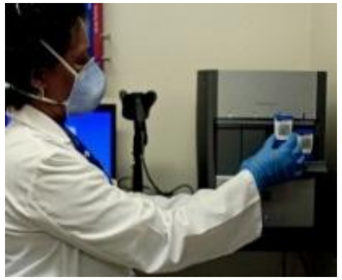
Diagnostic Studies





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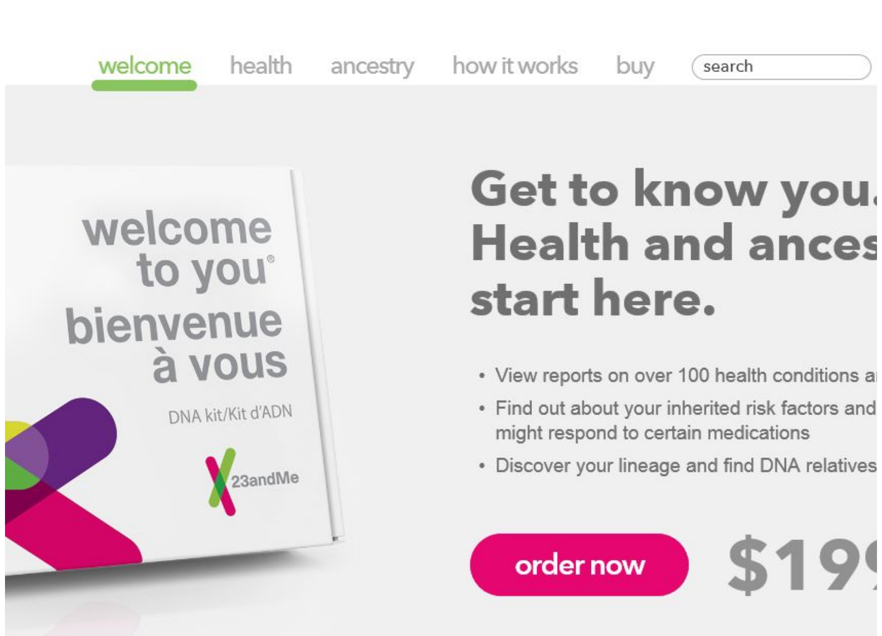
WHY SCREENING, DIAGNOSTIC AND PROGNOSTIC TESTS MATTER

- Diagnosis is the first and important step in the pathway to correct treatment
- Early and rapid diagnosis can reduce morbidity, improve patient outcomes, and reduce cost of care
- Tests can
  - identify disease & risk factors
  - predict prognosis
  - monitor therapy over time
  - promote healthy behaviours
  - tailor therapies (i.e. personalized medicine)
  - used for surveillance



Explosion of diagnostic technologies

This is all exciting, but…

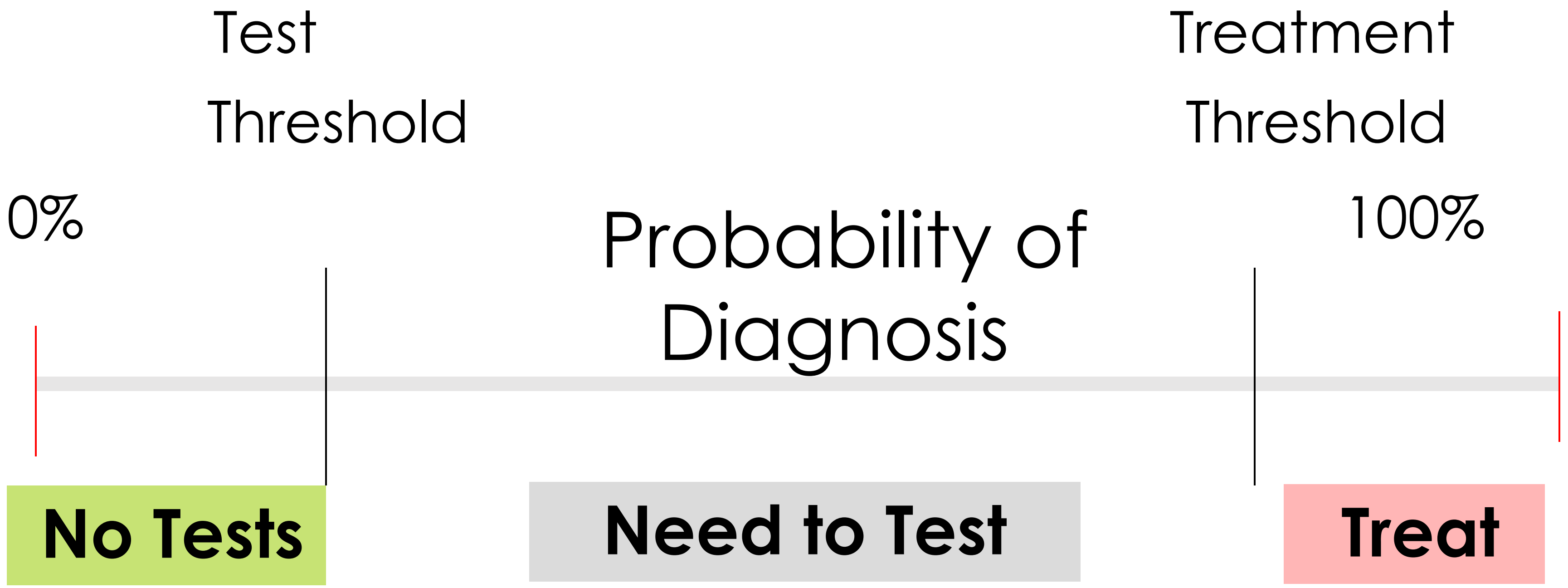
How do we know these new tests are accurate?

