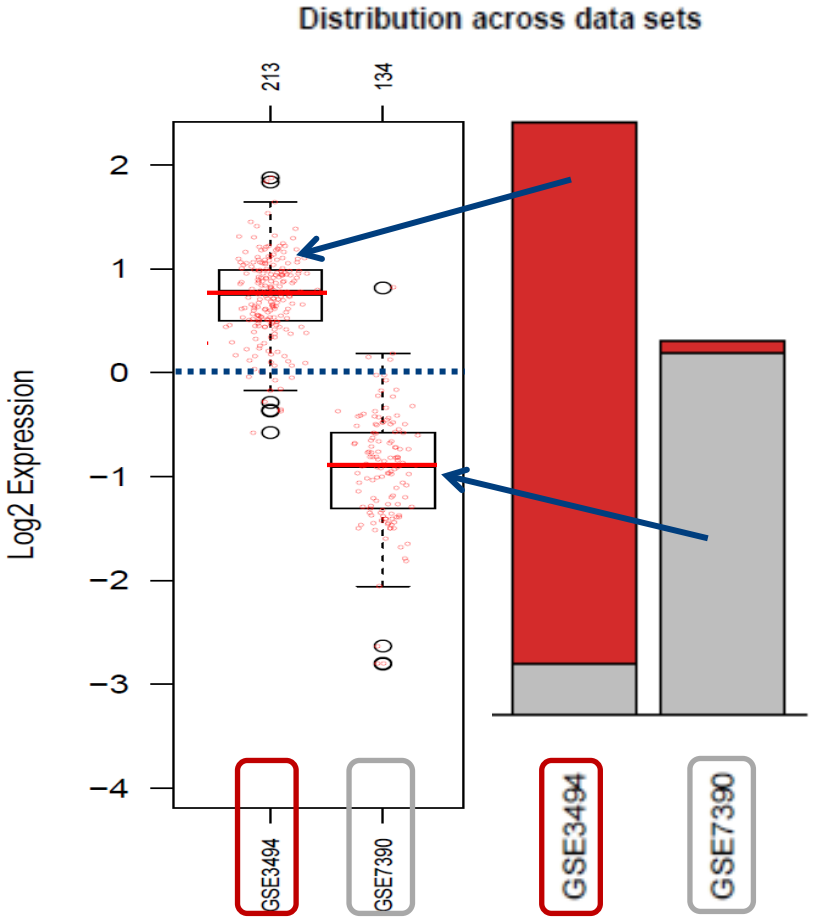

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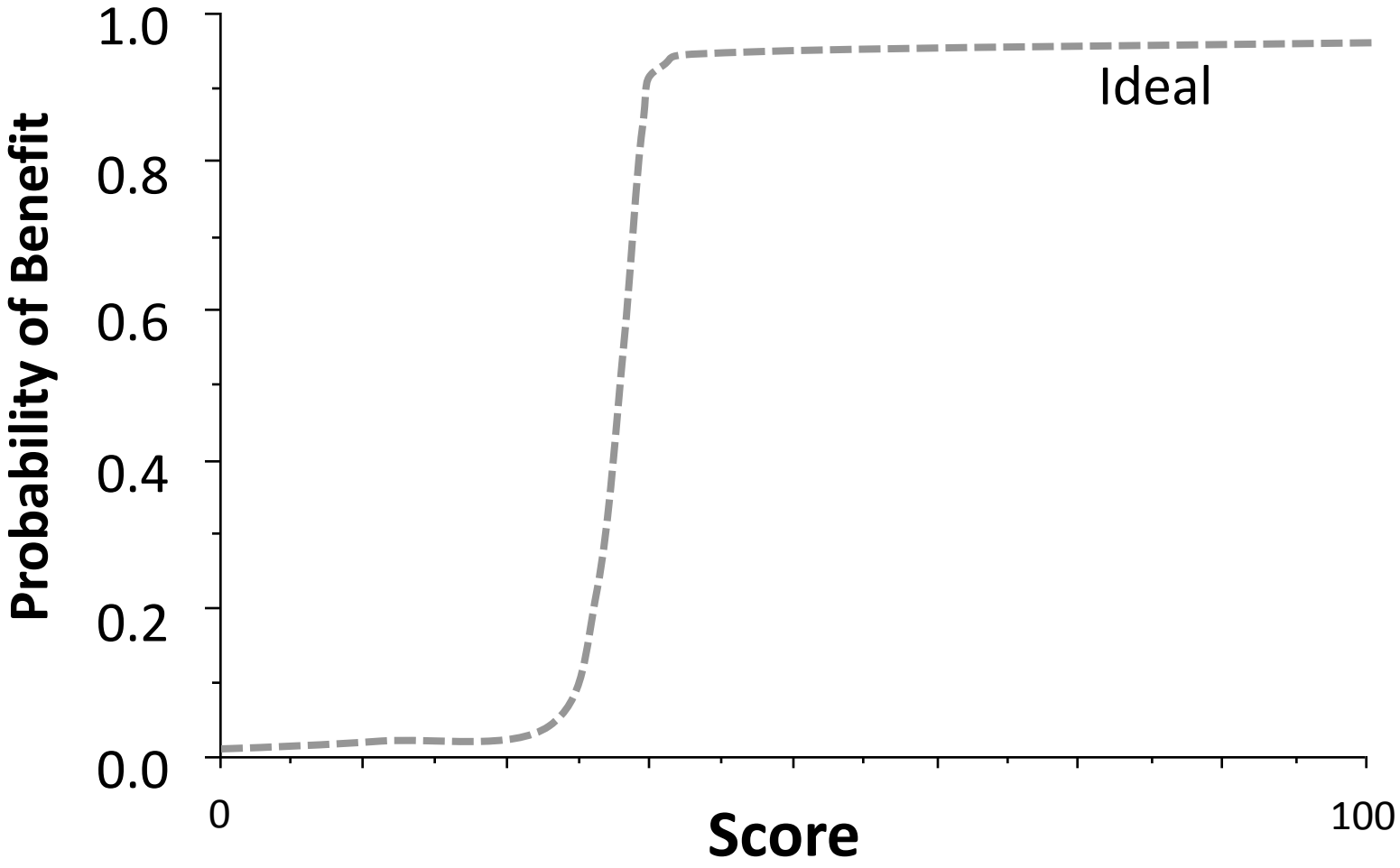
"Actionable" Predictive Biomarker?

