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What can affect the value of precision medicine?

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Example of stratified medicine: genotype-guided dosing of warfarin

- Two RCTs of **genotype-guided dosing** of coumarin derivatives (including warfarin) to treat atrial fibrillation or venous thromboembolism.
- These RCTs involved different comparisons:
  1. In England and Sweden:
     - Genotyped-guided dosing vs. standard care ("one-dose-fits-all")
  2. In The Netherlands and Greece:
     - Genotyped-guided dosing vs. clinical dosing algorithm ("*low-tech stratified medicine*")

Pirmohammed et al, New Engl J Med 2013
Verhoef et al, New Engl J Med 2013

EU-PACT
European Pharmacogenomics Approach to Coumarin Therapy

Genotype-guided dosing of warfarin

- Main conclusions (according to editorial by Furie NEJM, 2013): “these trials indicate that … pharmacogenetic testing has … at best, marginal usefulness, given the cost and effort required to perform this testing.”
- HOWEVER, improved safety remains important.
- Opportunities exist in:
  a. **formal dosing algorithms**, without concern for genotype;
  b. **patient adherence** and possibly more responsibility to patients;
  c. increased **diligence** by … personnel in testing, monitoring, and dosing.

Is personalised medicine always better?

Oral anticoagulants (OACs)

New oral anticoagulants (NOACs)

Audi

BMW

Mercedes-Benz

Other options

TESLA

NOACs: apixaban, dabigatran, rivaroxaban
Other: left atrial appendage occlusion

Consider all treatment options!

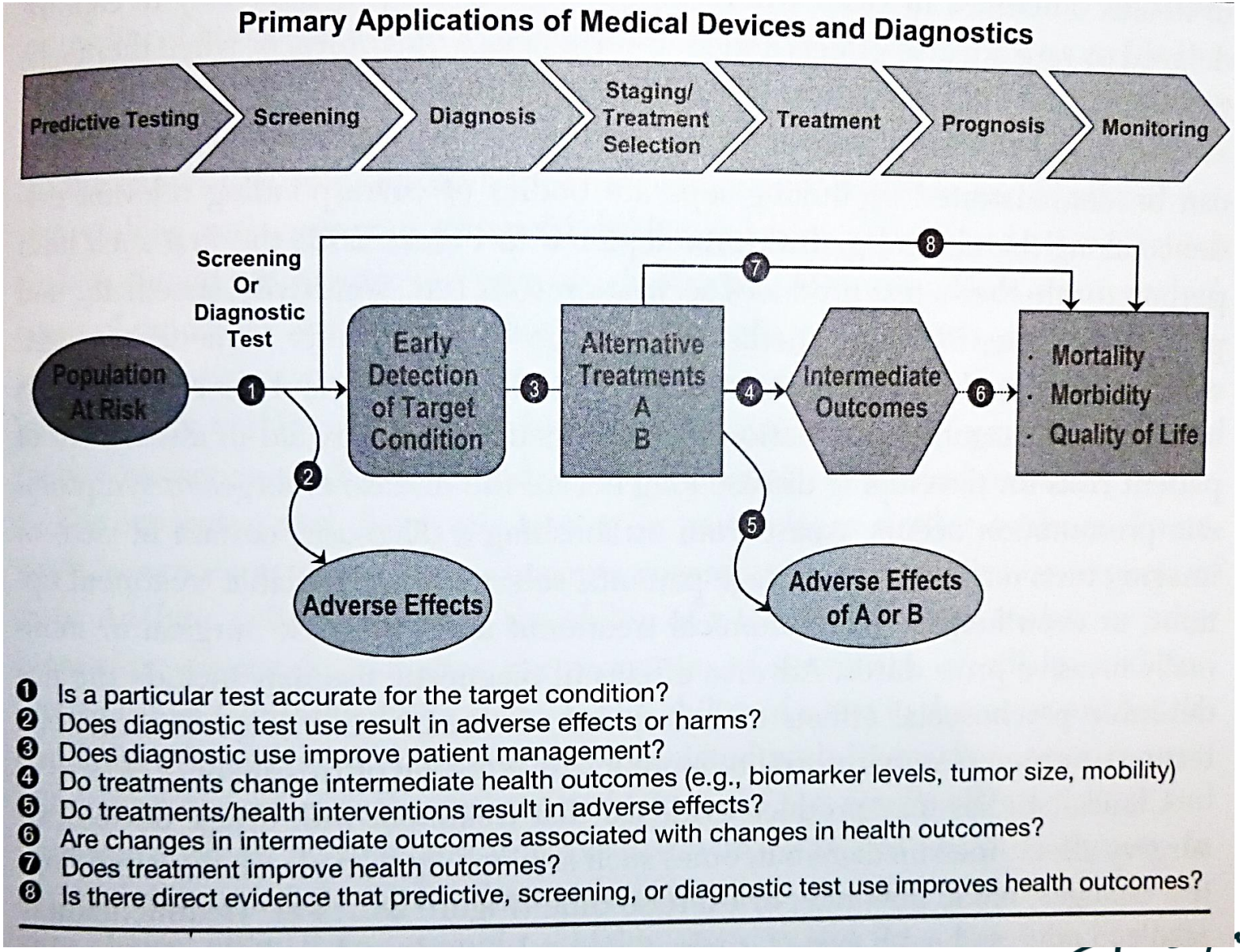
Figure 1 Base-case efficiency frontier depicting costs and QALYs for 8 stroke prevention strategies