- Diagnostic tests, just like drugs and vaccines, need adequate validation before they can be used on people.
  - Too many Covid19 tests have been fast-tracked to market, with little validation!
- Just like drug trials, we do diagnostic trials.

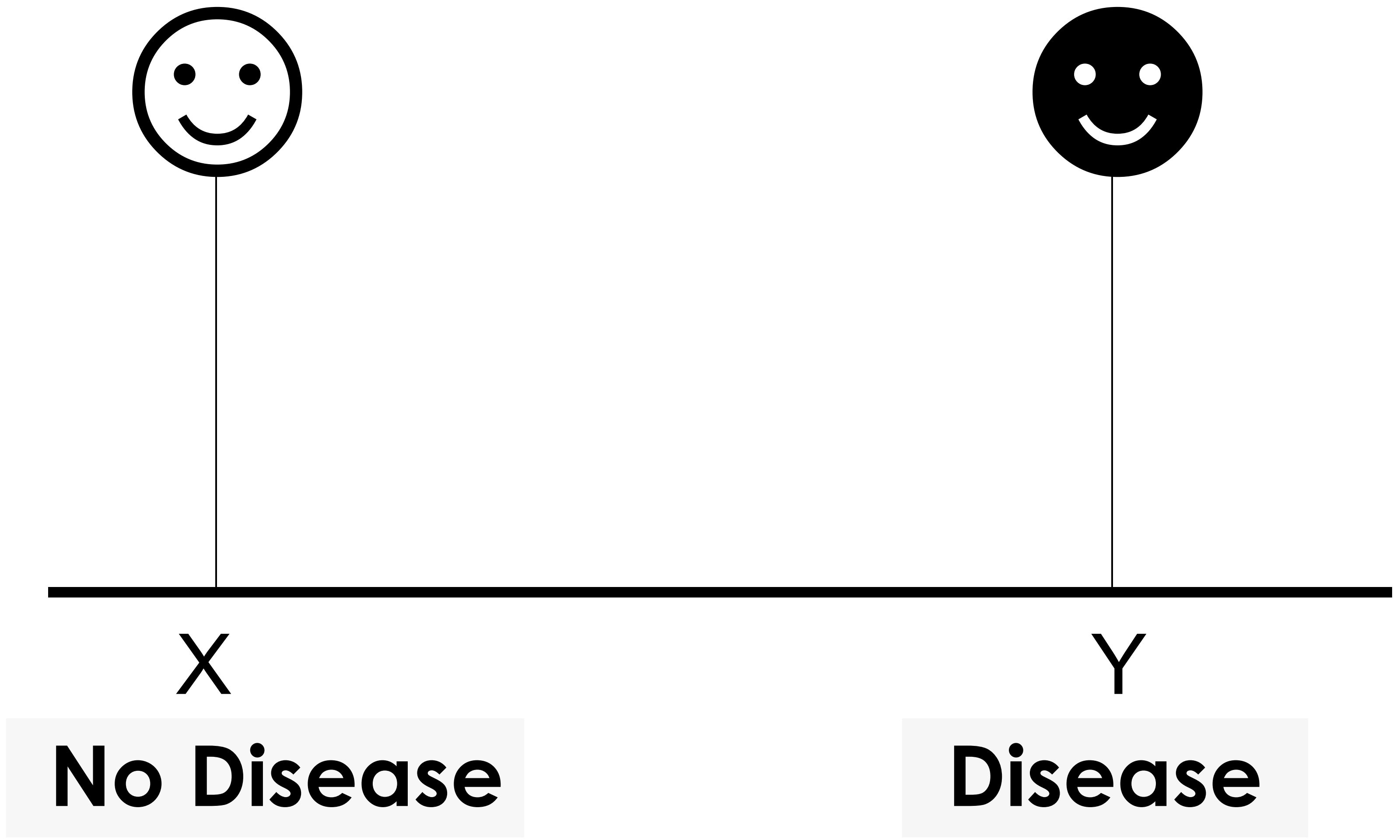
Diagnosis Vs Screening: they are different!