Clinical vs Statistical Significance



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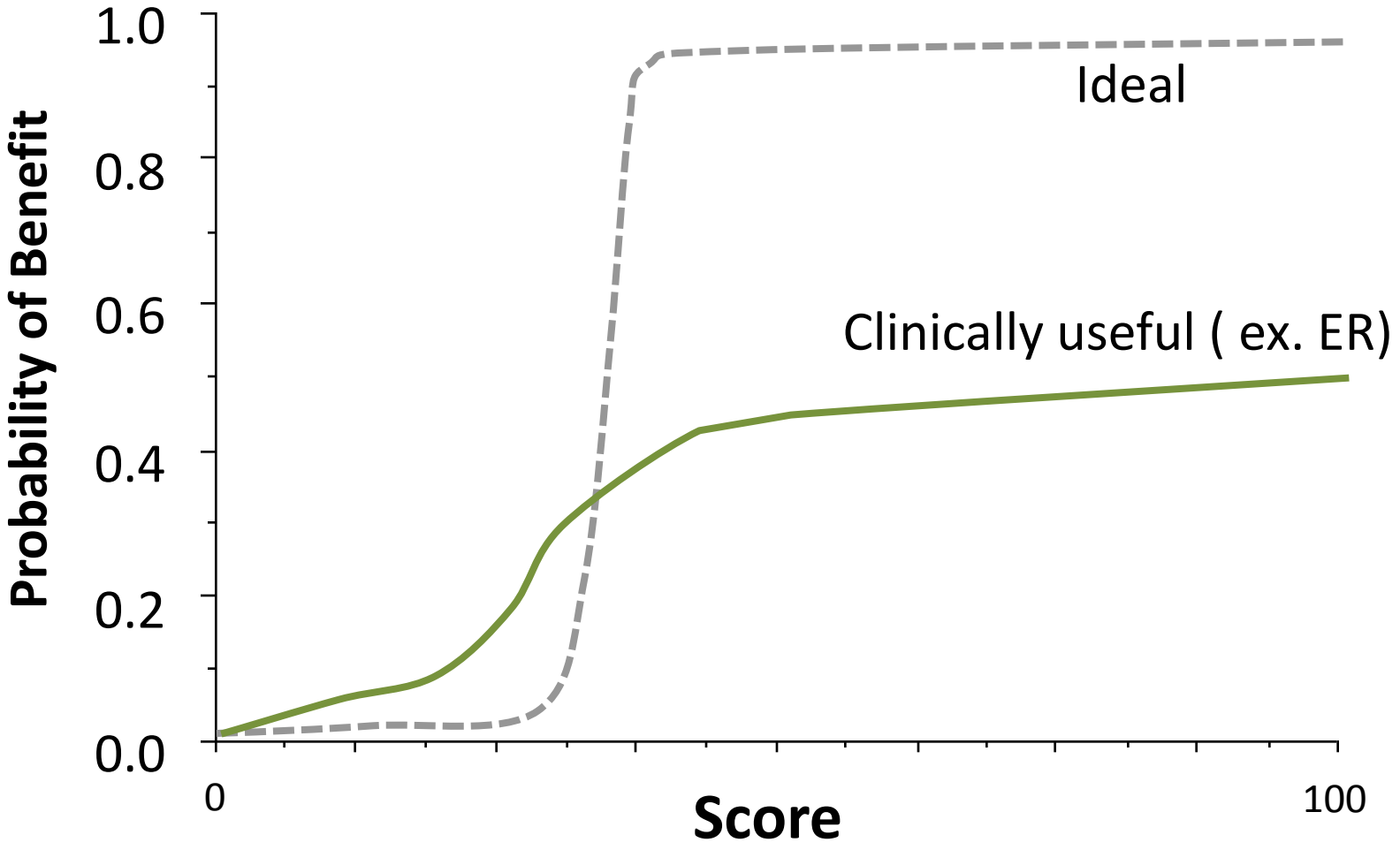