Lee et al,
TCT 2014

Which intervention is cost-effective?

Which interventions are not?

What is needed to assess the value of precision medicine?



Therapeutic and Diagnostic Device Outcomes Research: ISPOR, 2011

What data is needed to assess precision medicine?

1. Test characteristics (sensitivity/specificity, costs)
2. Treatment strategy (given a positive or negative test)
3. Prognosis (health) with true positives, false positives, true negatives, false negatives.

   - need to consider later treatments and their effects (e.g., what happens with a false positive result?)
4. Costs associated with true positives, false positives, true negatives, false negatives.

- In addition, we need to assess the quality of the data

Where do we find the data that we need?

Data needed	Possible sources
Test accuracy and costs	
Side-effects of a test (plus probabilities, costs)	
Treatment strategy with positive or negative test	
Health outcomes (prognosis) if patient is true positive; also if the patient is false positive, true negative, false negative)	
Costs associated with true positives, false positives, true negatives, false negatives	
Prior probability of positives (e.g., HER2-positive)	
Utility values of different outcomes	
Etc.	

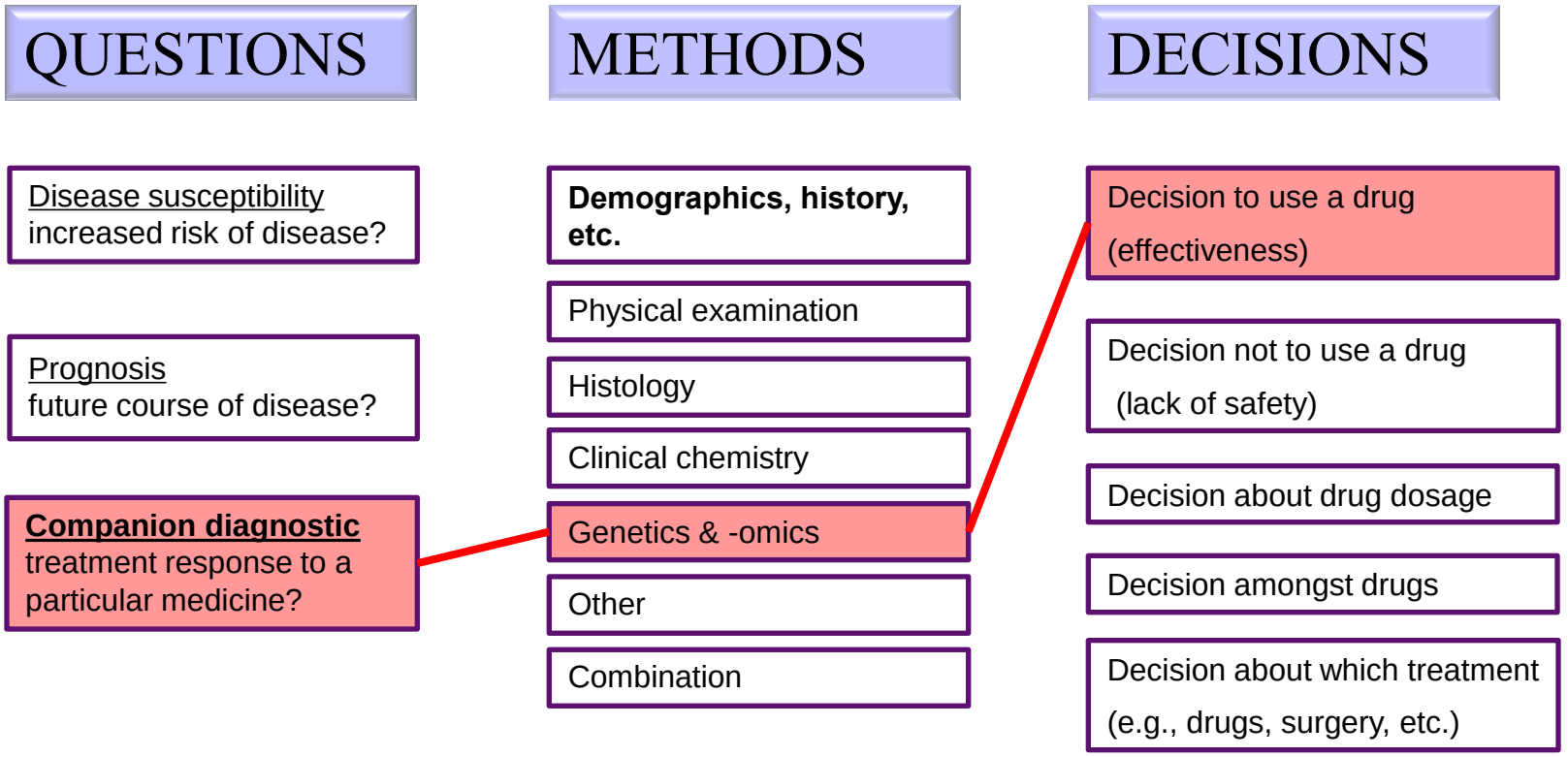
➢In addition, we need to assess the quality of the data