- A diagnostic test is done on sick people
  - patient presents with symptoms
  - pre-test probability of disease is high (i.e. disease prevalence is high)
- A screening test is usually done on asymptomatic, apparently healthy people
  - healthy people are encouraged to get screened
  - pre-test probability of disease is low (i.e. disease prevalence is low)

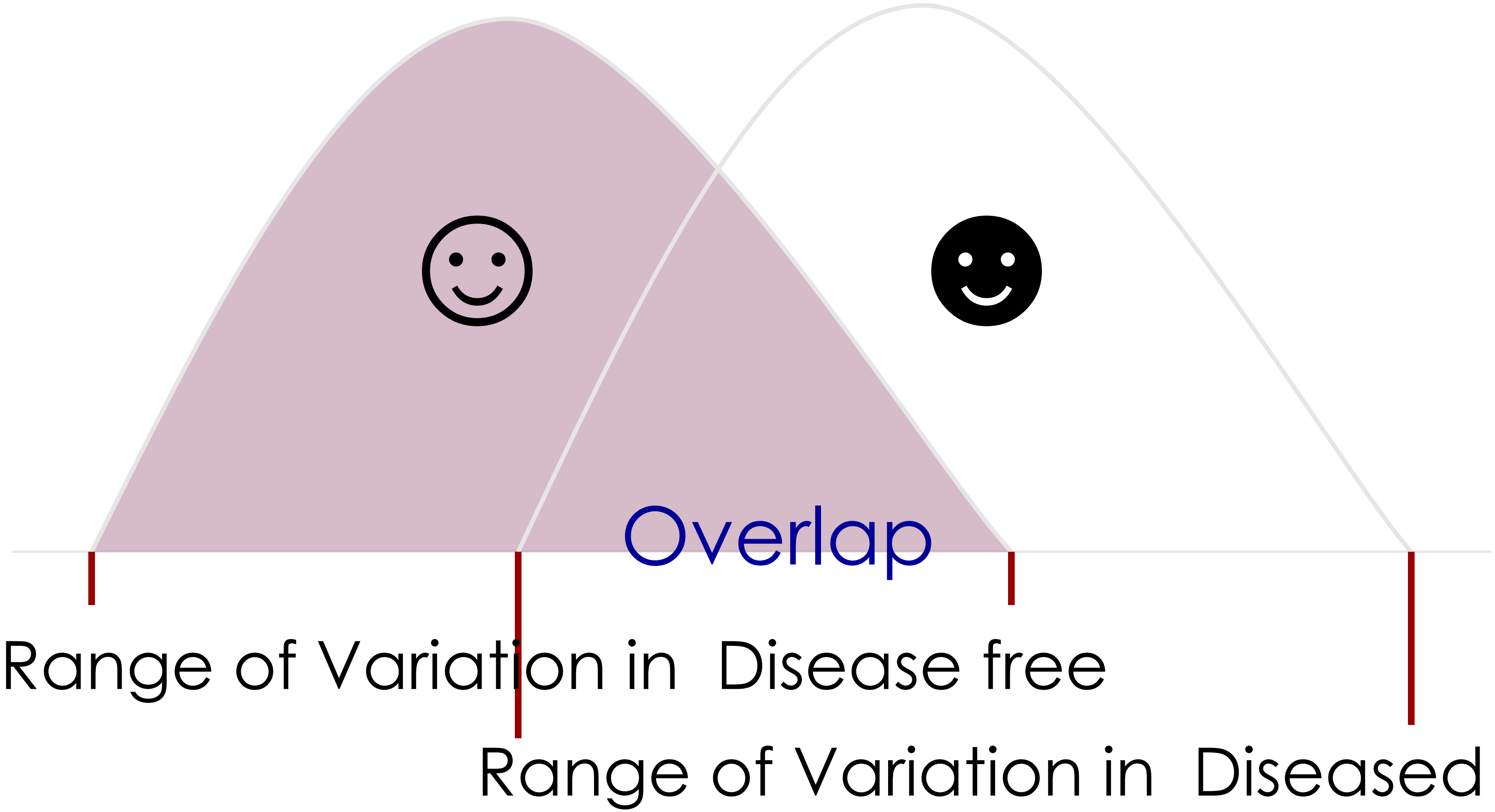
Process of diagnosis: all about probability!