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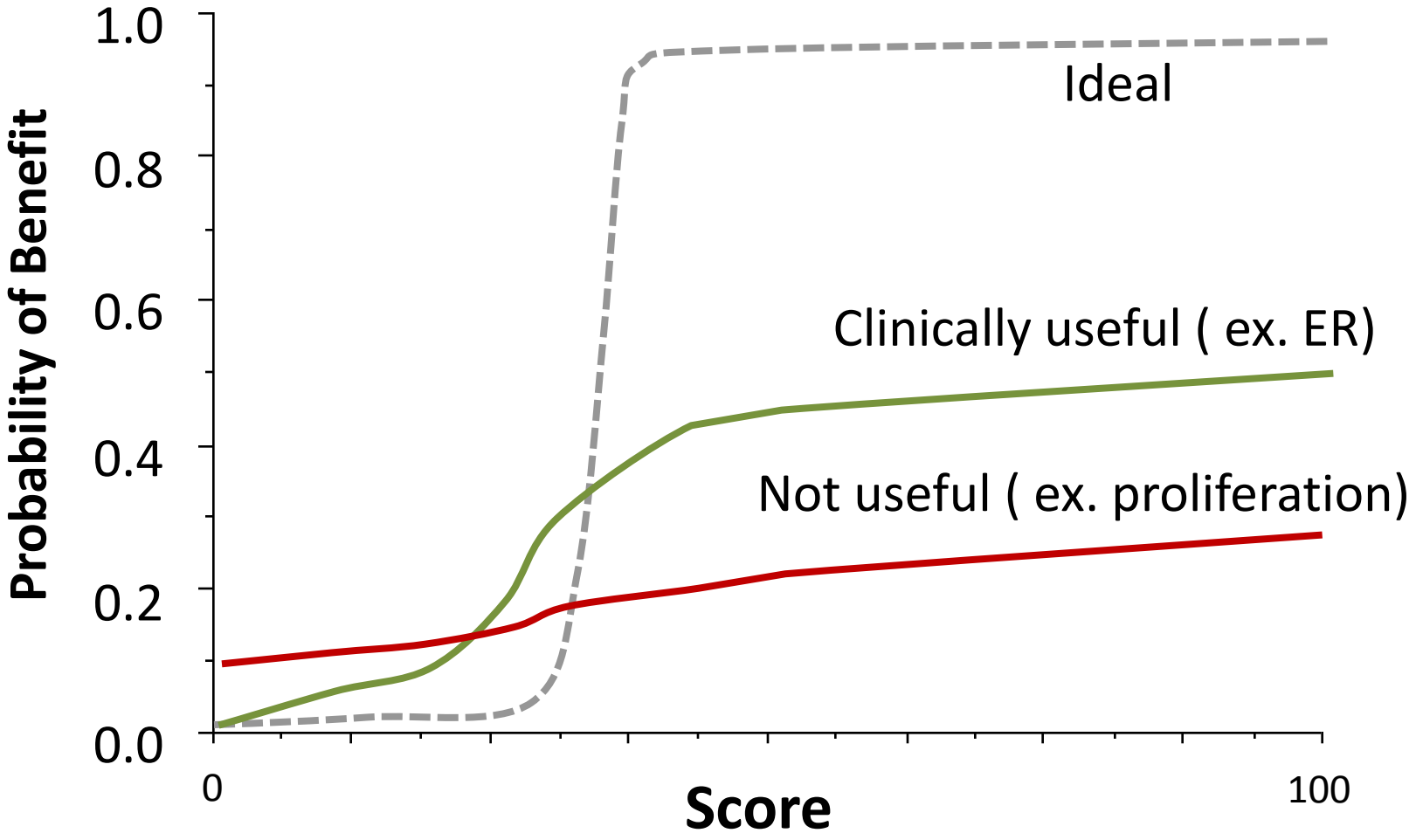


A Few of the Many Questions to Ask …

- **What is the role of biomarker in trial?**
- **Is there an assay? (discussion for lab)**
- **Should we take all comers or select?**
- **What is the appropriate endpoint?**
- **What is the appropriate design? (more on this in other talks)**

Phases of Drug Development

Preclinic
- Laboratory/animal models; Mechanism and target?

Phase 1
- Determine dose; Preliminary toxicity; Biomarker?
- N in low 10's

Phase 2
- Evidence of efficacy; Further experience with toxicity; Biomarker?
- N in high 10's to 100's

Phase 3
- Definitive evidence of efficacy; Toxicity; Validation of biomarker
- N in 100's to 1000's

Phase 4
- Post-marketing surveillance

Additional issues for co-development with biomarker:

Decide to select or not to select?

Show reliability of assay prior to, or with early clinical trials

Role of Marker in a Study

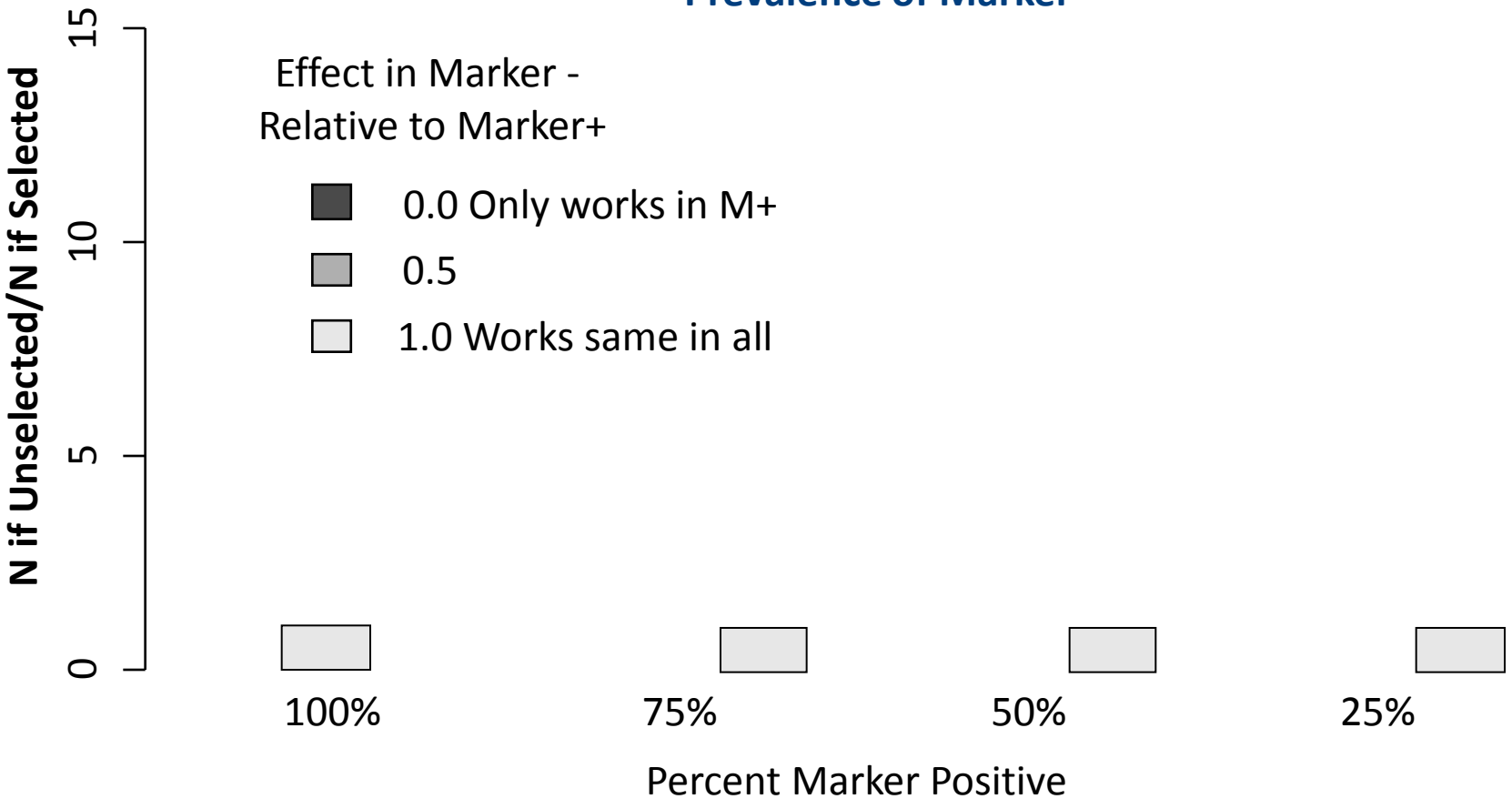
- *Integral* – assessed in order for study to proceed (i.e. eligibility or stratification); CLIA in USA
- *Integrated* – intended to validate assays and biomarker; trials test hypotheses with prespecified plans
- *Ancillary or exploratory* – trial data used to develop biomarker or assays, understand agent or biology

