From Biomarker to Diagnostic Tests

How good is a biomarker

Alex Sanchez-Pla[1] and Santiago Perez-Hoyos[2, 1]

[2]Vall d'Hebron Research Institute and

[1]Universitat de Barcelona

2025-02-23

Outline

What are Biomarkers

Biomarkers are everywhere

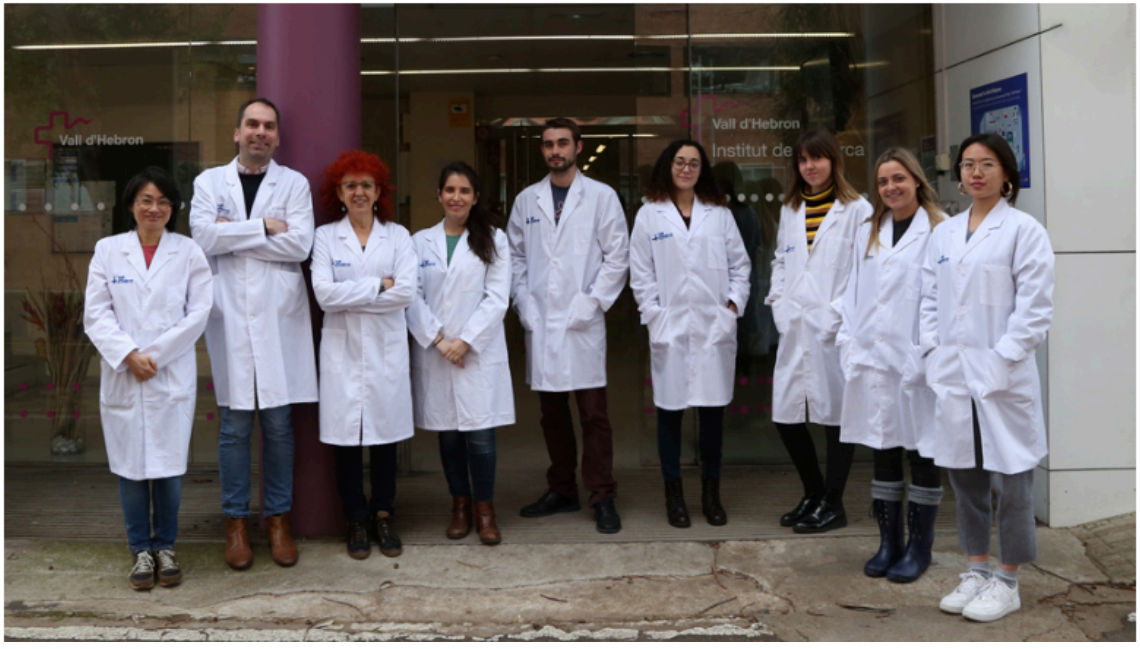
Jan '20
22

Millora en la identificació de biomarcadors mitjançant l'estandardització de l'ús de mostres de teixit humà

Biomarkers are everywhere

Jan '20
29

La càrrega microbiana és un marcador de resposta al trasplantament de microbiota fecal en pacients amb malaltia de Crohn



Biomarkers are everywhere

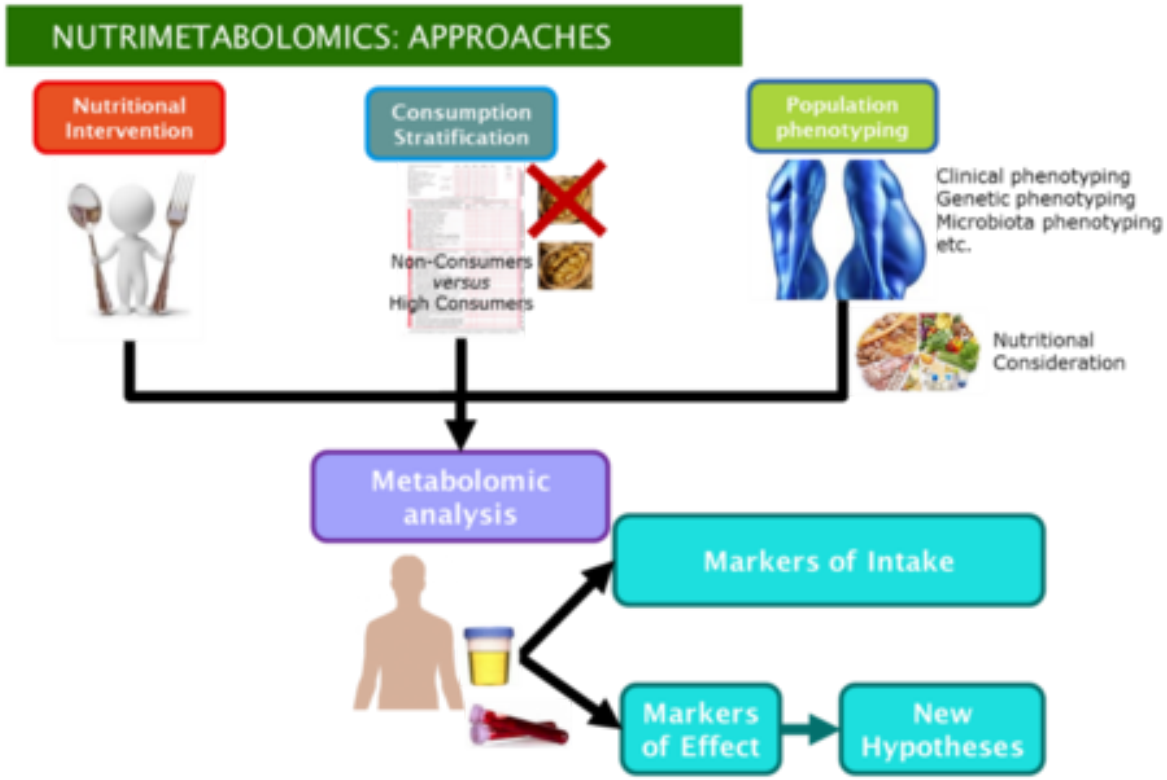
Dec '19
23

Researchers identify a new tumor biomarker in endometrial, lung, and colorectal cancer

Not only in diseases

BIOMARKERS & NUTRIMETABOLOMICS

UNIVERSITAT DE BARCELONA



So, what is a Biomarker?

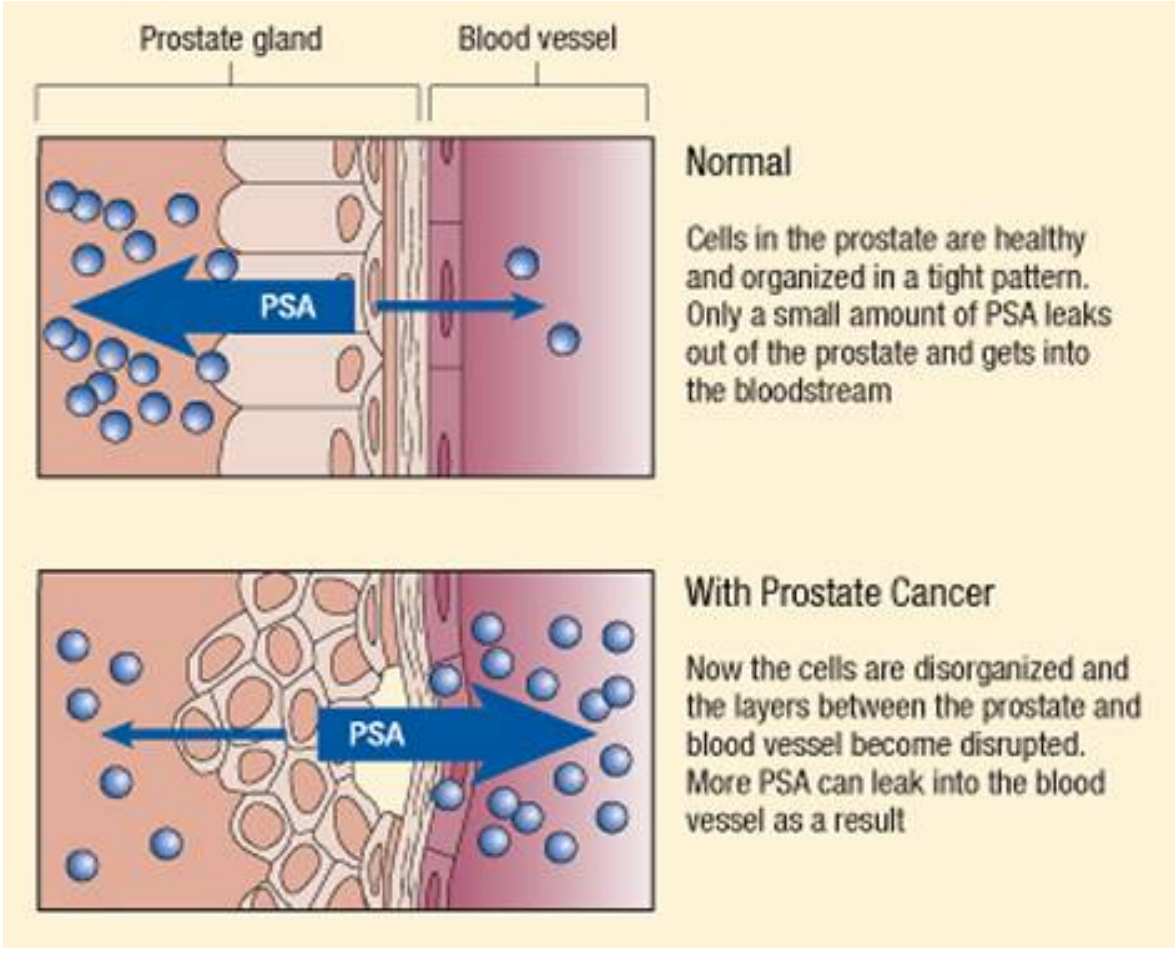
A characteristic, that is *objectively* measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

Biomarkers Definition Working Group, NIH Clin Pharmacol Ther 2001;69:89-95

Any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease

What are Biomarkers?
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3078627/

PSA: A prostate cancer biomarker



http://www.prostateuk.org/psa/psa.htm

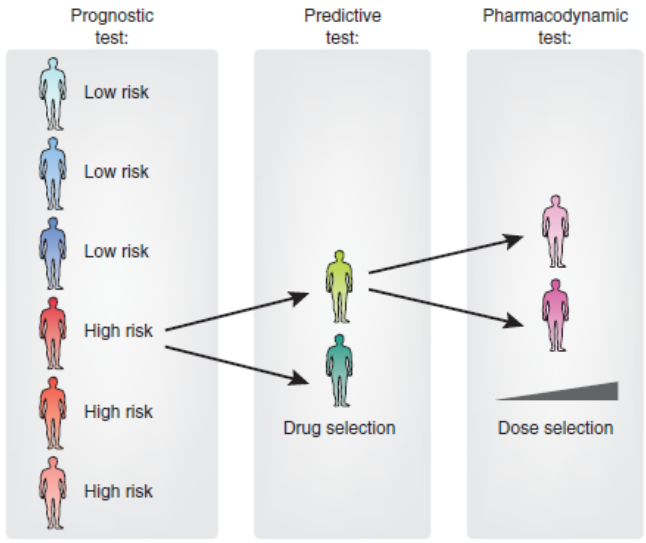
Types of biomarkers

Diagnostic biomarkers (not in the example): used to *diagnose or subclassify* a disease state.

Prognostic biomarkers: help identifying individuals at high risk of recurrence.

Predictive biomarkers help identifying those drugs to which patients are most responsive (or unresponsive).

Pharmacodynamic biomarkers can help identifying which drug dose to use for an individual.



Some biomarkers of distinct types

- **DIAGNOSTIC**
  - **BCR-ABL fusion leukemia (Philadelphia chromosome)**: Fusion gene present in most patients with chronic myelogenous leukemia (CML) and in some with ALL or AML.
  - **BRAF mutations**: Many types of cancer have been associated with distinct mutations in the BRAF gene.(BRAF mutations in cancer).
- **PROGNOSTIC**
  - **OncotypeDx** A gene expression test predicting the likelihood breast cancer recurrence.
- **PREDICTIVE**
  - **HER2 and herceptin** HER2 overexpression correlates with poor prognosis. Trastuzumab [Herceptin (H)] is a humanised IgG monoclonal antibody specific for the growth factor receptor HER2.

Some biomarkers in clinic

Biomarker	Molecular Compartment	Purpose
Markers With Accepted Clinical Utility		
EGFR mutation	Tumor DNA	Predictive
ALK gene fusion	Tumor DNA	Predictive (crizotinib)

NSC Lung

Biomarker	Molecular Compartment	Purpose
Markers With Accepted Clinical Utility		
ER-α/PgR (ESR1/PR)	Tumor protein	Diagnostic prognostic (weak) predictive
HER2(ERBB2)	Tumor protein	Diagnostic (classification) prognostic (favorable) predictive for anti-*HER2(ERBB2)* therapy
Oncotype Dx	Tumor RNA	Prognostic predictive

Breast

Biomarker	Molecular Compartment	Purpose
Markers With Accepted Clinical Utility		
KRAS mutations [except c.38G>A (p.G13D)]*	Tumor DNA	Predictive (negative for anti-EGFR therapy); negatively prognostic in several first-line randomized studies
MSI and/or MMR protein loss	Tumor DNA for MSI testing with PCR; tumor IHC for MMR proteins	Screening (Lynch syndrome)
		Prognostic (recurrence, overall survival)
		Predictive (lack of benefit, possibly worse outcome with adjuvant single-agent fluoropyrimidine therapy)
CEACAM5 (CEA)	Patient serum	Surveillance
BRAF c.1799T>A (p.V600E) mutation	Tumor DNA	Prognostic (strong negative prognostic marker)
		Predictive (negative for anti-EGFR therapy)

Colon

Biomarker	Molecular Compartment	Purpose
Markers With Accepted Clinical Utility		
PSA(*KLK3*)	Serum protein	Diagnostic

Prostate

Biomarker	Molecular Compartment	Purpose
Markers With Accepted Clinical Utility		
1p/19q codeletion (unbalanced translocation)	Tumor DNA	Diagnostic (oligodendroglioma)
IDH mutation (*IDH1*) c. 395 G>A p.R132H (*IDH2*)	Tumor DNA, tumor protein	Positive is favorably prognostic; also a diagnostic marker
MGMT methylation	Tumor DNA	Prognostic, predictive (benefit for chemotherapy), pharmacodynamic (pseudorecurrence)