The Perfect Diagnostic Test



Variations In Diagnostic Tests



So, cut-points matter a lot!

- Many tests produce continuous numbers, and doctors tend to use cut-points to make decisions
- Cut-points are a compromise – they are not perfect
- Same test can produce different results, based on cut-points used
- Cut-points can change over time

There is no perfect test!

Thomas Bayes

Thomas Bayes (The correct identification of this portrait has been [1] questioned.)

Born	c. 1702 London
Died	April 17th 1761 Tunbridge Wells
Nationality	British

LII. *An Essay towards solving a Problem in the Doctrine of Chances. By the late Rev. Mr.* Bayes, *communicated by Mr.* Price, *in a letter to* John Canton, *M. A. and F. R. S.*

Dear Sir,

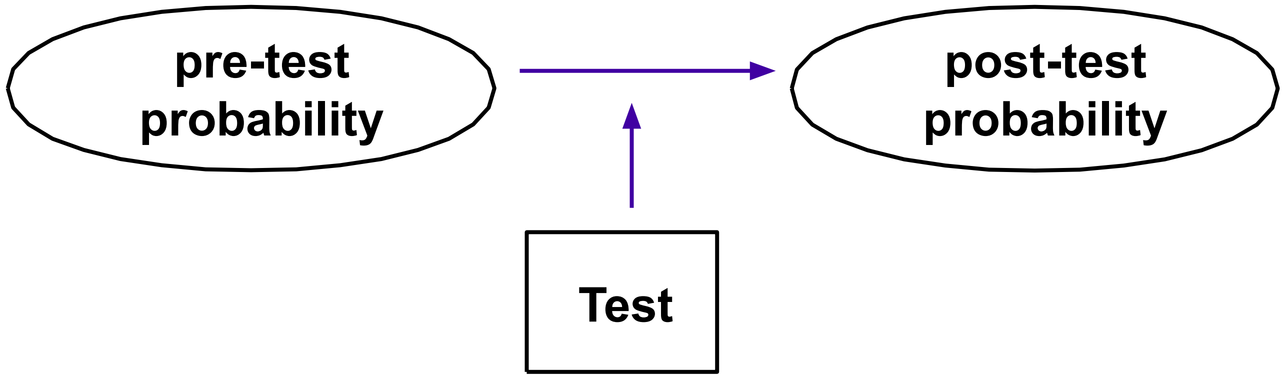
Read Dec. 23, 1763. I now send you an essay which I have found among the papers of our deceased friend Mr. Bayes, and which, in my opinion, has great merit, and well deserves to be preserved. Experimental philosophy, you will find, is nearly interested in the subject of it; and on this account there seems to be particular reason for thinking that a communication of it to the Royal Society cannot be improper.