Dancey, J. E., K. K. Dobbin, et al. (2010). "Guidelines for the development and incorporation of biomarker studies in early clinical trials of novel agents." Clin Cancer Res **16**(6): 1745-55.

To Select or Not To Select

Relative Efficiency of Unselected vs Selected Designs Depends on:

- Performance of Assay
- **Distribution of Effect**
- **Prevalence of Marker**



After Simon and Maitournam. CCR 2004

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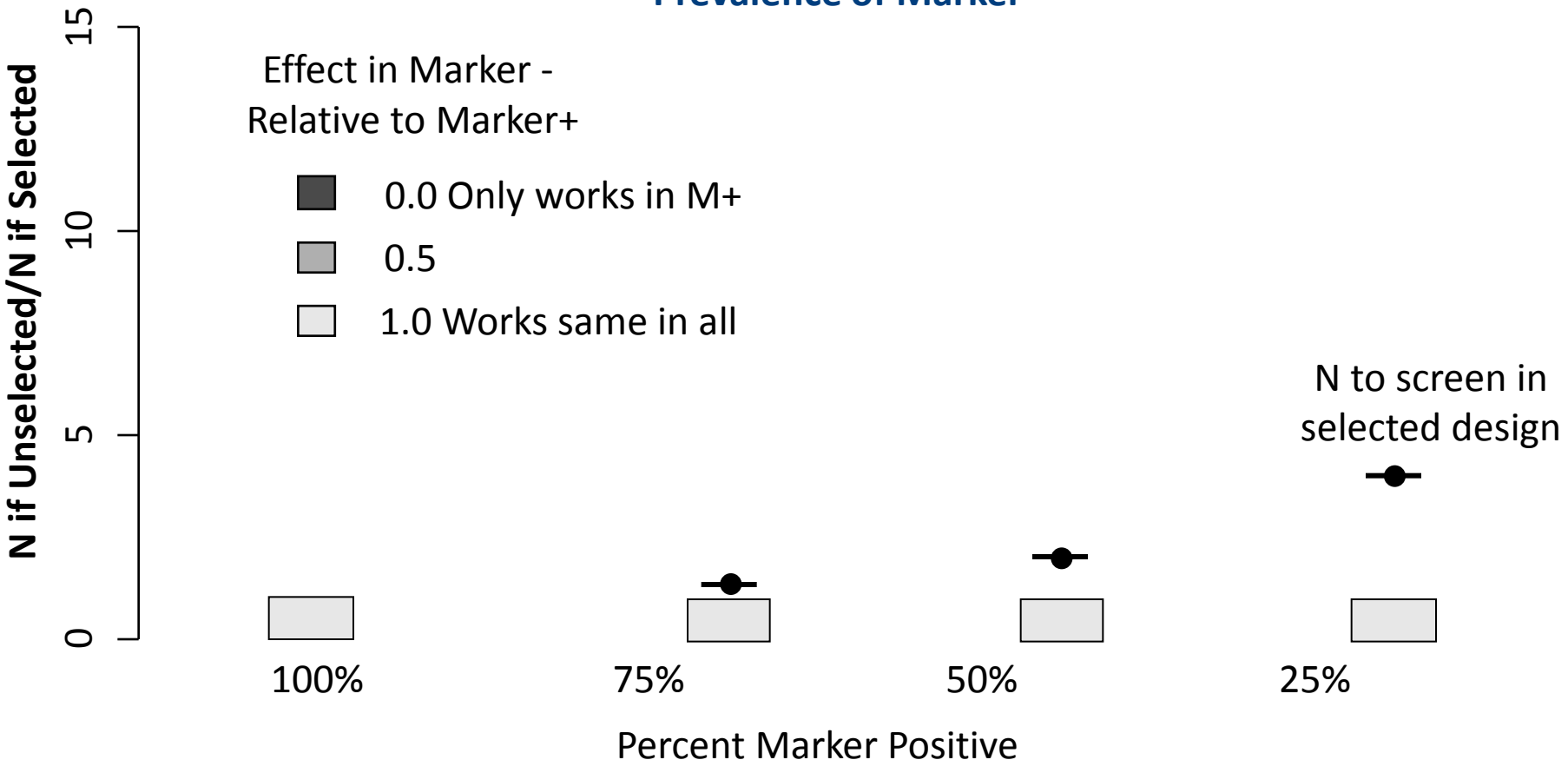