Glioma

NCCN

Biomarkers in drug development

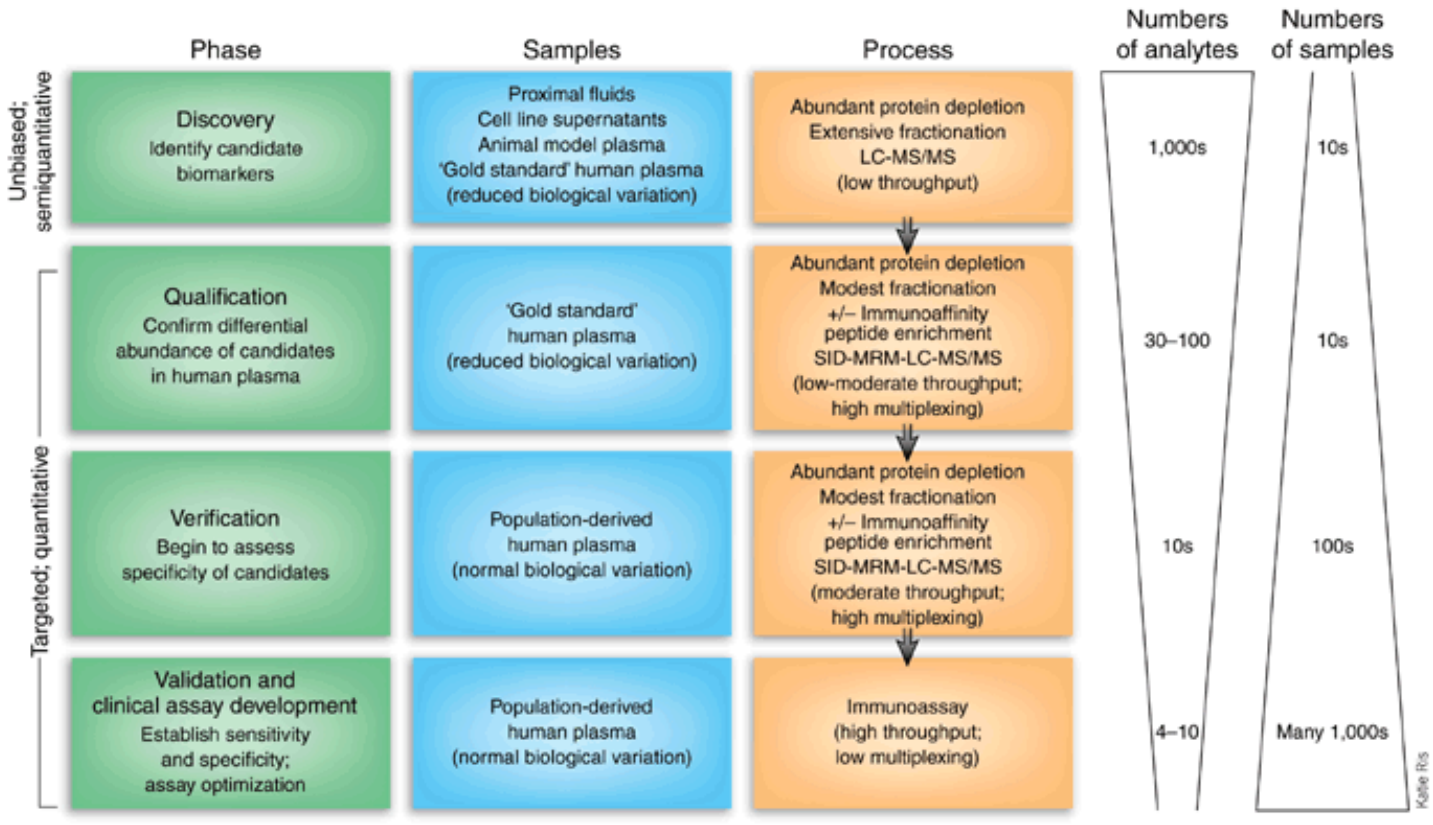
Biomarkers can assist drug development while helping to answer relevant questions such as:

- How does a drug work in the body
- Is the drug safe or effective?
- What dose of the drug is effective?
- Related with the Response to a Treatment
    - Is there a response?
    - Is it big enough/different enough from others?

Treatment trial - FDA regulatory approval process

The biomarker development process

Biomarker development phases



Rifai , N., M.A. Gillette, and S.A. Carr , Protein biomarker discovery and validation: the long and uncertain path to clinical utility. Nat Biotechnol , 2006. 24 (8): p. 971-83.

Biomarker development

Genomics

- Relevant disease genes, expression profiles, signaling pathways

Proteomics

- Protein expression and post translational modifications

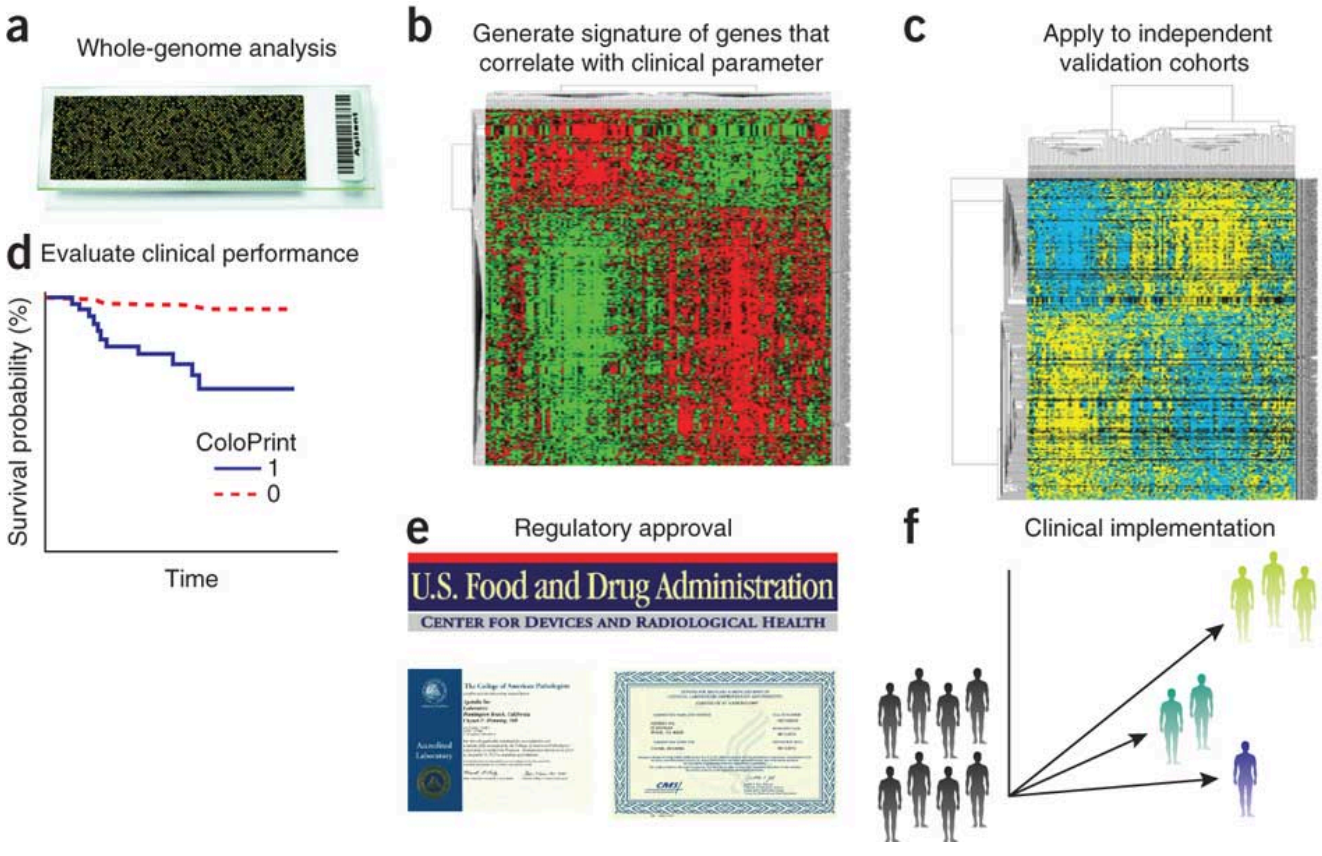
Metabolomics

- Small molecule metabolites specific to disease

Imaging

- Imaging changes reflect disease state

A gene expression biomarker



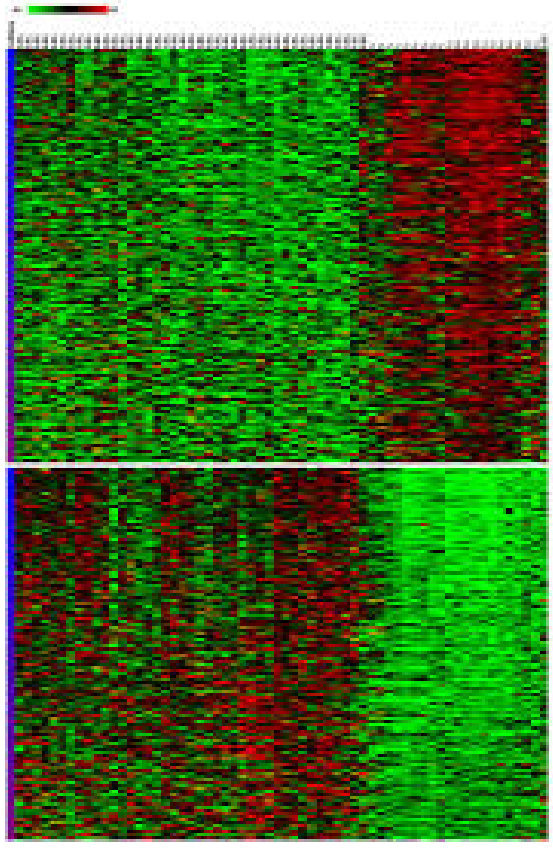
Taming the dragon: genomic biomarkers to individualize the treatment of cancer. Nature Medicine. 304–312. (2011)

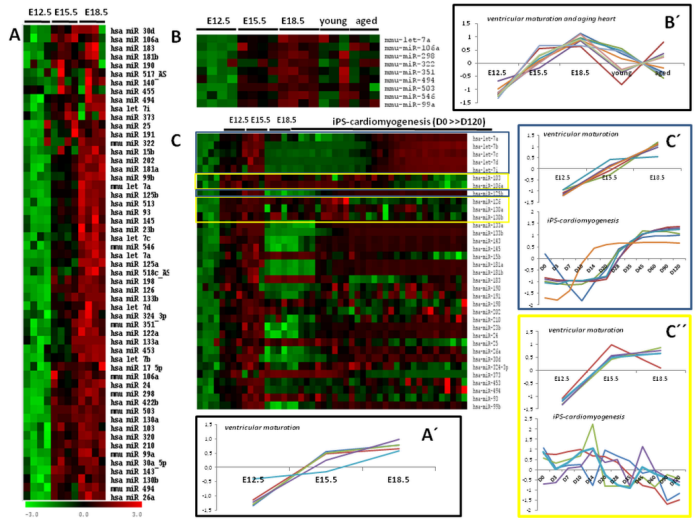
A gene expression biomarker

(a) Unbiased discovery of a gene expression profile starts with the large scale analysis of gene expression on a series of tumor samples of known clinical outcome.

A gene expression biomarker

(b) Using bioinformatics, the set of genes is identified that correlates best with the relevant clinical parameter.

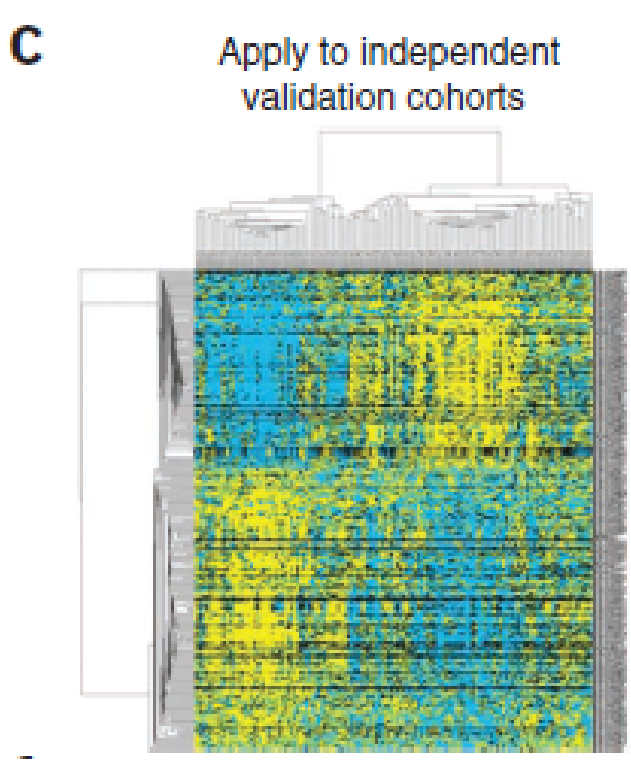


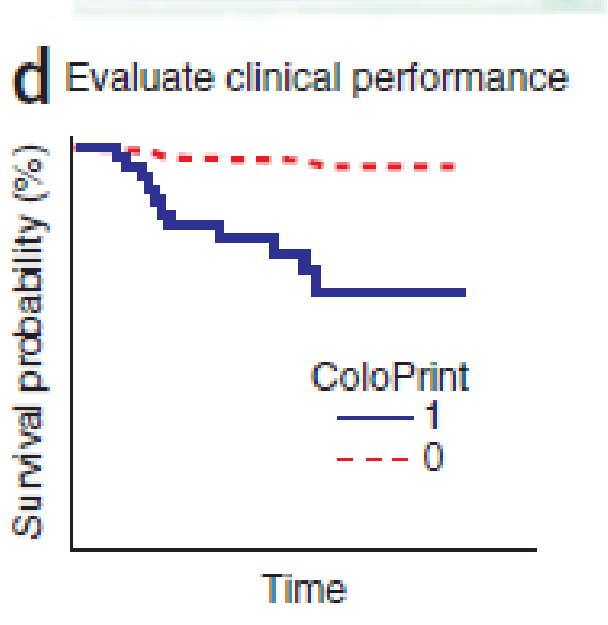


A gene expression biomarker

(c) The 'gene signature‘ derived must be validated on a large cohort of additional clinical samples of known outcome,

(d) The clinical performance is evaluated in comparison with the generally accepted clinical parameters.