He had, you know, the honour of being a member of that illustrious Society, and was much esteemed by many as a very able mathematician. In an introduction which he has writ to this Essay, he says, that his design at first in thinking on the subject of it was, to find out a method by which we might judge concerning the probability that an event has to happen, in given circumstances, upon supposition that we know nothing concerning it but that, under the same circumstances, it has happened a certain number of times, and failed a certain other number of times. He adds, that he soon perceived that it would not be very difficult to do this, provided some rule could be found, according to which we ought to estimate the chance that the probability for the happening of an event perfectly unknown, should lie between any two named degrees of prob-

All we can hope to do is increase or decrease probabilities, and Bayes' theorem helps with this process

BAYES' THEORY

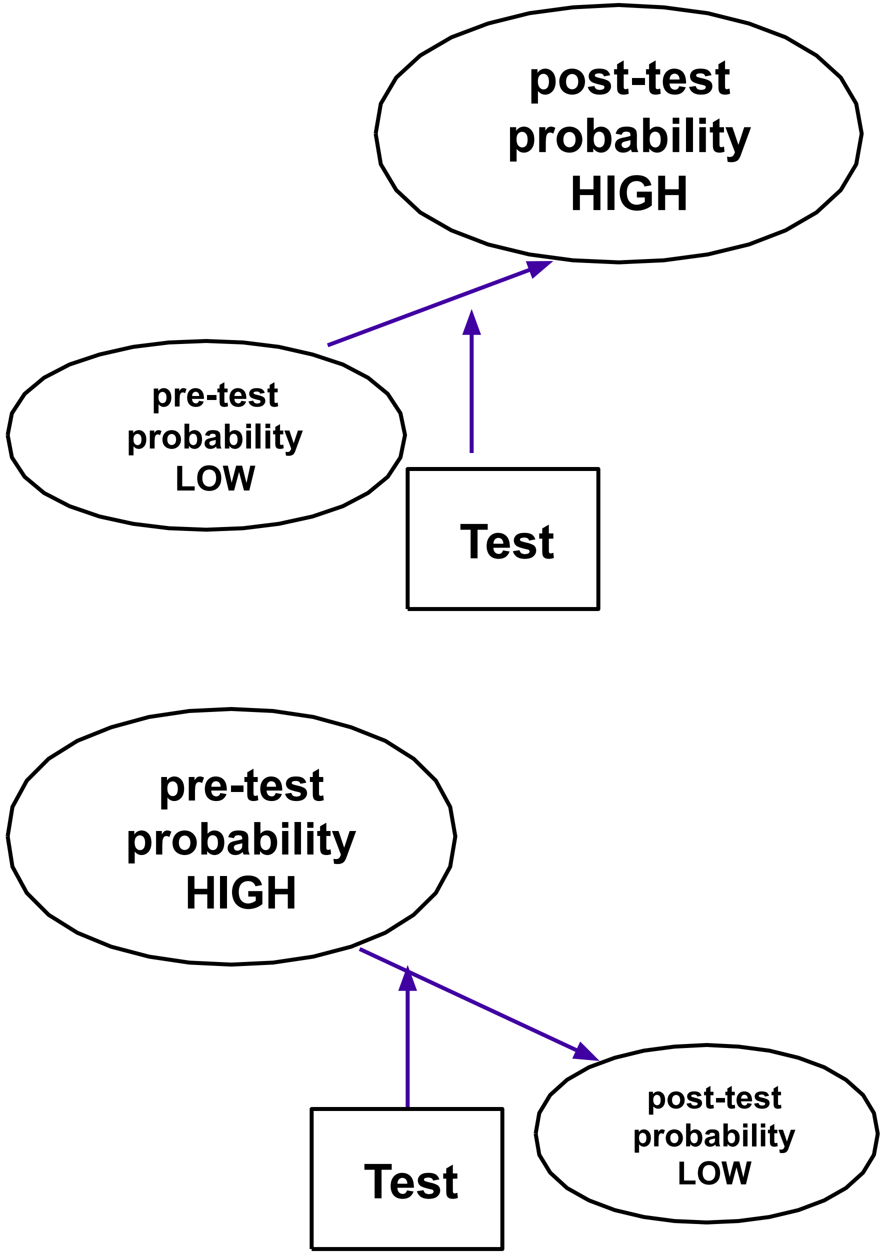
What you thought before + New information = What you think now