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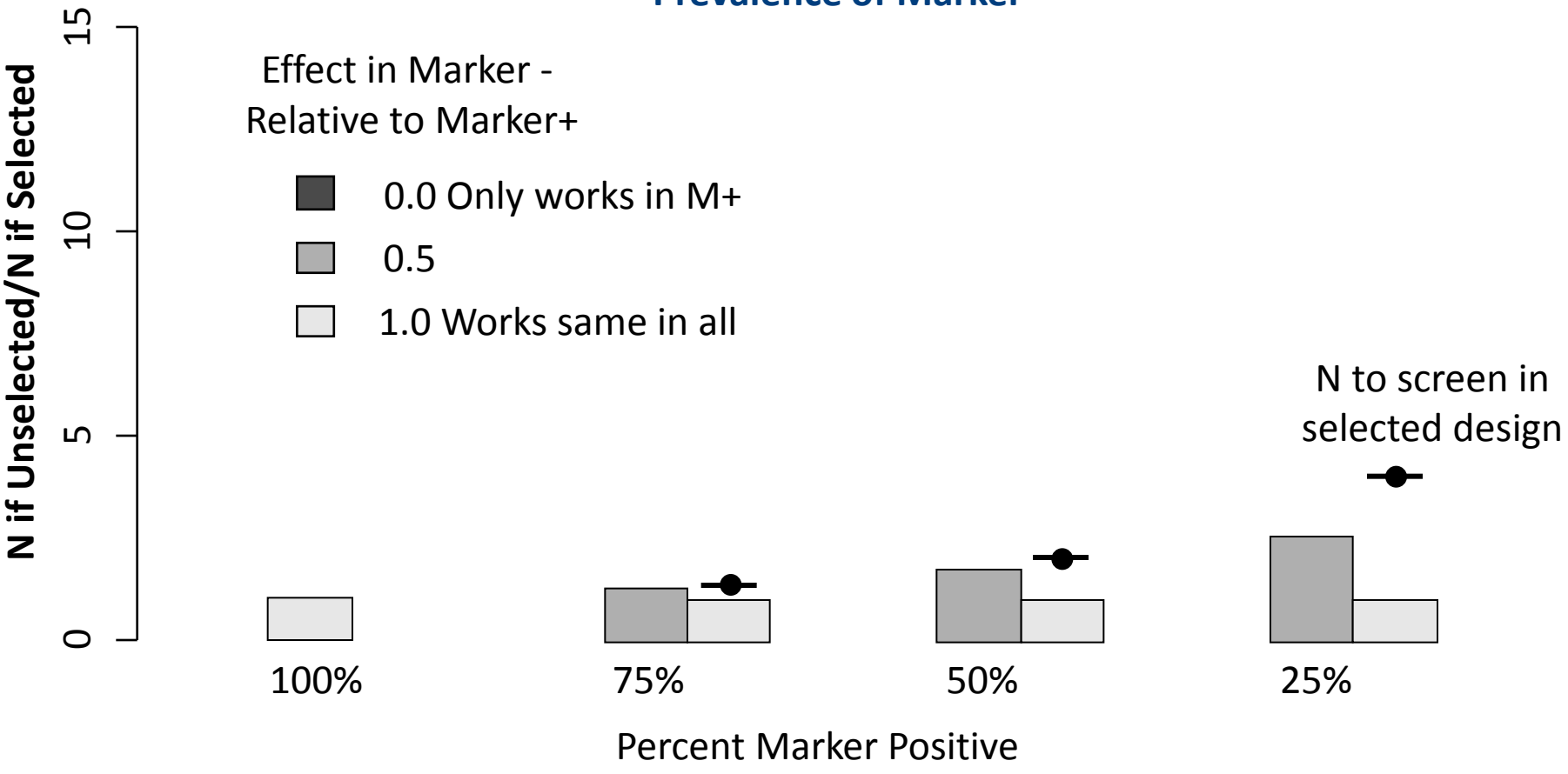

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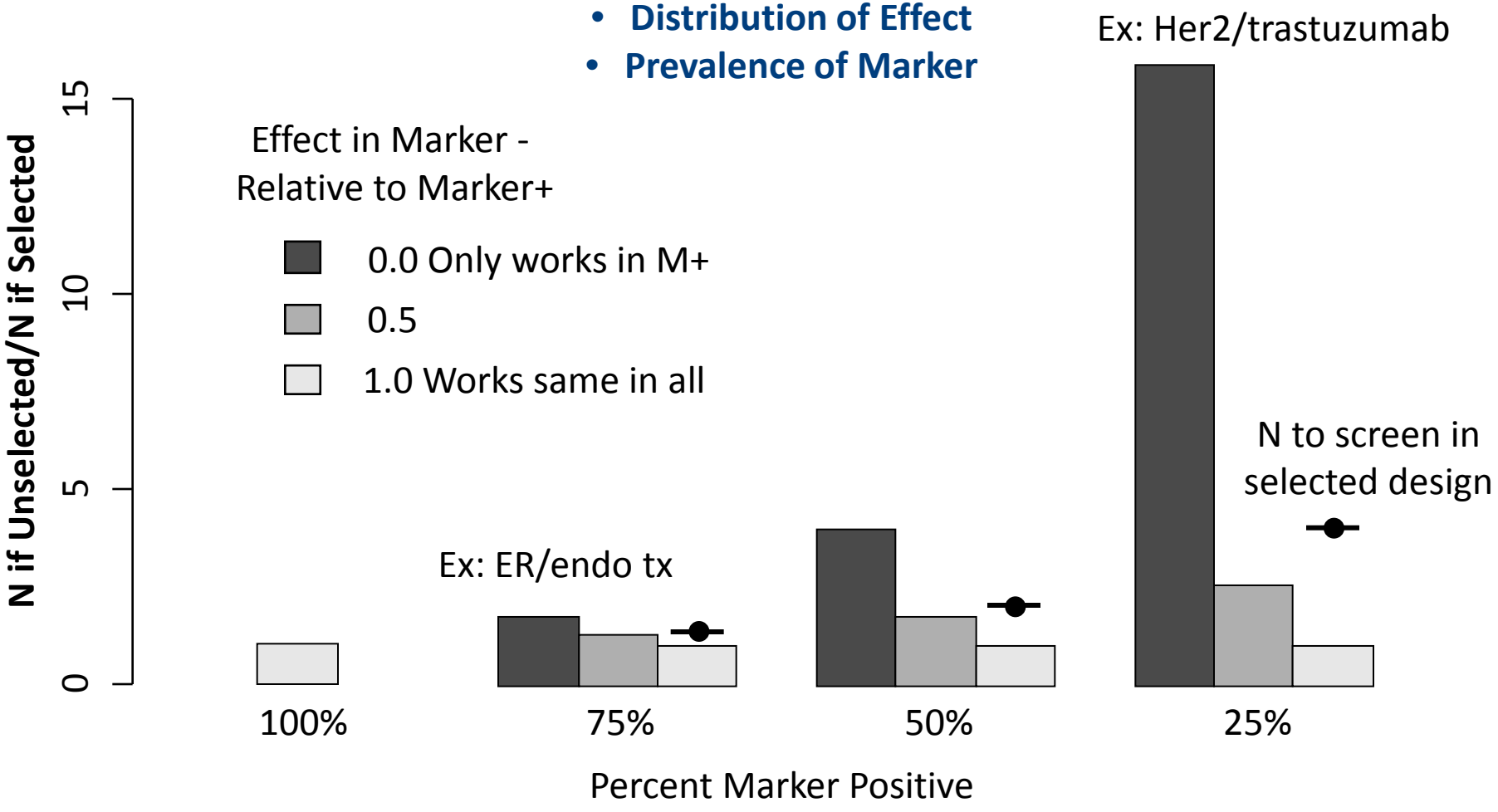