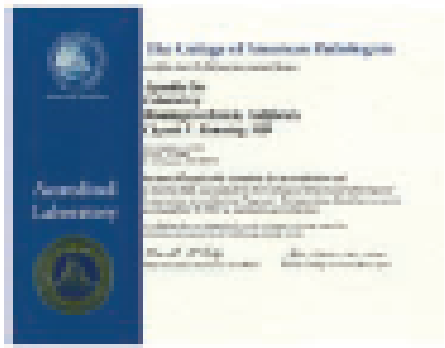
A gene expression biomarker

(e) Regulatory approval is the last step for completing the translation from bench to bedside.

e Regulatory approval

U.S. Food and Drug Administration

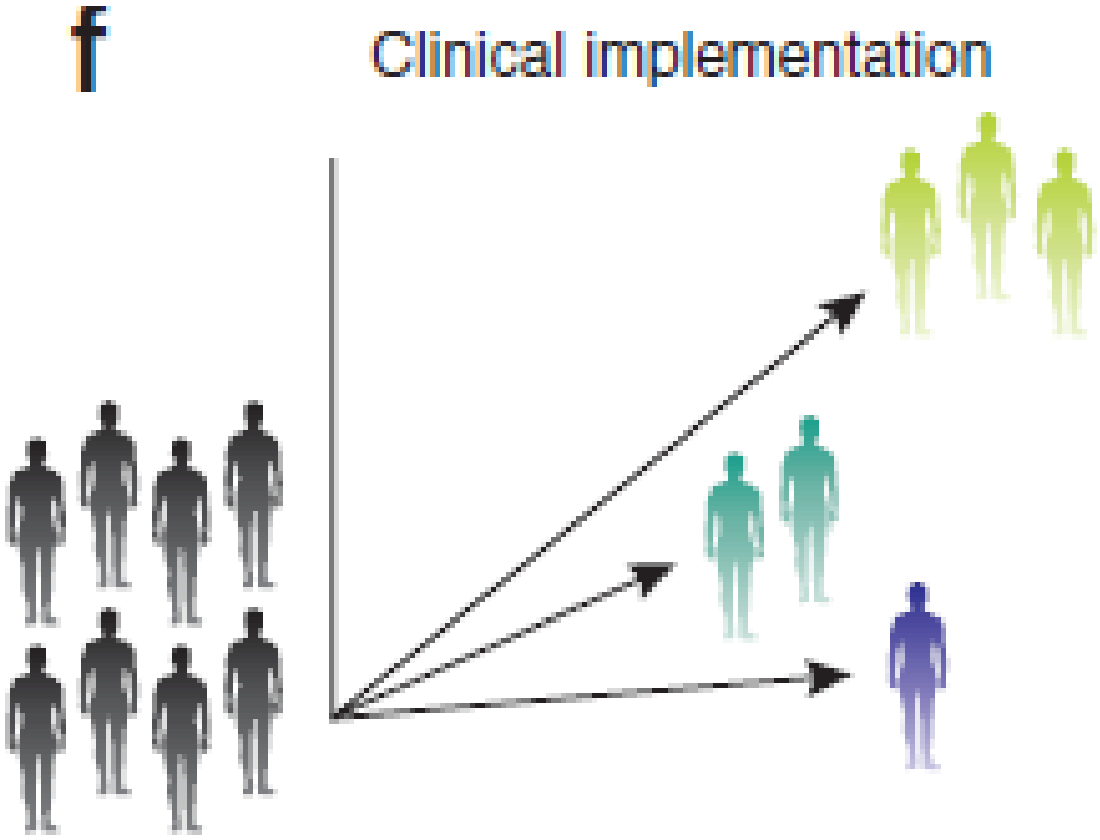
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH



]

A gene expression biomarker

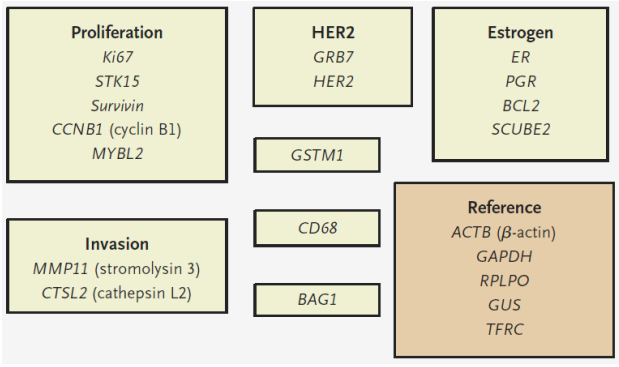
(f) Only after this process is completed can these tests be used to stratify patients by molecular signatures.



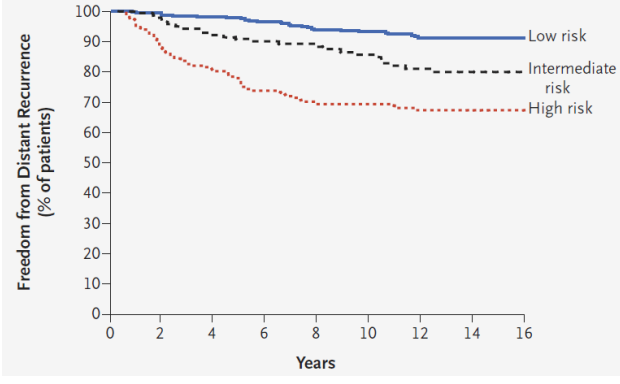
]

Oncotype DX: A success story

- Breast cancer patients treated with hormone therapy alone recur only in 15% within 10 years, 85% may not need additional chemotherapy.
- Oncotype DX predicts risk of recurrence, useful to identify patients who would not need adjuvant chemotherapy.
- A *recurrence score* was derived from the analysis of 21 genes allowing to classify patients in "low", "intermediate" and "high" risk.



Clinical validation



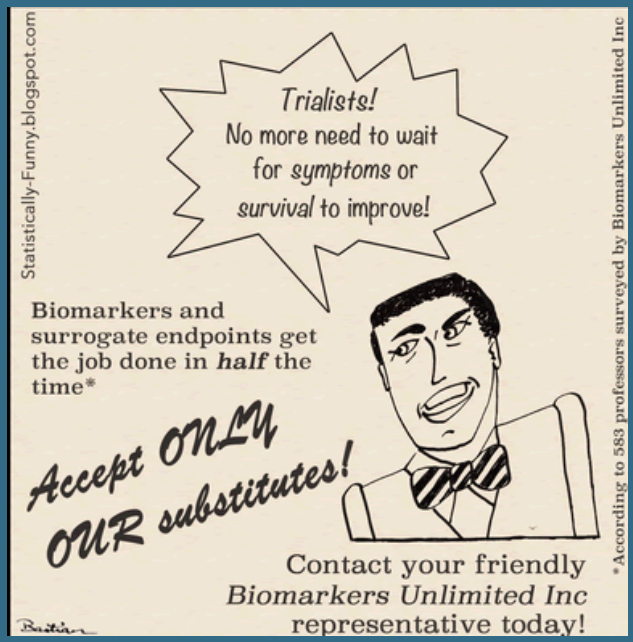
Age at surgery	0.08	0.71 (0.48–1.05)
Clinical tumor size	0.23	1.26 (0.86–1.86)
Recurrence score	<0.001	3.21 (2.23–4.61)

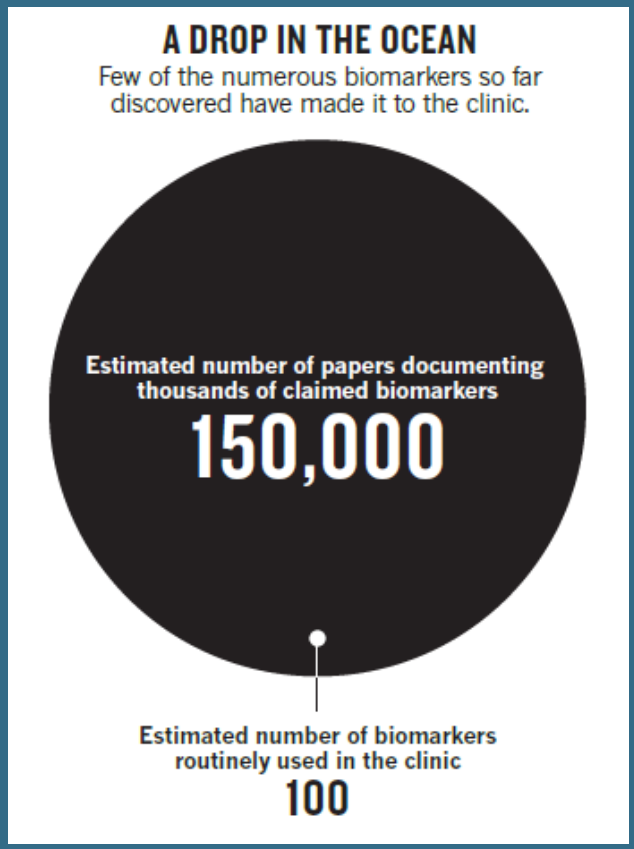
Exercise

- Many papers claim to have discovered “a new biomarker for...”
  - Many of these biomarkers are published in a scientific journal,
  - But they never reach the clinic.
- Look for examples of successful (or unsuccessful) biomarkers and make a quick slide where you explain:
  - Name of the biomarker
  - What is it intended to do?
  - What type of biomarker is it
  - Source of information
  - Is it known to have been applied to clinics
  - Name of the people who have prepared the slides

Use this link to add your slide to the presentation

Can we trust our biomarkers?





An array of problems?

DNA microarrays have been used extensively in the 1st decade of XXIst to derive all type of biomarkers .

Soon, claims against microarrays were raised.

- Lack of reproducibility between studies.
- Few coincidences between gene lists.
- Predictions on new test data did not reproduce those in training data.
- The step to the clinic always waiting .

PLoS MEDICINE

a peer-reviewed open-access journal published by the Public Library of Science

Home Browse Articles About For Readers For Authors and Reviewers

EDITORIAL OPEN

Why Bigger Is Not Yet Better: The Problems with Huge Datasets

THE LANCET

Search for In All Fields GO Advance

Home | Journals | Collections | Audio | Conferences | Education | Resource Centres | For Authors

The Lancet, Volume 365, Issue 9458, Pages 454 - 455, 5 February 2005

doi:10.1016/S0140-6736(05)17878-7 Cite or Link Using DOI

< Previous Article | Next Article >

Microarrays and molecular research: noise discovery?

John PA Ioannidis a b c

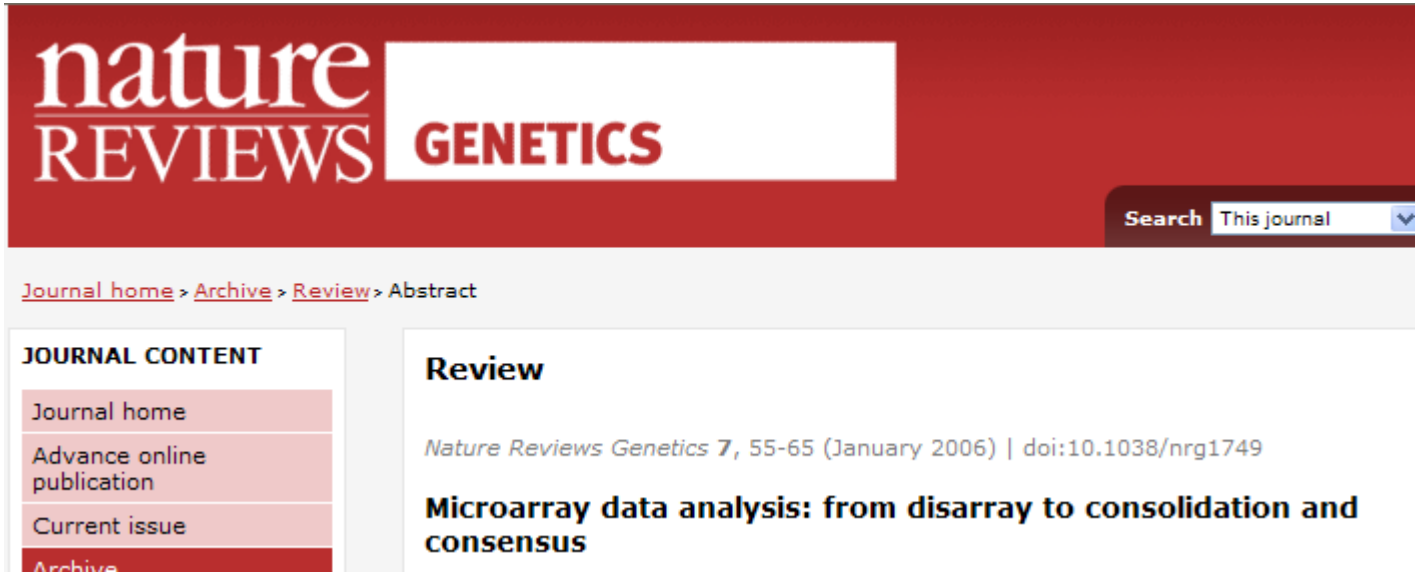
The promise of microarrays has been of apocalyptic dimensions. As put forth by one of their inventors, "all human illness can be studied by microarray analysis, and the ultimate goal of this work is to develop effective treatments or cures for every human disease by 2050". [1] All diseases are to be redefined, all human suffering reduced to gene-expression profiles. Cancer has been the most common early target of this revolution [2] and publications in the most prestigious journals have heralded the dis ...

An array of problems

Despite the huge amount of published microarray data in cancer, little is being converted into clinical practice. Validating initial data is proving to be a key challenge, reports SIMON FRANTZ.

“It was not that bad...”

- More studies showed, however, that most problems could be appropriately circumvented applying well the right methodology.

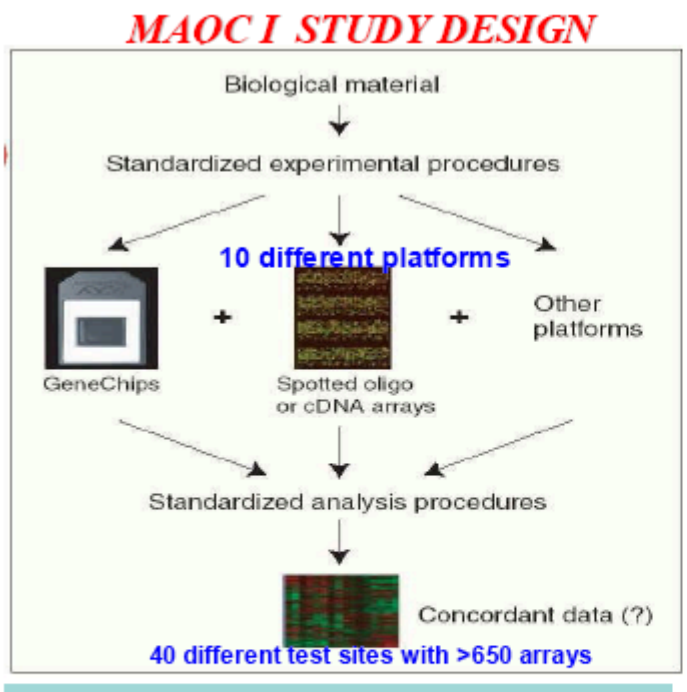


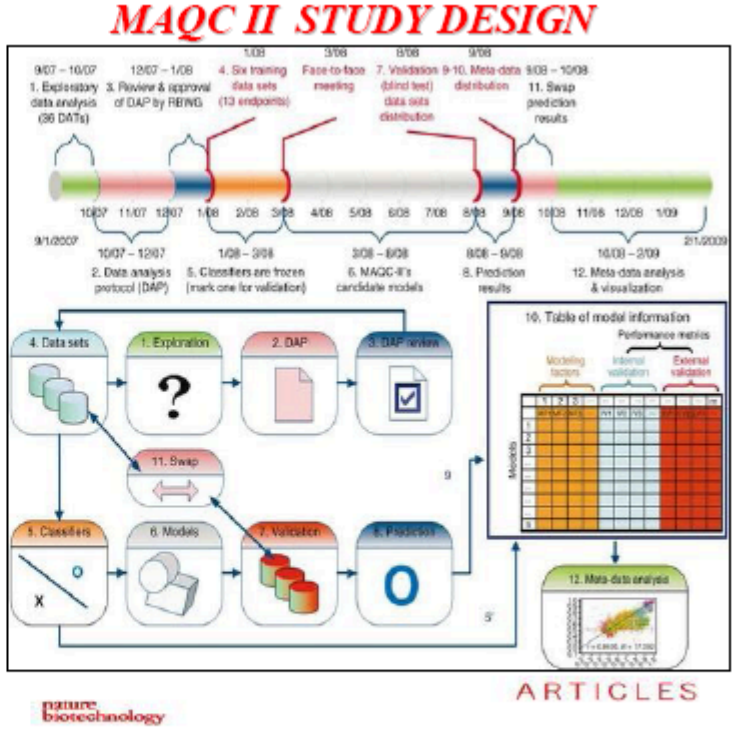
Critical Review of Published Microarray Studies for Cancer Outcome and Guidelines on Statistical Analysis and Reporting

Alain Dupuy, Richard M. Simon

How to do things better ...