Components of (precision) medicine

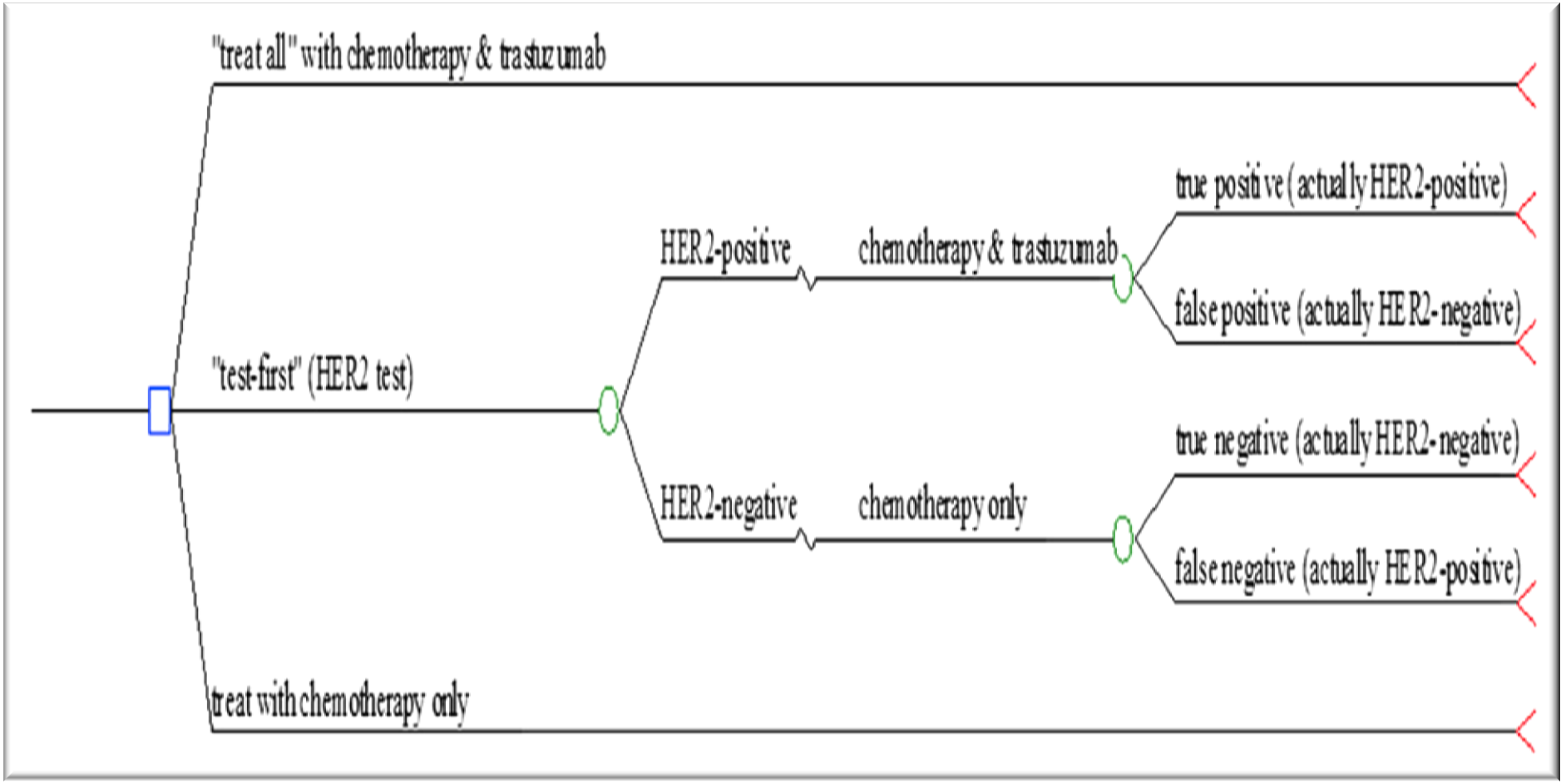
QUESTIONS	METHODS	DECISIONS
Disease susceptibility increased risk of disease?	**Demographics, history, etc.**	Decision to use a drug (effectiveness)
Prognosis future course of disease?	Physical examination	Decision not to use a drug (lack of safety)
Companion diagnostic treatment response to a particular medicine?	Histology	Decision about drug dosage
	Clinical chemistry	Decision amongst drugs
	Genetics & -omics	Decision about which treatment (e.g., drugs, surgery, etc.)
	Other	
	Combination	

Many combinations relate to precision medicine (personalised medicine, stratified medicine, etc.)!

HER2 & trastuzumab (Herceptin)