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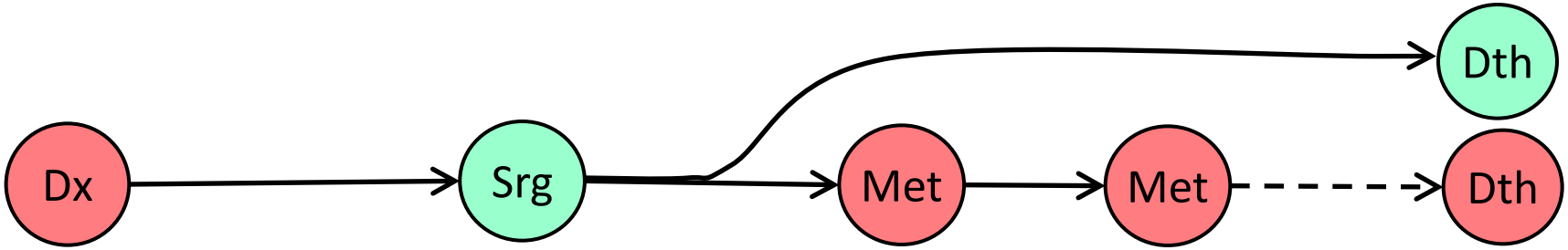

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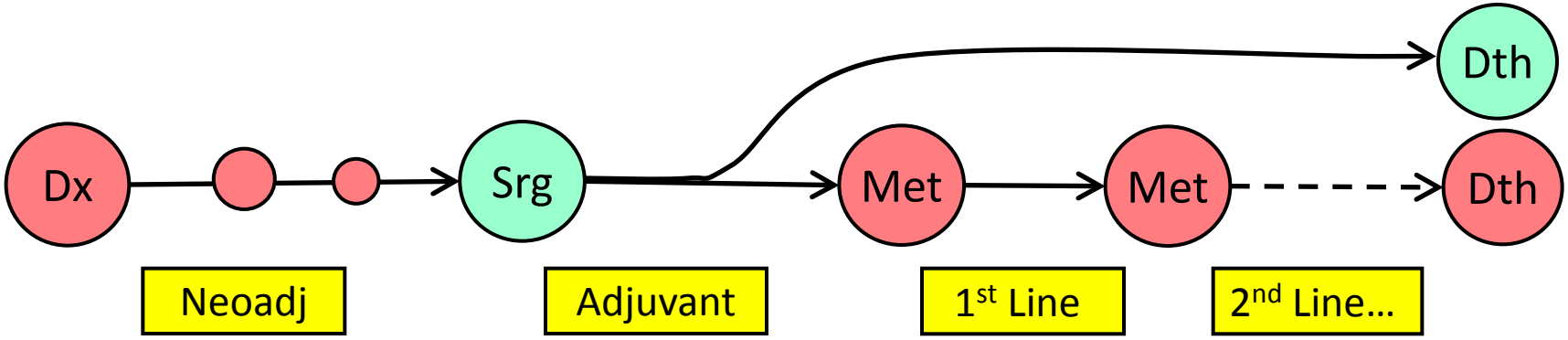

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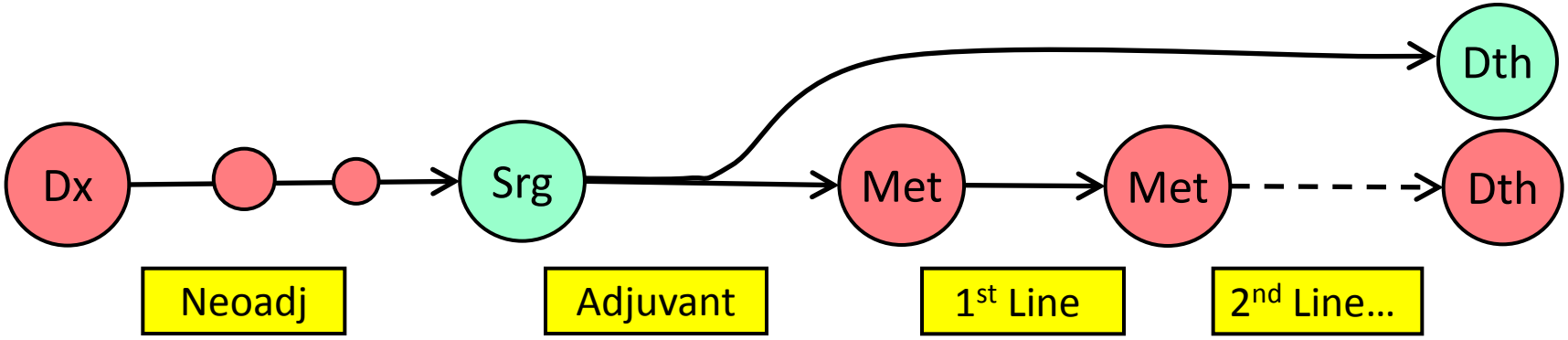