- Large quality control studies (MAQC) were promoted to investigate reliability and applicability of the technique.





Some consensus (Allison 2006)

Altogether a consensus exists *mostly between data scientists* on how to do things to avoid the *array of problems*

- Design the experiment with your objectives in mind.
- Biological replication is essential.
- There is strength in numbers : power & sample size
- Pooling biological samples can be useful .
- When selecting diferentially expressed genes
  - Using FC alone as a differential expression test is not valid
  - Using p- value alone may fail if there is no biological significance.
  - Important to combine FC and p- values
  - Multiple testing has to be adequately accounted for
- When predictive models are built, know and control sources of bias, especially through validation and cross-validation.

Allison DB et al. (2005) Microarray data analysis: from disarray to consolidation and consensus Nat Rev gene. 7: 55 – 65 doi:10.1038/nri1749

In Summary (1)

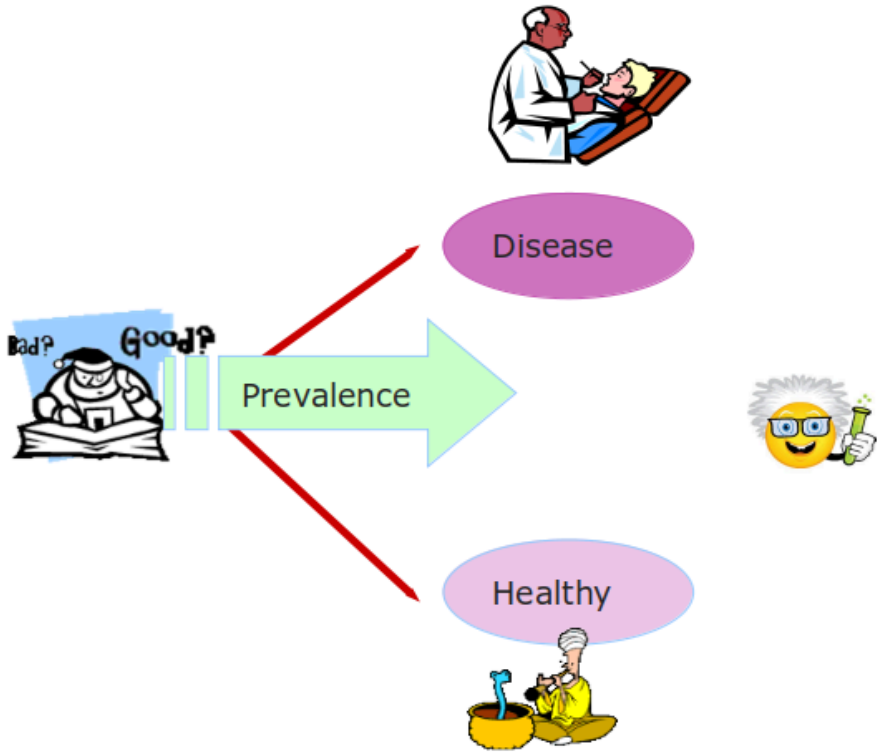
- Biomarkers can be properly defined – with different nuances depending on their goal .
- It is possible to derive biomarkers following an adequate biomarker development process .
- Biggest threat for biomarkers is lack of reproducibility.
- Adhering to correct statistical & methodological principles increases the chances that biomarkers can last longer

From biomarkers to diagnostic tests

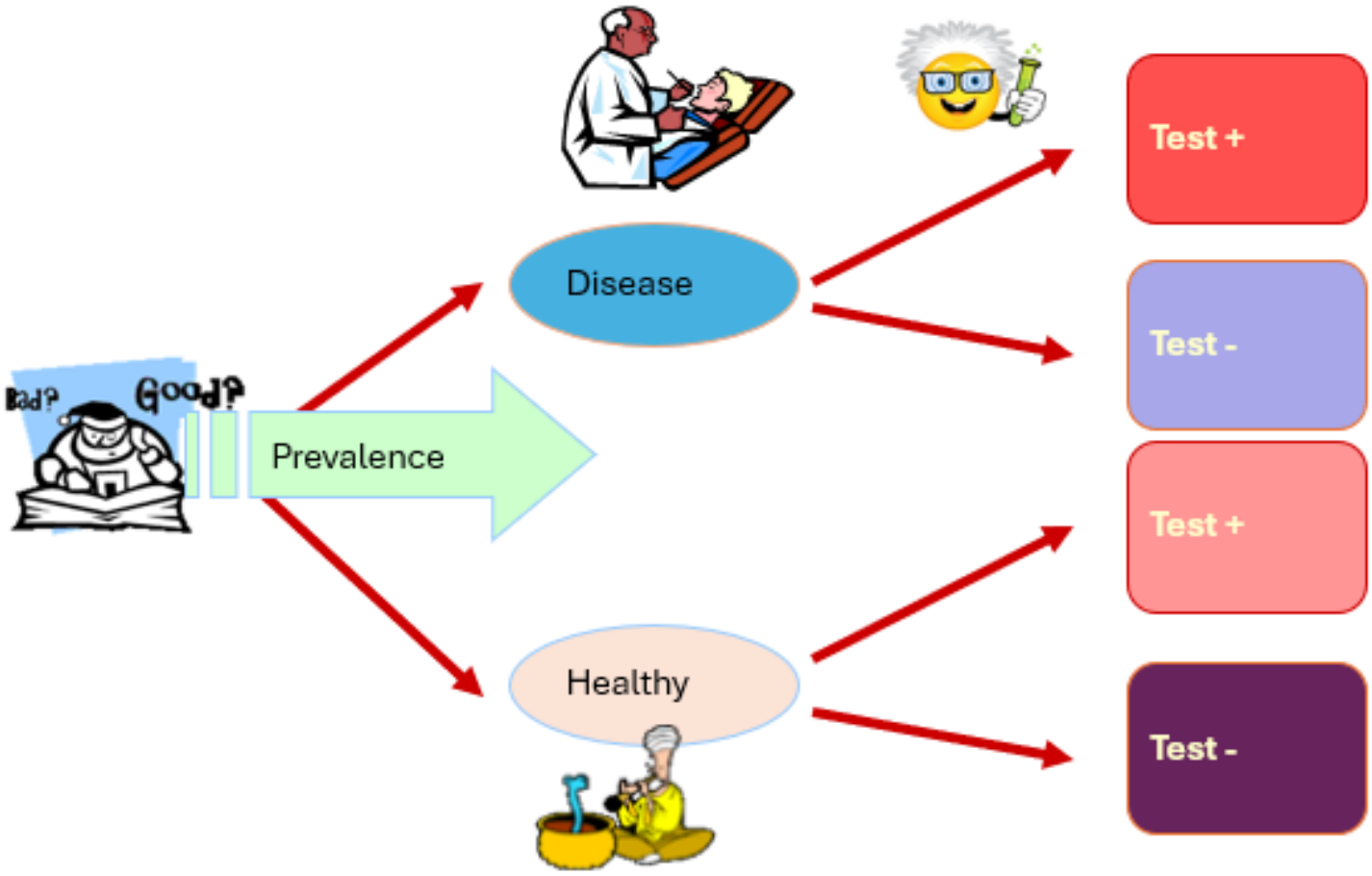
From biomarkers to diagnostic tests

- Biomarkers are often used to build tests to diagnose a disease:
- E.g. A threshold on PSA can be used to suggest a Prostate Cancer
  - If [PSA] <= 4, healthy
  - If 4 < [PSA] <= 10 dubious
  - If [PSA] > 10 Prostate Cancer
- But diagnostic tests, as all tests, are faced with the dicotomy Reality/Diagnosis which, as in the case of hypothesis tests, yields the possibility of having false positives and false negatives.
- Next we show how this can be quantified in *dichotomous* diagnostic tests and which measures can be used to decide *how reliable a (biomarker-based) diagnostic test is*.