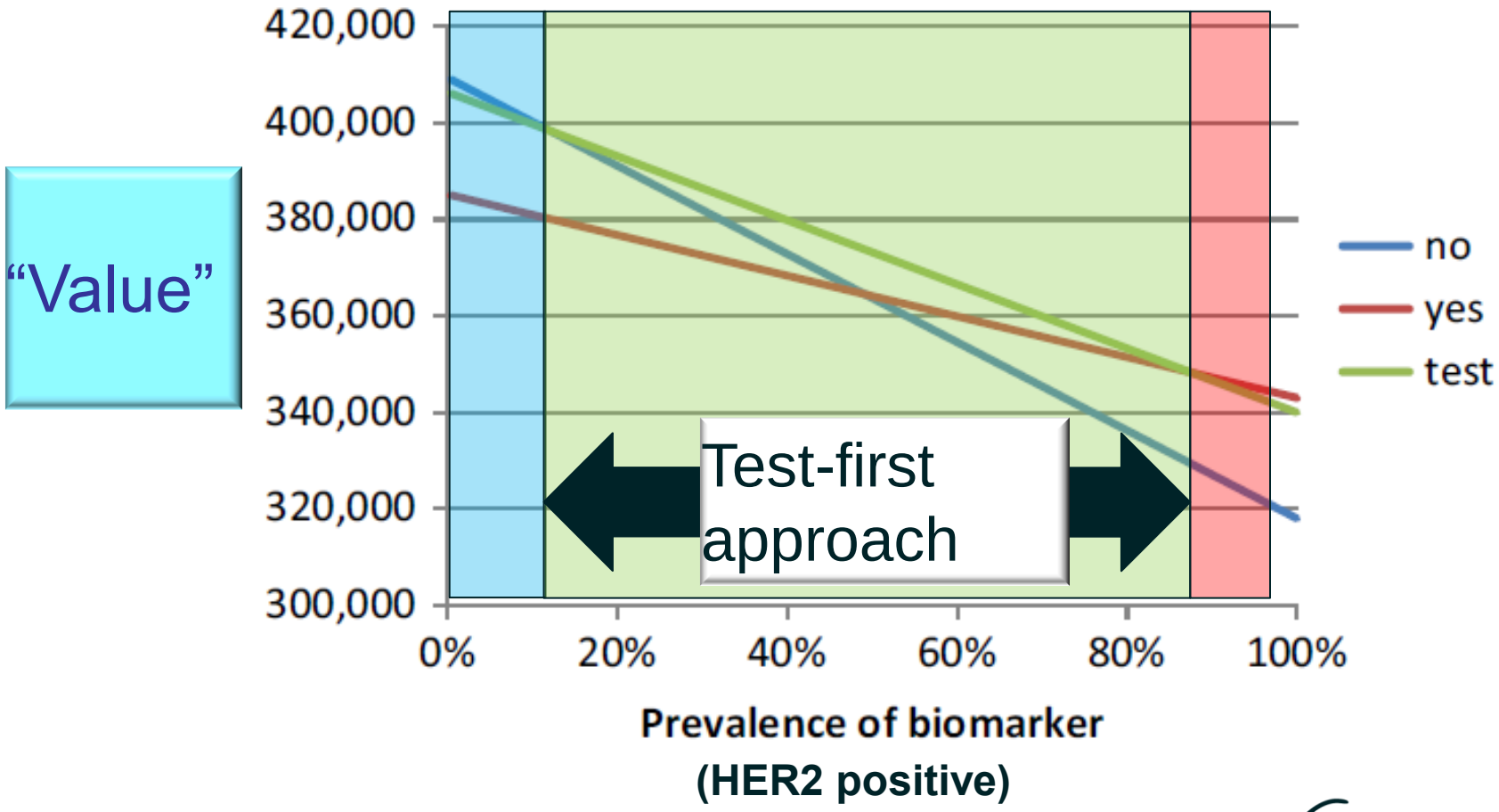


An example of precision medicine (Herceptin/trastuzumab)