Mid-dev trials

Late trials

Early dev trials

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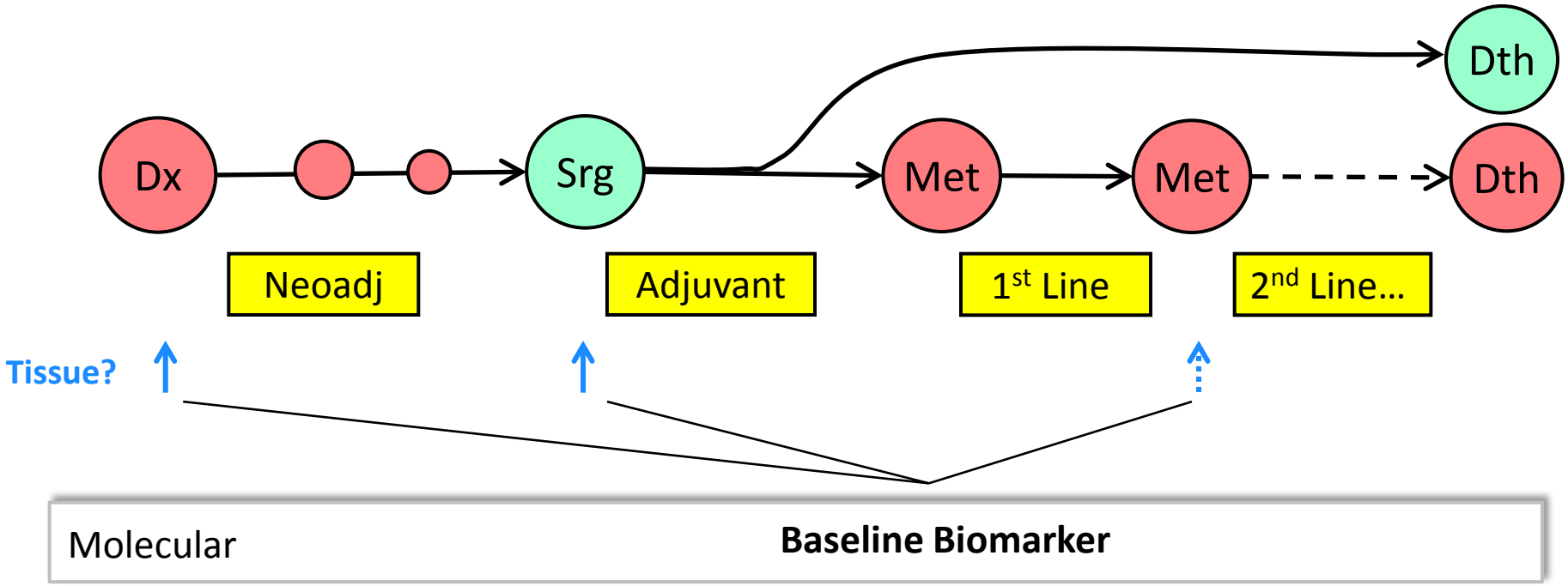

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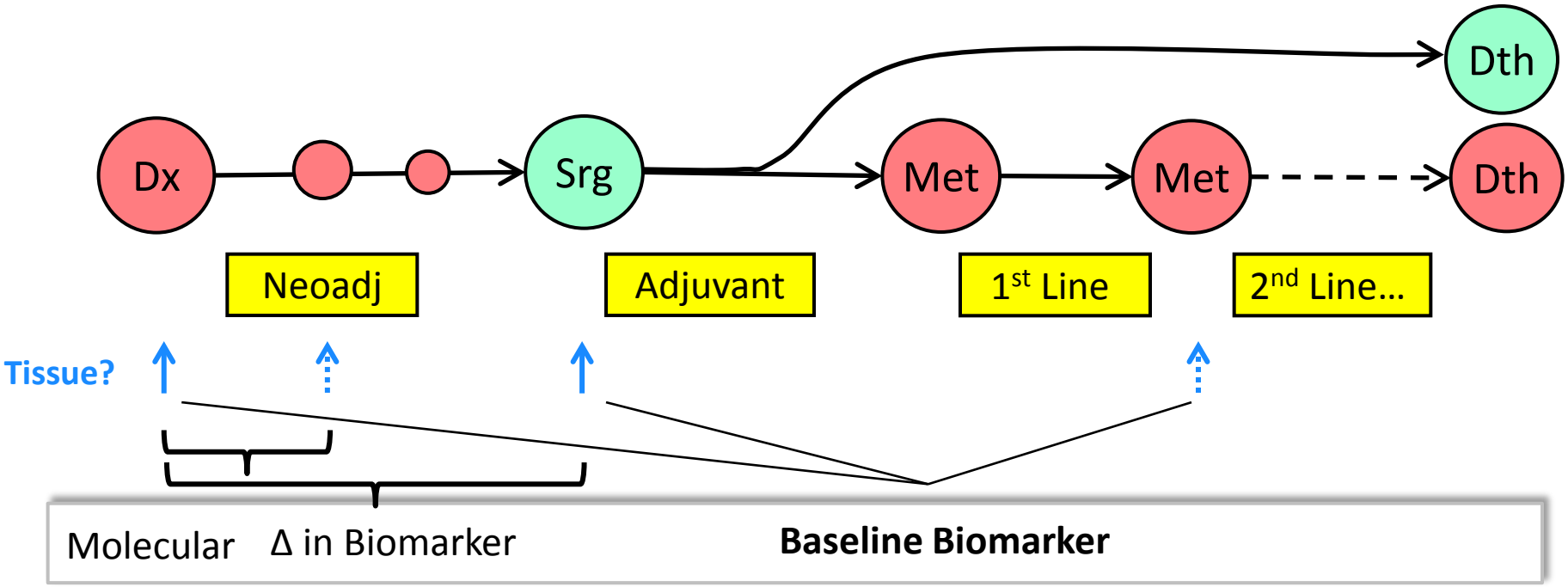