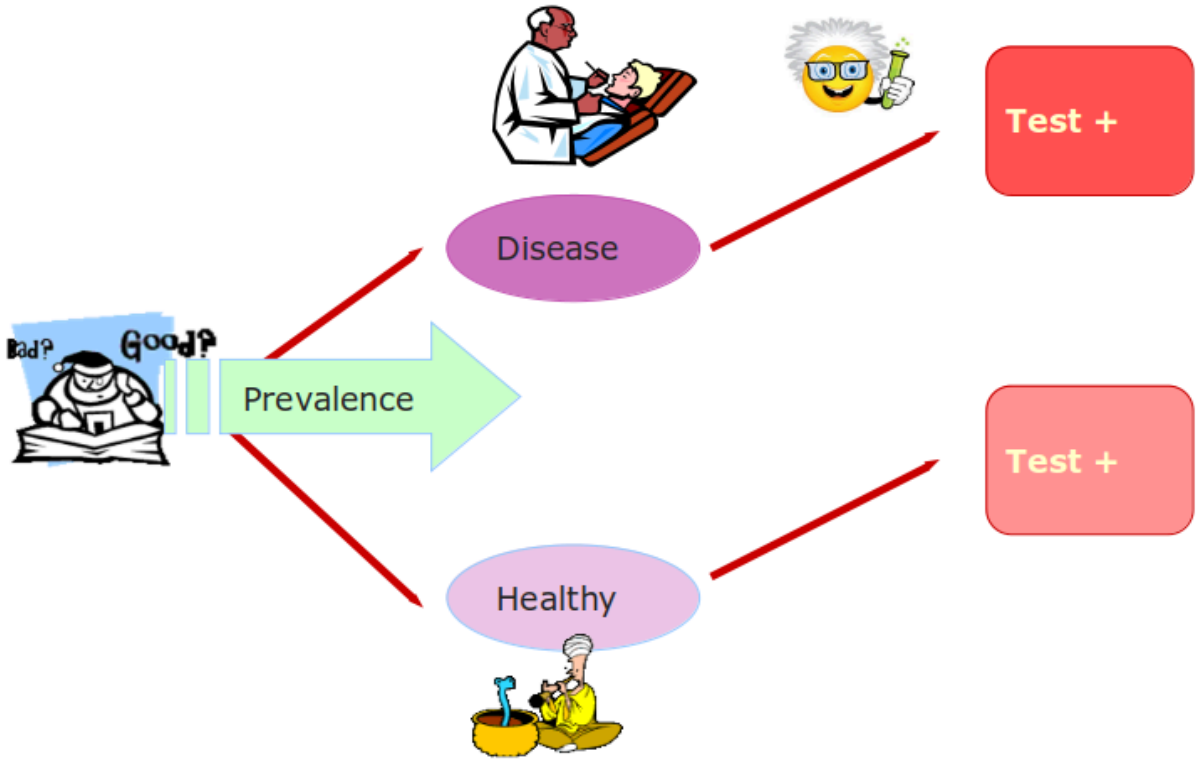
Diagnostic Measures



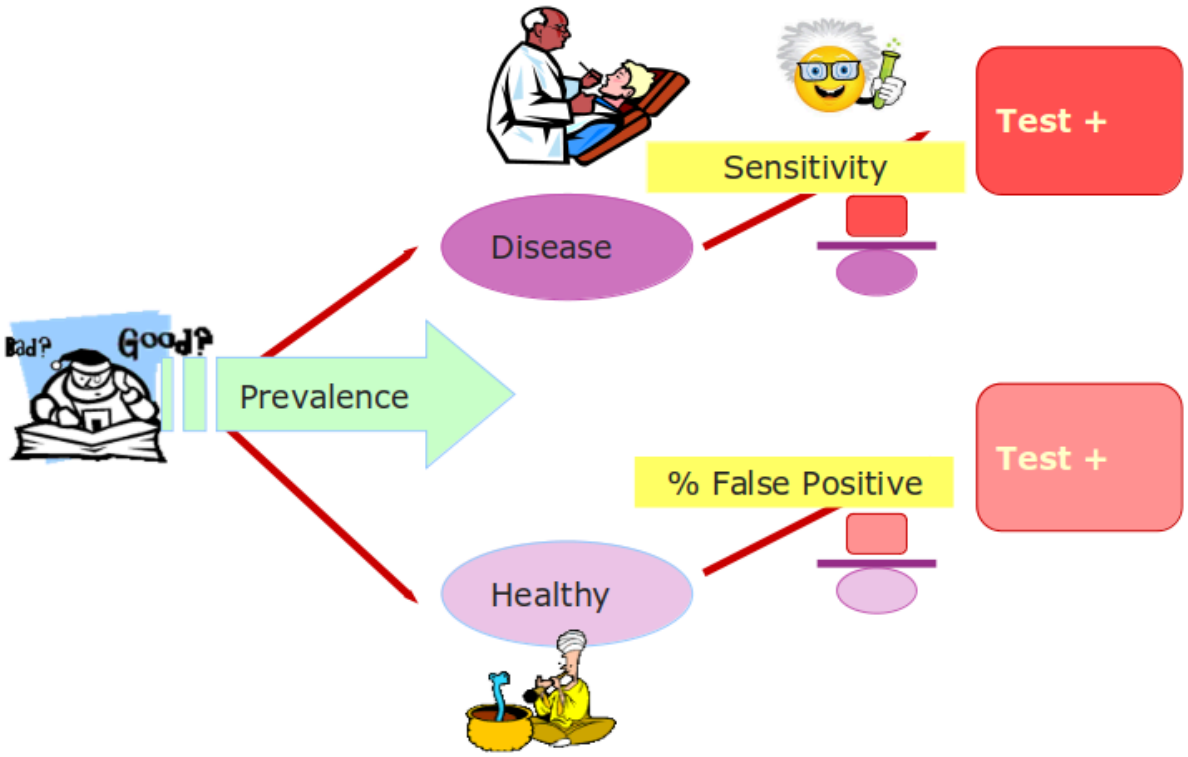
Diagnostic Measures: 4 scenarios



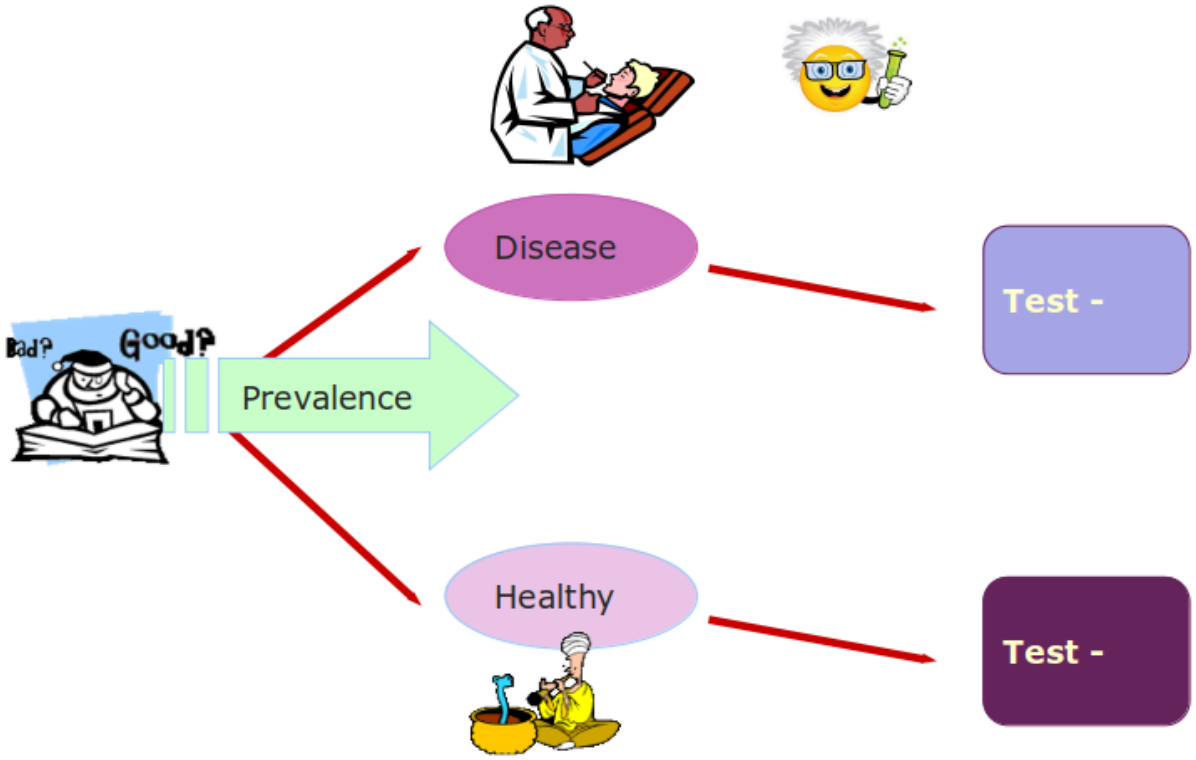
Diagnostic Measures



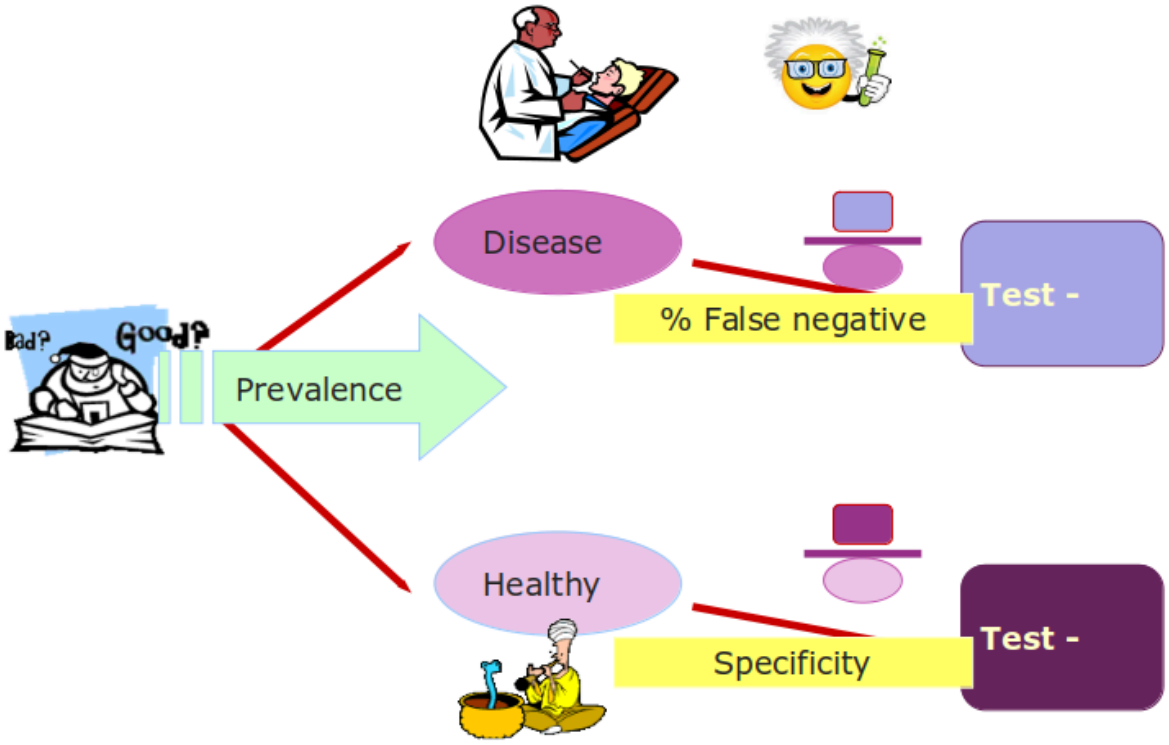
Sensitivity



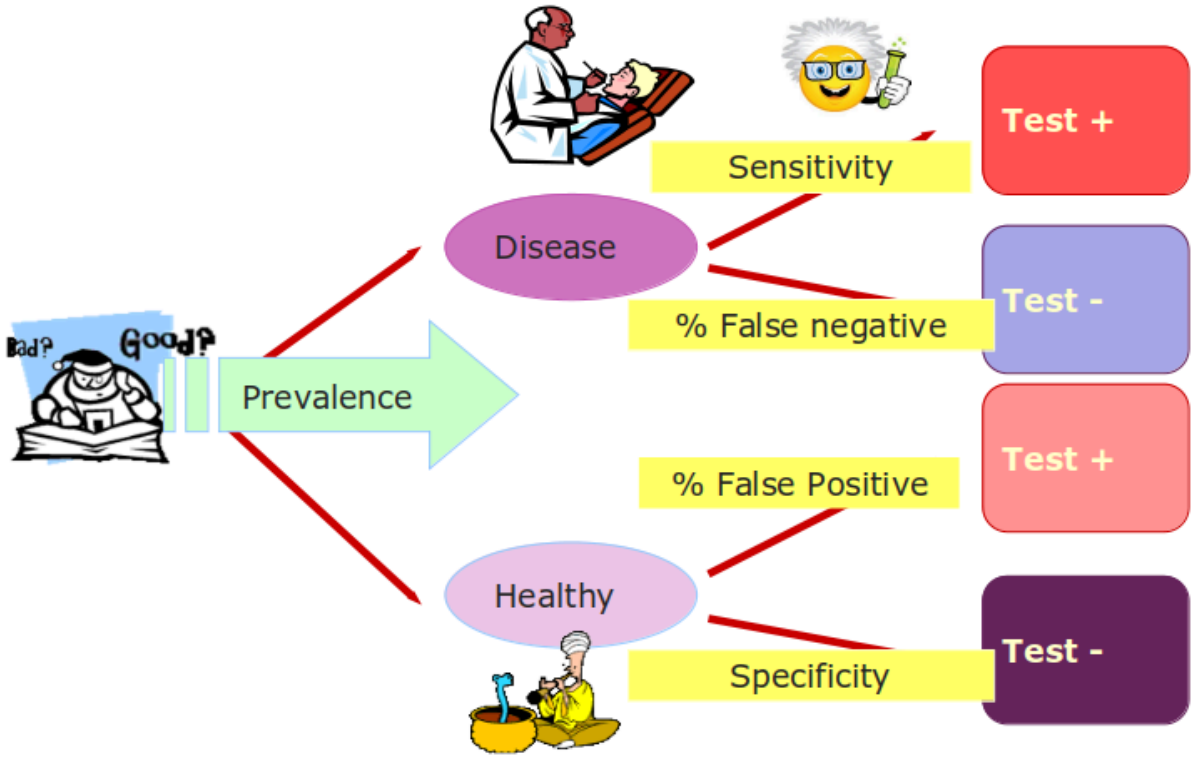
Diagnostic Measures



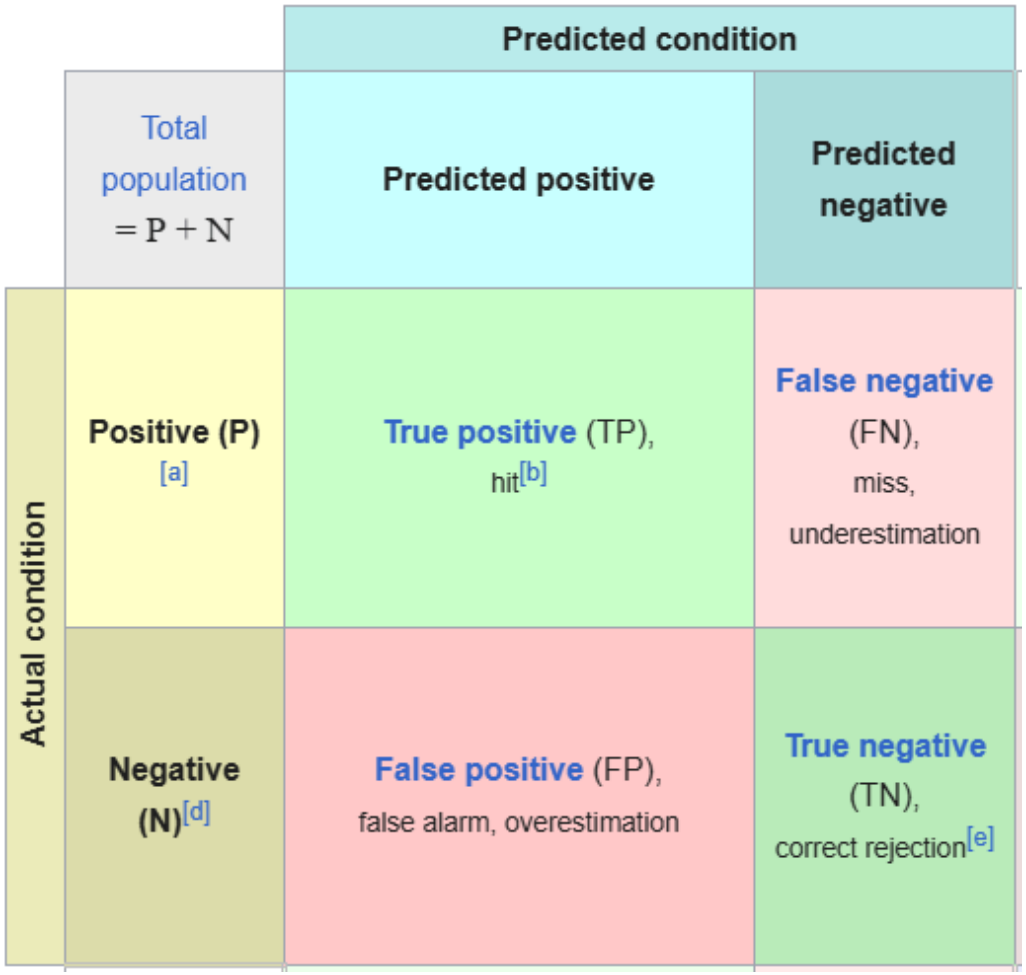
Specificity



Diagnostic Measures



Evaluating binary tests



		Predicted condition	
	Total population $= P + N$	**Predicted positive**	**Predicted negative**
Actual condition	**Positive (P)** [a]	**True positive** (TP), hit[b]	**False negative** (FN), miss, underestimation
	Negative (N)[d]	**False positive** (FP), false alarm, overestimation	**True negative** (TN), correct rejection[e]

https://en.wikipedia.org/wiki/Evaluation_of_binary_classifiers

Example: Prostate cancer diagnosis

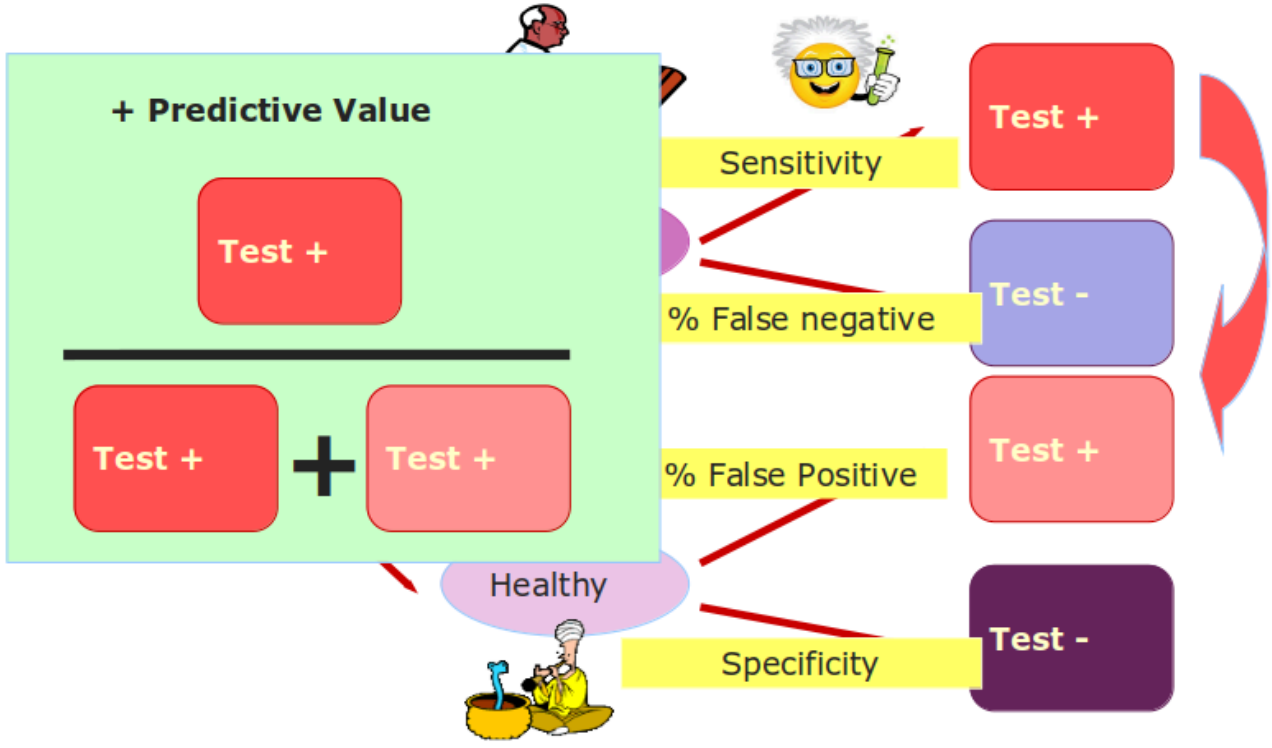
- In a study there have been collected **2641** samples of patients *suspected* to have prostate cancer.
- Patients have undergone two tests
  - Rectal examination
  - Prostate biopsy
- Ideally if they yield identical results biopsies -which are expensive and not risk-free- would be unnecessary.