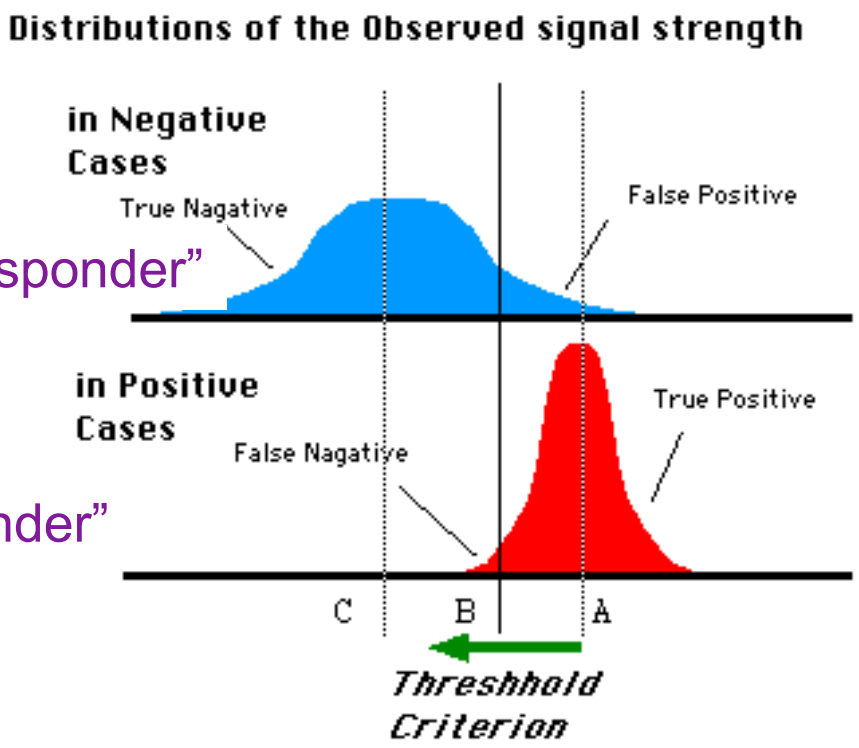


Different treatment strategies are available.
Is the test-first approach the most cost-effective option?

The cost-effectiveness of precision medicine vs. the alternatives depends on different factors



Diagnostic test: where is the threshold between a responder and a non-responder?



"Non-responder"

"Responder"

Possible results amongst people with the disease:
- TP (true-positive)
- FN (false-negative)

Possible results amongst other people:
- TN (true-negative)
- FP (false-positive)

A threshold (D_T) determines which results are positive (abnormal) and which are negative (normal)

Conclusions regarding precision medicine and trastuzumab (Herceptin)

- The cost-effectiveness of a stratified medicine approach using Herceptin depends on various factors, including:
  1. The prevalence of HER2-positive tumours
  2. Test characteristics (sensitivity, specificity, costs)
  3. Treatment strategy with a positive/negative test
  4. Prognosis with/without treatment (health outcomes)
  5. Costs of treatment and disease

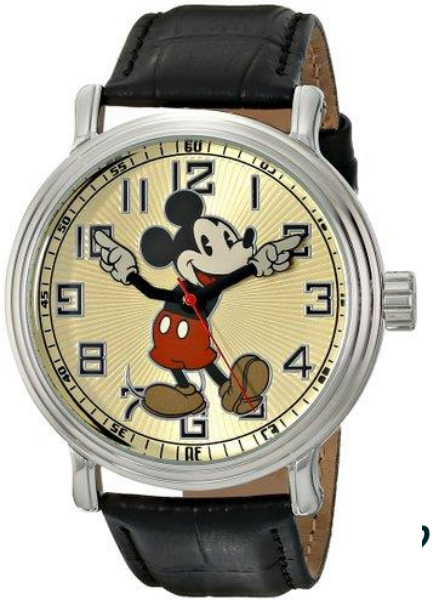
  AND: Whether healthcare professionals and patients will do what they're supposed to do!

What can possibly go wrong in daily practice?

- Consider how well the treatment strategies will work in the ‘real world’.

- Precision medicine is like a fine watch

  It may be sophisticated ...
  but a simpler approach
  may actually work better in practice



Reasons why precision medicine won't be more cost-effective than one-size-fits-all

1. **Incorrect comparator** is used (cetuximab, warfarin)
2. **Costs** of testing are too high (warfarin)
3. **Costs** of active treatment are too high (e.g. cetuximab)
4. **Costs** of active treatment are low (e.g., statins)
5. **Test accuracy** is insufficient
6. **Effectiveness of active treatment** is insufficient even when it works! (warfarin)
7. **Patient heterogeneity** is too low (prior probabilities are too low or high)(trastuzumab)
8. **Quality of care** factors: e.g., tests are used incorrectly (wrong patient, wrong time)

Is ‘precision medicine’ intrinsically the best?

- Precision medicine MAY improve health and MAY even reduce costs.
- BUT:
  - its theoretical value depends on many factors
  - its real-world value depends on many more
- Precision medicine is **not always cost-effective** vs. one-size-fits-all approaches!