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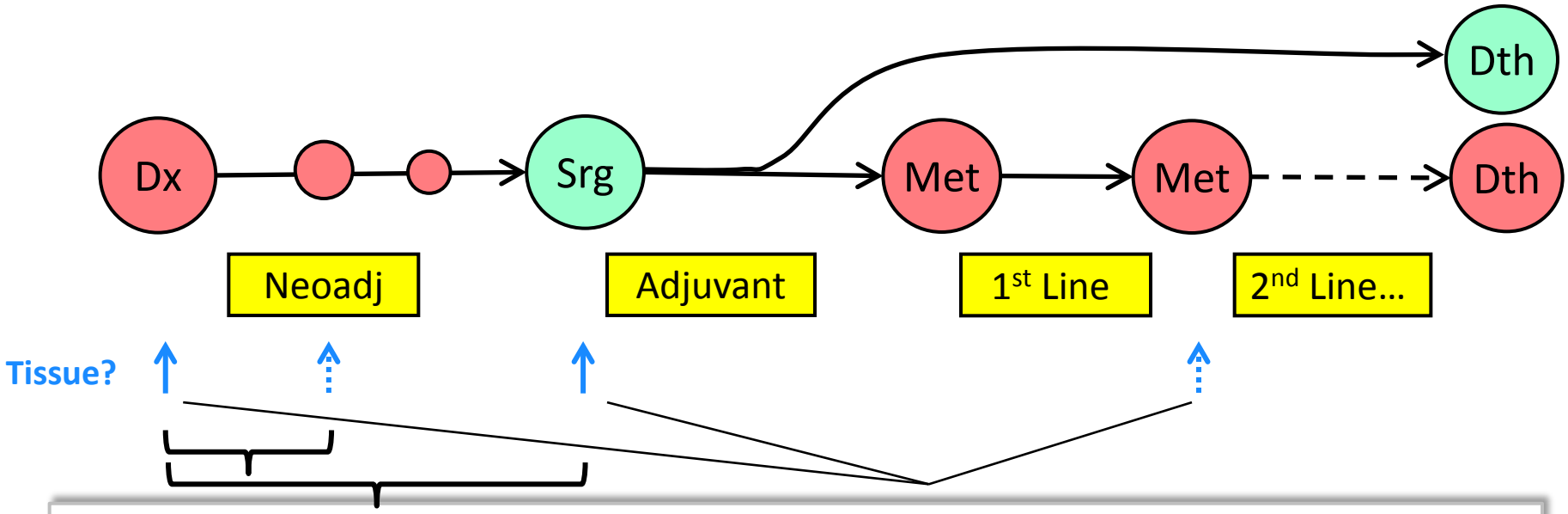
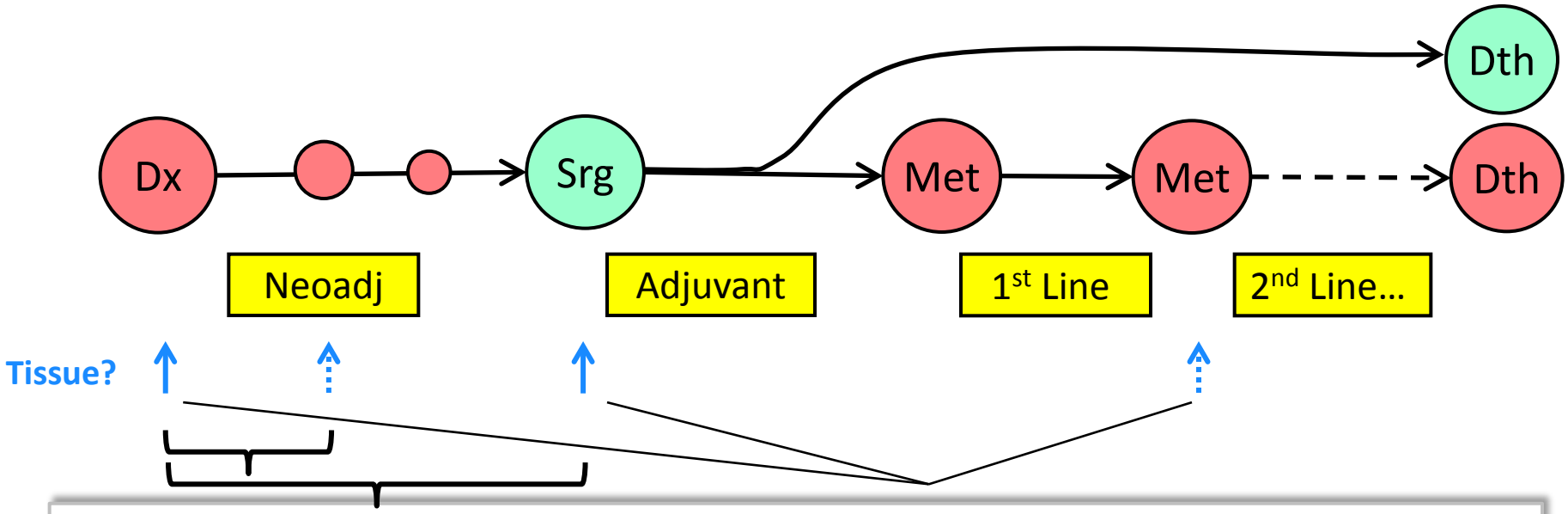


Molecular	Δ in Biomarker	**Baseline Biomarker**		
Response	X		X	…
DFS		X		
TTR		X		
PFS			X	…
OS		X	X	…

Mid-dev trials Late trials Early dev trials

What is an Appropriate Endpoint (Cancer)?



Molecular	Δ in Biomarker	Baseline Biomarker		
Response	X	Driven by PREDICTIVE effects	X	…
DFS		X		
TTR		X		
PFS	Driven by PROGNOSTIC & PREDICTIVE effects		X	…
OS		X	X	…

Mid-dev trials | Late trials | Early dev trials

Prognostic and Predictive Markers

- *What's the difference?*
  - Prognostic markers relate to natural history of the disease
  - Predictive (treatment guiding) markers relate to benefit from a specific therapy
- *Why should I care?*
  - It is easy to be confused
  - It makes a difference in designing studies and determining how a biomarker should be used

Discussion?