Example: Tests are not equivalent

		Biopsy result		
		Disease	Healthy	TOTAL
Rectal examination	Disease	634	269	903
	Healthy	487	1251	1738
	TOTAL	1121	1520	2641

- **Sensitivity** = 634 / (634+487) = 0.5656 = 56.6% $\longrightarrow$ *43.4% with cancer had a normal rectal examination*
- **Specificity** = 1251 / (269+1251) = 0.8230 = 82.3% $\longrightarrow$ *17.7% of the patients without disease were incorrectly diagnosed*

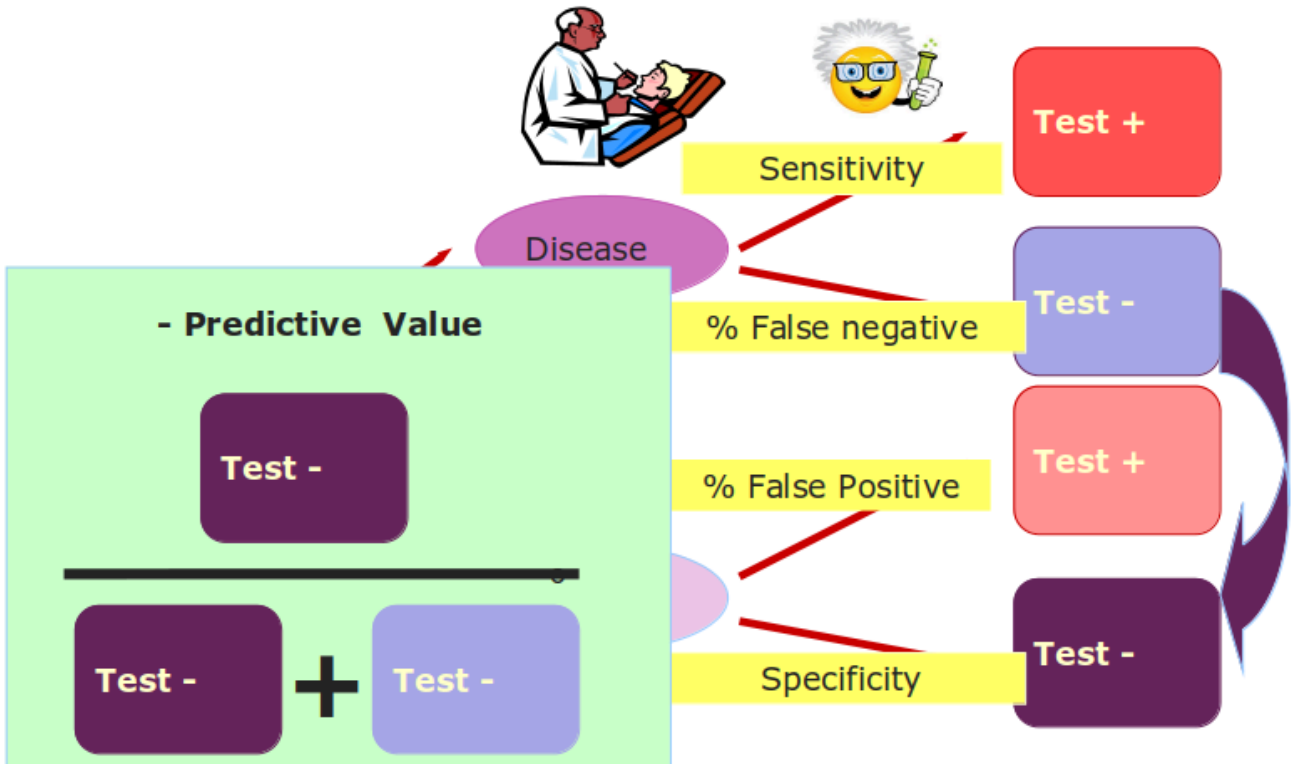
Positive predictive value (PPV)



If the test is **positive**:

*What is the probability that the patient is **really affected**?"*

Negative predictive value (NPV)



If the test is **negative**:

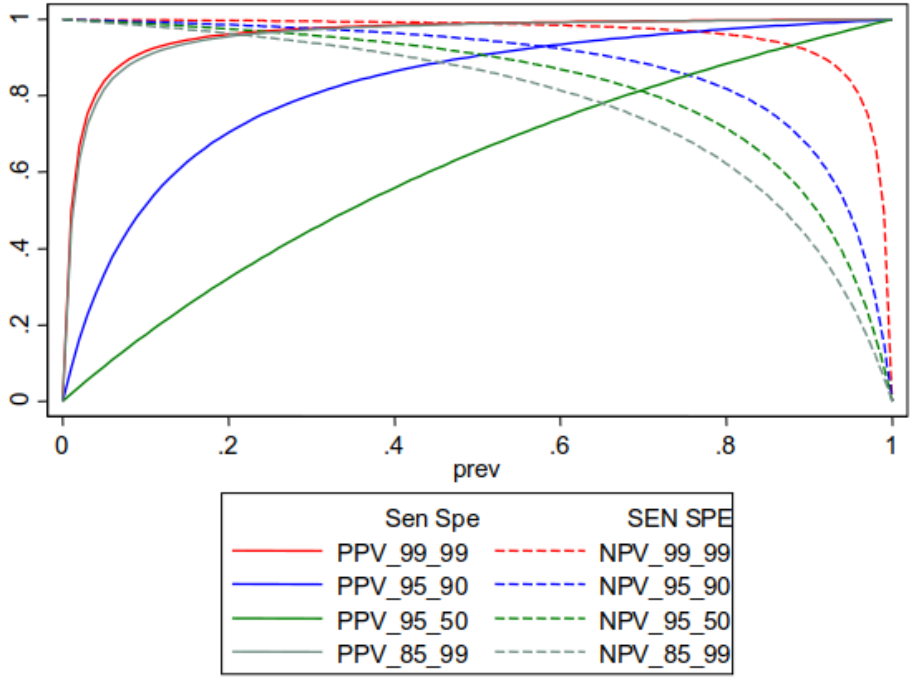
*What is the probability that the patient is really **not affected**?"*

Example: PPV and NPV

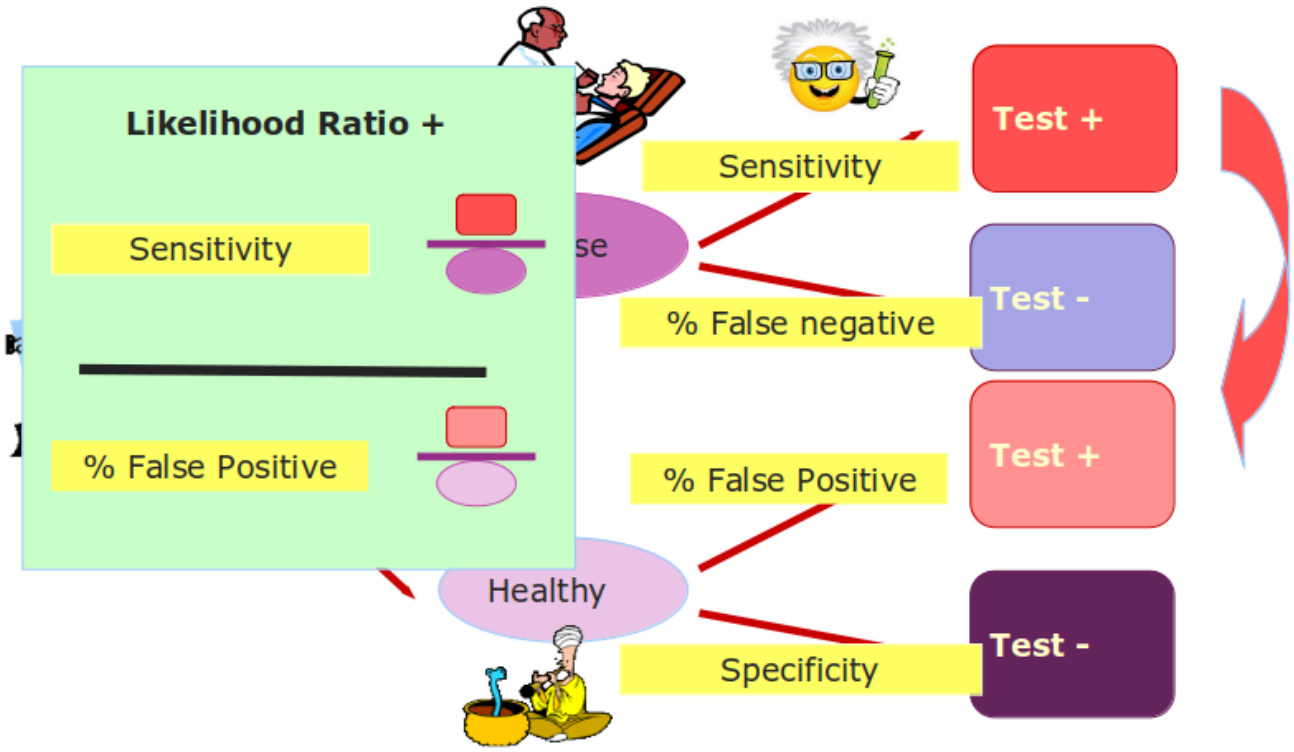
		Biopsy result		
		Disease	Healthy	TOTAL
Rectal examination	Disease	634	269	903
	Healthy	487	1251	1738
	TOTAL	1121	1520	2641

- **Positive Predictive Value** = 634 / (634+269) = 0.702 = 70.2% $\longrightarrow$ *A person who tested positive has a 70.2% of probability of* ***having cancer***
- **Negative predictive value** = 1251 / (487+1251) = 0.719 = 71.9% $\longrightarrow$ *A person who tested negative has a 71.9% of probability of* ***not having cancer***

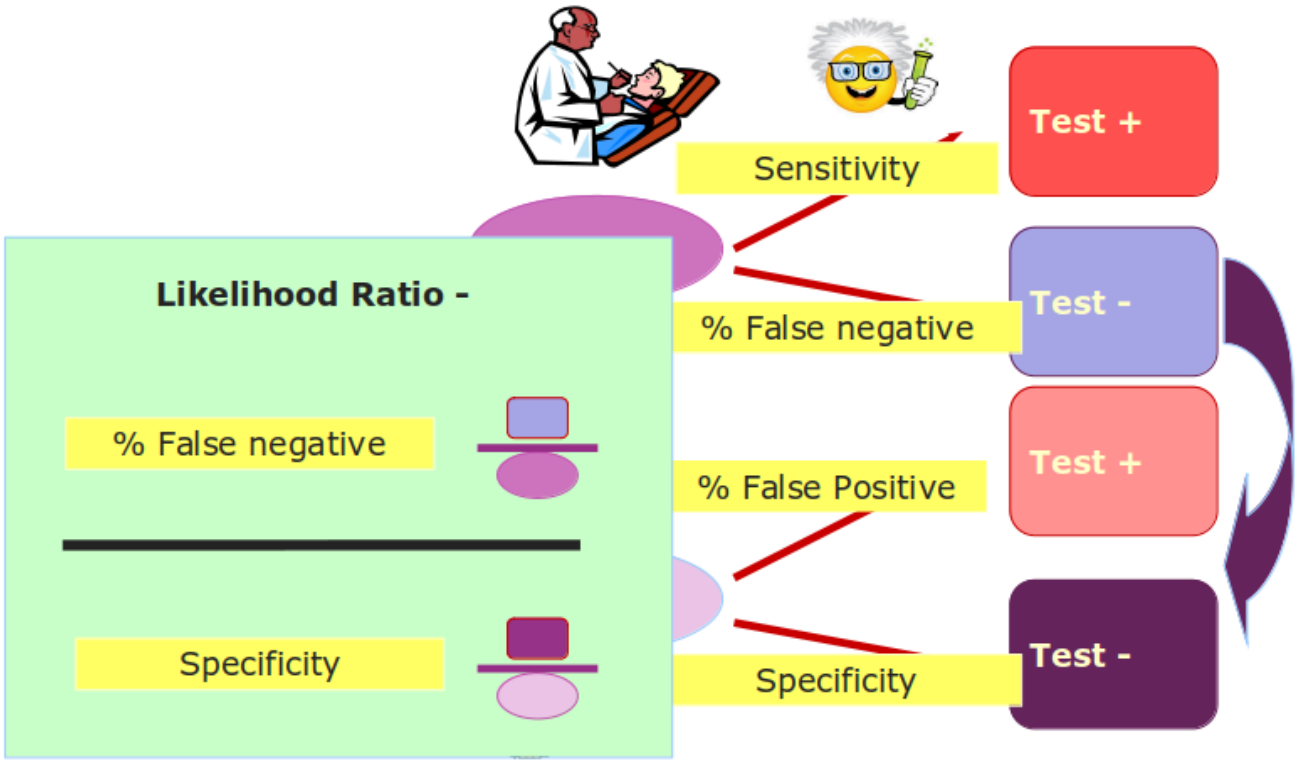
PPV and NPV depend on prevalence



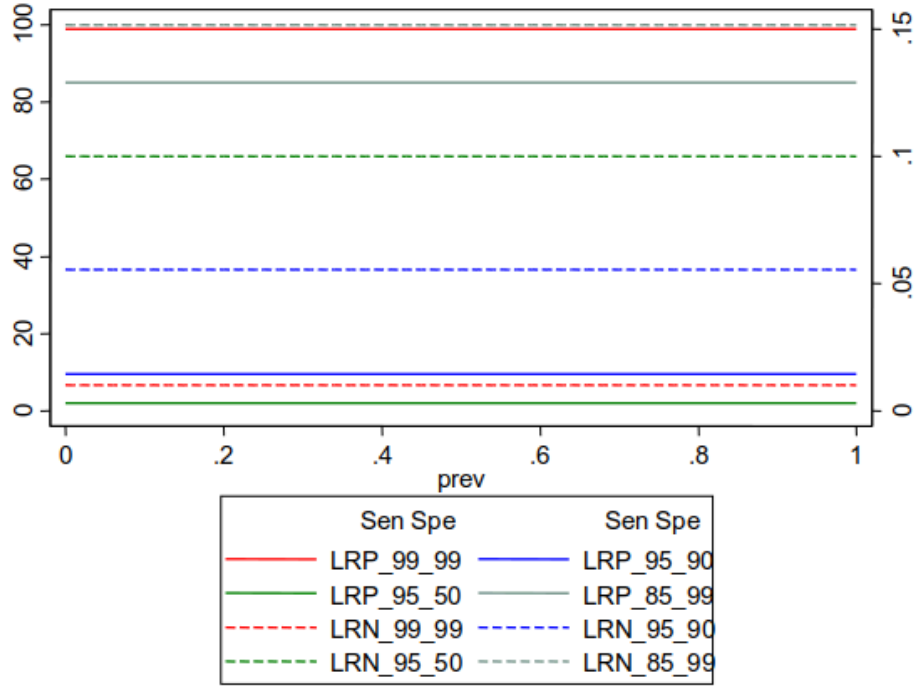
Positive Likelihood Ratio (+LR)



Negative Likelihood Ratio (-LR)



+LR/-LR independent of prevalence



Interpreting likelihood ratios

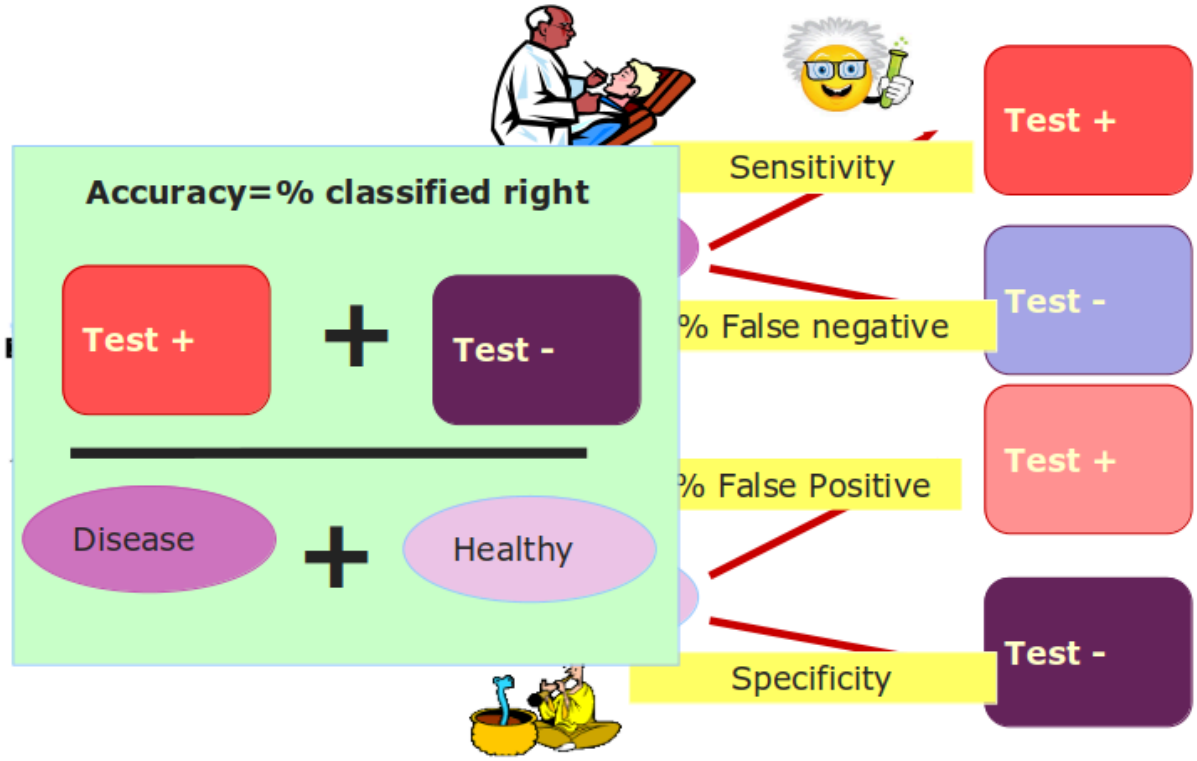
- Ideally a positive likelihood of ratio of 1 means that disease and health are equally likely.
- From here,
  - the higher the +LR more likely is the disease.
  - the smaller the +LR less likely is the disease.
- Usual thresholds
  - 5-10 disease is highly likely
  - 0.2-10 likelihood of disease not changed
  - 0.1-0.2 disease is less likely

Example: +LR and -LR

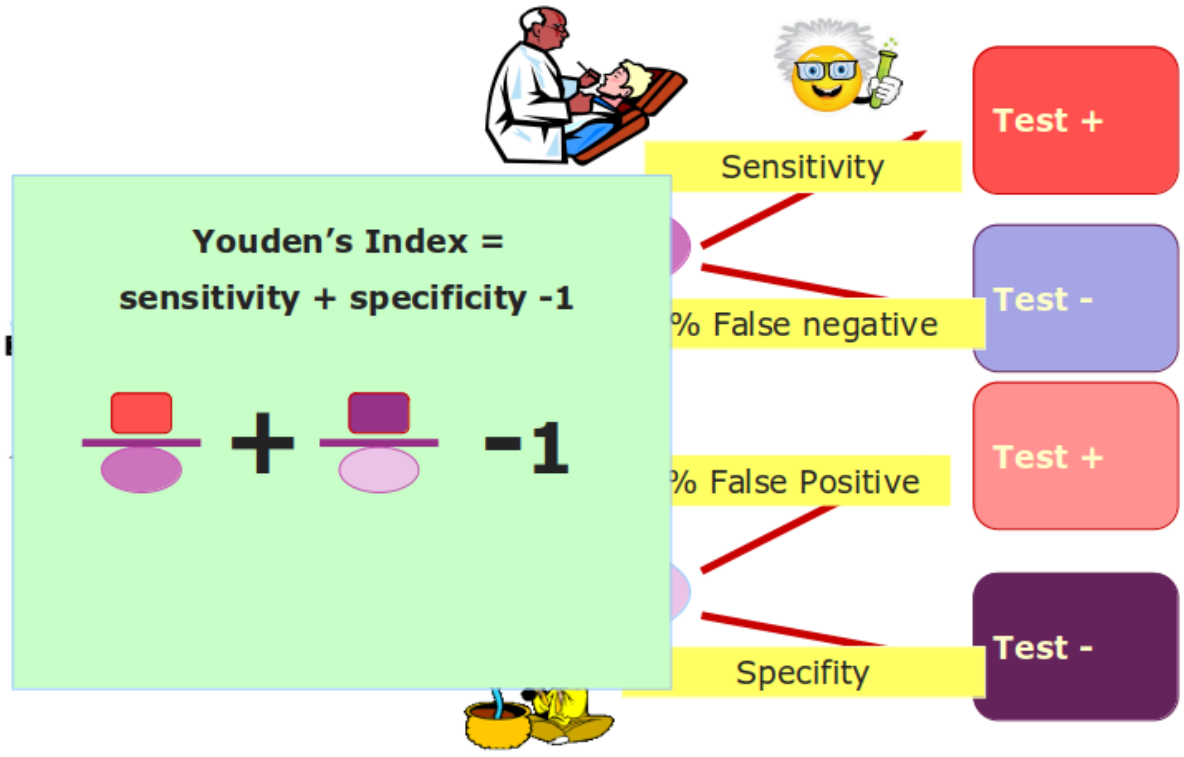
		Biopsy result		
		Disease	Healthy	TOTAL
Rectal examination	Disease	634	269	903
	Healthy	487	1251	1738
	TOTAL	1121	1520	2641

- **Positive Likelihood Ratio** = Sens/%FP = 0.5656 / (1-0.8230) = 3.1954
- **Negative Likelihood Ratio** = Spec/ %FN = (1-0.8230) / 0.5656 = 0.312942

Accuracy

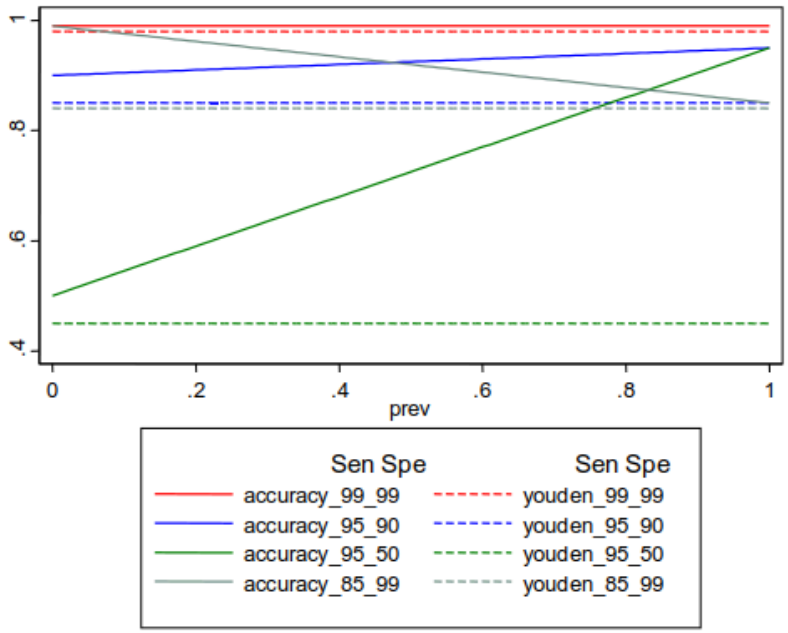

Accuracy=% classified right
Test +
+
Test -
Disease
+
Healthy
Sensitivity
% False negative
% False Positive
Specificity
Test +
Test -
Test +
Test -

Youden's Index



Accuracy vs Youden's Index

Accuracy depends on prevalence but,
Youden's Index do NOT depend on prevalence.



Computing diagnostic measures

with R

```
library(dplyr); library(ggplot2); library(epiR)
```

```
##
## Adjuntando el paquete: 'dplyr'

## The following objects are masked from 'package:stats':
##
##     filter, lag

## The following objects are masked from 'package:base':
##
##     intersect, setdiff, setequal, union

## Cargando paquete requerido: survival

## Package epiR 2.0.80 is loaded

## Type help(epi.about) for summary information

## Type browseVignettes(package = 'epiR') to learn how to use epiR for applied
```

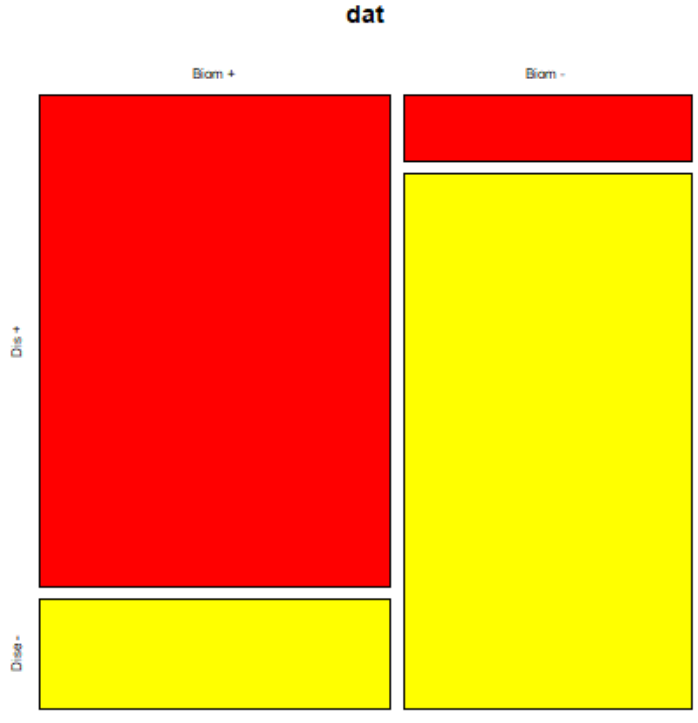
Computing diagnostic measures

with R

```
knitr::kable(dat)
```

	Dis +	Dise -
Biom +	90	20
Biom -	10	80

```
plot(dat,title("Diagnostic data"), col=c(
```



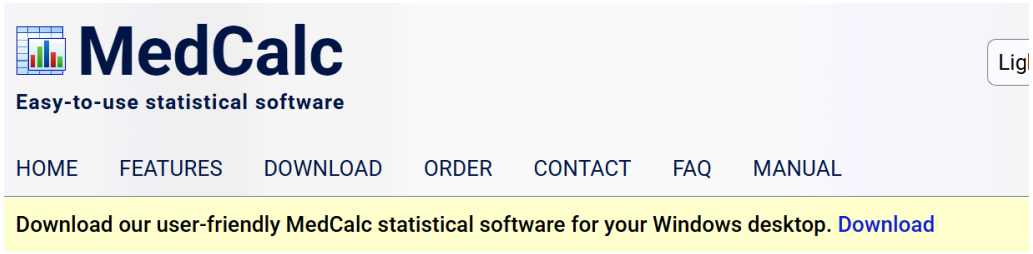
Diagnostic measures with R

```
rval ← epi.tests(dat)
print(rval)
```

```
##           Outcome +    Outcome -      Total
## Test +           90           20        110
## Test -           10           80         90
## Total           100          100        200
##
## Point estimates and 95% CIs:
## -------------------------------------------------------------
## Apparent prevalence *                  0.55 (0.48, 0.62)
## True prevalence *                      0.50 (0.43, 0.57)
## Sensitivity *                          0.90 (0.82, 0.95)
## Specificity *                          0.80 (0.71, 0.87)
## Positive predictive value *            0.82 (0.73, 0.89)
## Negative predictive value *            0.89 (0.81, 0.95)
## Positive likelihood ratio              4.50 (3.02, 6.70)
## Negative likelihood ratio              0.12 (0.07, 0.23)
## False T+ proportion for true D- *      0.20 (0.13, 0.29)
## False T- proportion for true D+ *      0.10 (0.05, 0.18)
## False T+ proportion for T+ *           0.18 (0.11, 0.27)
## False T- proportion for T- *           0.11 (0.05, 0.19)
## Correctly classified proportion *      0.85 (0.79, 0.90)
## -------------------------------------------------------------
## * Exact CIs
```

Medcalc free statistical calculator

https://www.medcalc.org/calc/



MedCalc

Easy-to-use statistical software

HOME FEATURES DOWNLOAD ORDER CONTACT FAQ MANUAL

Download our user-friendly MedCalc statistical software for your Windows desktop. Download

Free statistical calculators

Statistical tests | Sample size calculation

Means & Standard deviations

- Test for one mean
- Comparison of means
- Comparison of standard deviations

Proportions

- Test for one proportion
- Comparison of proportions
- McNemar test on paired proportions
- Fisher's exact test for 2x2 table

Chi-squared test

- One-way Chi-squared test
- Two-way Chi-squared test

Correlation

Rates

- Confidence interval for a rate
- Comparison of two rates

Test evaluation

- Comparison of Coefficients of Variation
- Inter-rater agreement (Kappa)

Relative risk & Odds ratio

- Relative risk
- Odds ratio

Diagnostic test

- Diagnostic test evaluation
- Likelihood ratios (2xk table)

Diagnostic measures with Medcalc

	Disease				
Test	**Present**	**n**	**Absent**	**n**	**Total**
Positive	True Positive	a= 90	False Positive	c= 20	a + c = **110**
Negative	False Negative	b= 10	True Negative	d= 80	b + d = **90**
Total		a + b = **100**		c + d = **100**	

Disease prevalence

If the ratio of cases in the Disease Present and Disease Absent groups does not reflect the disease prevalence, enter:

disease prevalence (%):

OK

Diagnostic measures with Medcalc

Statistic	Value	95% CI
Sensitivity	90.00%	82.38% to 95.10%
Specificity	80.00%	70.82% to 87.33%
Positive Likelihood Ratio	4.50	3.02 to 6.70
Negative Likelihood Ratio	0.12	0.07 to 0.23
Disease prevalence (*)	50.00%	42.87% to 57.13%
Positive Predictive Value (*)	81.82%	75.15% to 87.01%
Negative Predictive Value (*)	88.89%	81.51% to 93.56%
Accuracy (*)	85.00%	79.28% to 89.65%

Exercise

- How do previous results change if values in the table are modified as:

```
dat← as.table(matrix(c(90, 200,10,800), nrow=2, byrow=TRUE))
colnames(dat) ← c("Dis+","Dis-")
rownames(dat) ← c("Biom+","Biom-")
knitr::kable(dat)
```

	Dis+	Dis-
Biom+	90	200
Biom-	10	800

Exercise

- In J Trop Pediatr in January 2006, a rapid serological test was presented for the diagnosis of Helicobacter pylori infection.
- The test was applied to 81 children. Usual microbiological tests ("Gold Standard") to find out if they were really infected were additionally performed.
- The results are provided below

	Disease	**Healthy**
Positive	24	1
Negative	3	53

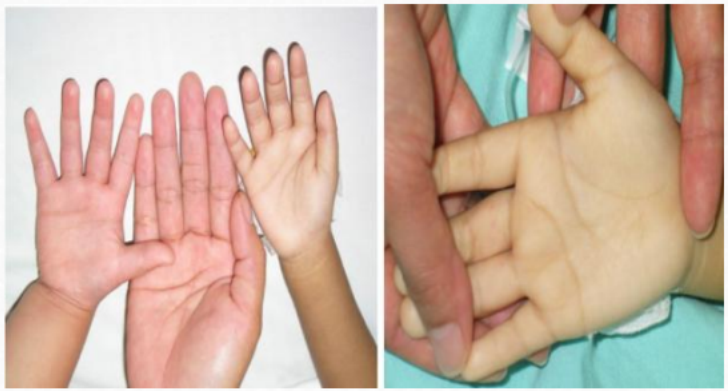
- Evaluate the properties of the test. Would you recomend its use?

Exercise

- The "palmar pallor sign" has been related to the presence of anemia.
- It was evaluated in a jungle region of Colombia to see if it could be useful as a rapid test for diagnosing anemia.
- A blood count was taken in 167 children and it was found out that 48 had anemia and 119 did not.

- The palmar pallor sign was positive in 16 anemics and negative in 95 non-anemic was negative.

- Evaluate the properties of the test. Would you recomend its use?

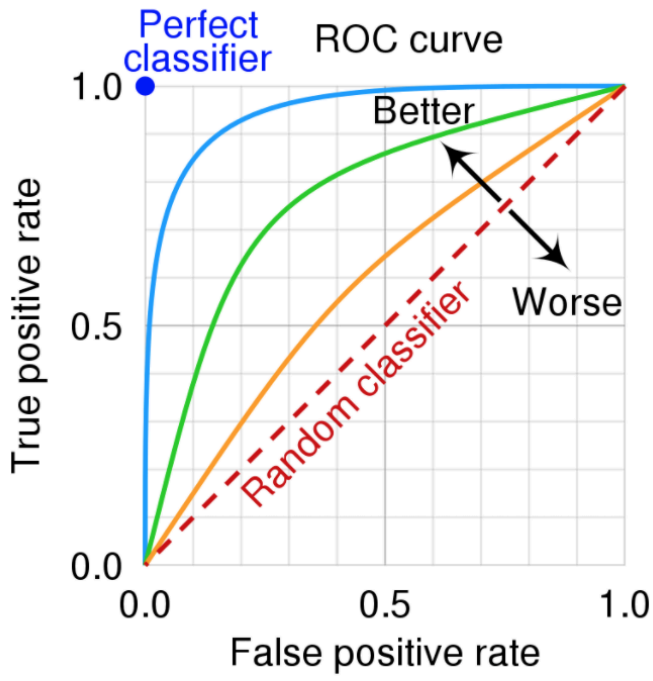


Quantitative biomarkers

- Many tests provide dichotomous values such as TRUE/FALSE, Presence/Absence, etc.
    - The analysis of their diagnostic properties is straightforward.
- How can we use *continuous biomarkers*, such as the expression of a gene, which is known to be related with the diagnostic,
    - A reasonable option is to analyze different cutting points that would provide a dichotomous classification
    - And select cutpoint that *best* separates the two groups.
- This is done using Receiver Operation Characteristic functions also known as "ROC" curves.

ROC curves

- A graphical plot that shows the diagnostic ability of a binary classifier as its discrimination threshold is varied.
- It is created by plotting the true positive rate (TPR) against the false positive rate (FPR) at various threshold settings.
  - TPR = Sensitivity
  - FPR = 1-Specificity



The *Area Under the Curve* (AUC) is a rough measure of the performance of the classifier

ROC curves in R

```
diab ← haven::read_sav("diabetes.sav")
roc_curve ← pROC::roc(factor(diab$MORT), diab$EDAT,auc=TRUE)
```

```
## Setting levels: control = 0, case = 1
```

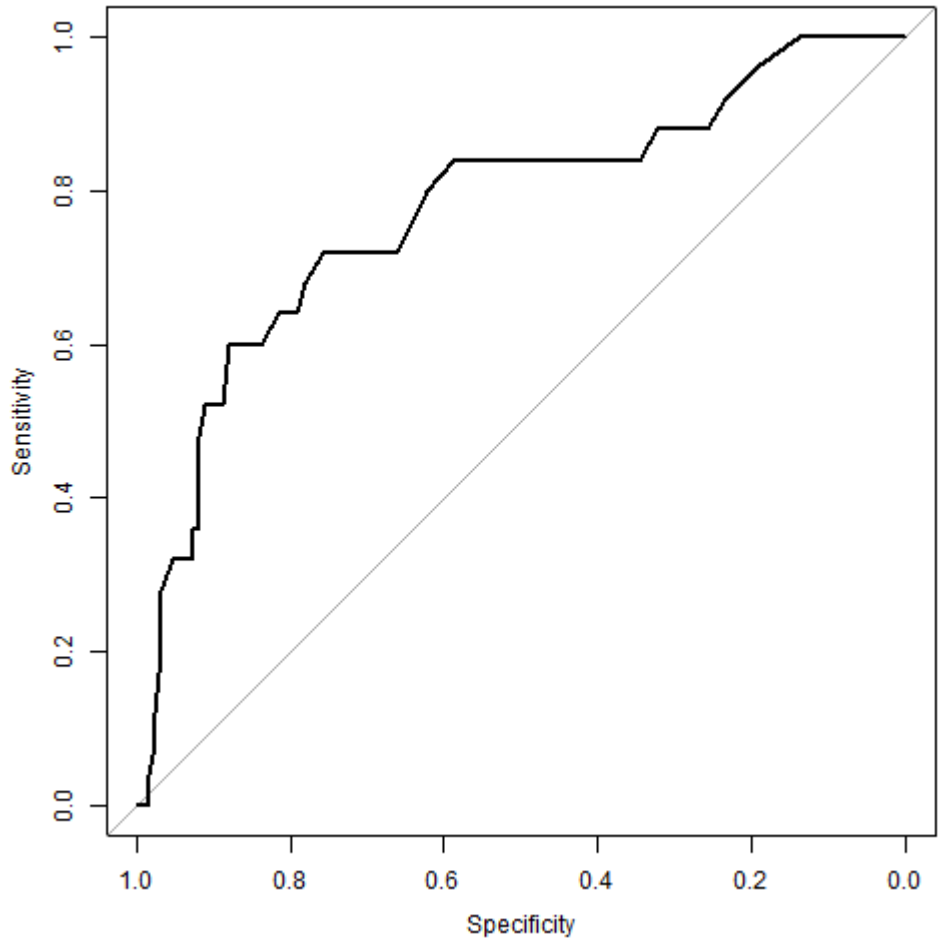
```
## Setting direction: controls < cases
```

```
print(roc_curve)
```

```
##
## Call:
## roc.default(response = factor(diab$MORT), predictor = diab$EDAT,     auc =
##
## Data: diab$EDAT in 124 controls (factor(diab$MORT) 0) < 25 cases (factor(di
## Area under the curve: 0.775
```

ROC curves in R

```
plot(roc_curve)
```



Building the biomarker from ROC

- The ROC curve shows how the relation between sensitivity and specificity changes for distinct cutoffs (each of the marker values).
- In order to decide the "best" cutoff a balance between sensitivity and specificity has to be agreed.
- There are distinct possibilities depending on the case:
    - Set one of the measures (usually sensitivity) to the desired value and take as cutoff the marker's value that provides this.
    - Look for that marker's value that maximize the combination SENS & SPEC, for example that maximize YOUDEN's index.

Youden's index in R

```
best_coords ← pROC::coords(roc_curve, "best", best.method = "youden'

best_coords ← unlist(best_coords)


best_cutoff_df ← data.frame(
  Metric = c("Optimal Cutoff", "Sensitivity", "Specificity", "Youden'
  Value = c(best_coords["threshold"], best_coords["sensitivity"], bes
)

# Mostrar el data frame
print(best_cutoff_df)
```

```
##                     Metric      Value
## threshold   Optimal Cutoff 61.5000000
## sensitivity    Sensitivity  0.6000000
## specificity    Specificity  0.8790323
## youden      Youden's Index  1.4790323
```

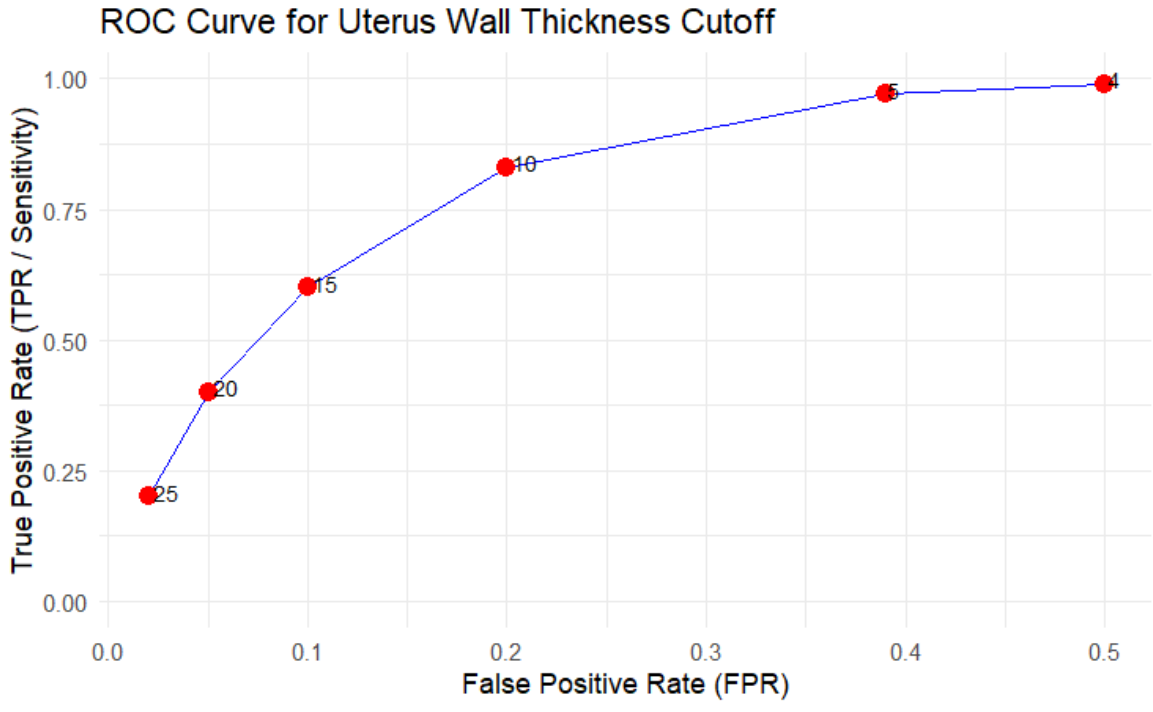
Example

- Ultrasounds can be used to detect thinning of the uterus Wall as an indicative of a posible tumor.
- "Abnormal Wall Thickness" can be declared at distinct thickness, which, for a given sample (not shown) yields distinct sensitivity and specificity values.
- Build a ROC curve for these and find out the *best* cutoffs for this problem.

Cutoff for abnormal wall thickness	Sentivity (%)	Specificity (%)	1-Specificity(%)
>4 mm	99	50	50
>5 mm	97	61	39
>10 mm	83	80	20
>15 mm	60	90	10
>20 mm	40	95	5
>25 mm	20	98	2

Objetive: To maximize the number of TP (correct diagnosis of cancer) with an aceptable number of FP (biopsies made when there was no cancer)

Example (continued)



- To maximize TP take a cutoff with high sensitivity (cutoff: "> 5mm").
- To maximize both SENS and SPEC take cutoff: "> 10 mm" where Youden's index (SENS + SPEC -1) is maximized

Exercise

- In the "Osteoporosis" dataset build two ROC curves based on the two continuous variables "imc" and "bua"
- Which classifier is better?
- How would you compare the two classifiers?

Building and Validating Biomarkers

Building and Validating Biomarkers

- This part has been omitted from these slides.
- On overview of how to build and validate classifiers is provided in the *Statistical Pill* :

Busqueu la fama, i aquí és on aneu a començar a pagar: Estratègies per a la construcció de models i biomarcadors

References and Resources

References and resources

- Allison DB et al. (2005) Microarray data analysis: from disarray to consolidation and consensus Nat Rev gene. 7: 55–65
- Dupuy A, Simon RM. Critical review of published microarray studies for cancer outcome and guidelines on statistical analysis and reporting. J Natl Cancer Inst . 2007;99(2):147-157. doi:10.1093/ jnci /djk018
- Majewski , I., Bernards , R. Taming the dragon: genomic biomarkers to individualize the treatment of cancer. Nat Med 17, 304–312 (2011).
- Roepman P. The future of diagnostic gene-expression microarrays: bridging the gap between bench and bedside. Bioanalysis . 2010;2(2):249-262. doi:10.4155/bio.09.172
- Xia J, Broadhurst DI, Wilson M, Wishart DS. Translational biomarker discovery in clinical metabolomics: an introductory tutorial. Metabolomics Off J Metabolomic Soc . 2013;9(2):280-299. doi:10.1007/s11306-012-0482-9