Post-test odds = Pre-test odds x Likelihood ratio

Bayesian approach to diagnosis

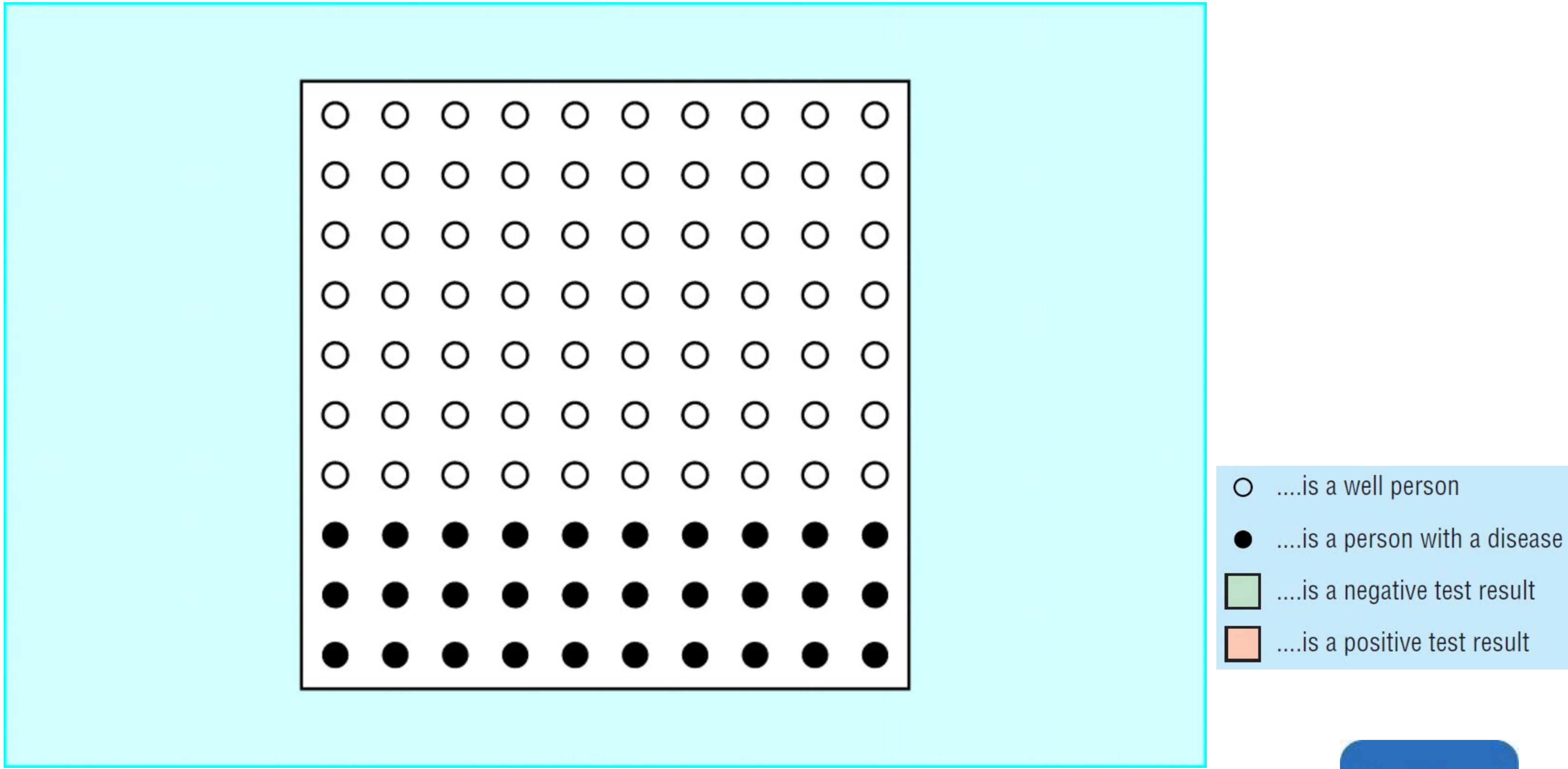
- An accurate test will help reduce uncertainty
- The pre-test probability is revised using test result to get the post-test probability
- Tests that produce the biggest changes from pretest to post-test probabilities are most useful in clinical practice [very large or very small likelihood ratios]



Steps in evaluating a diagnostic test

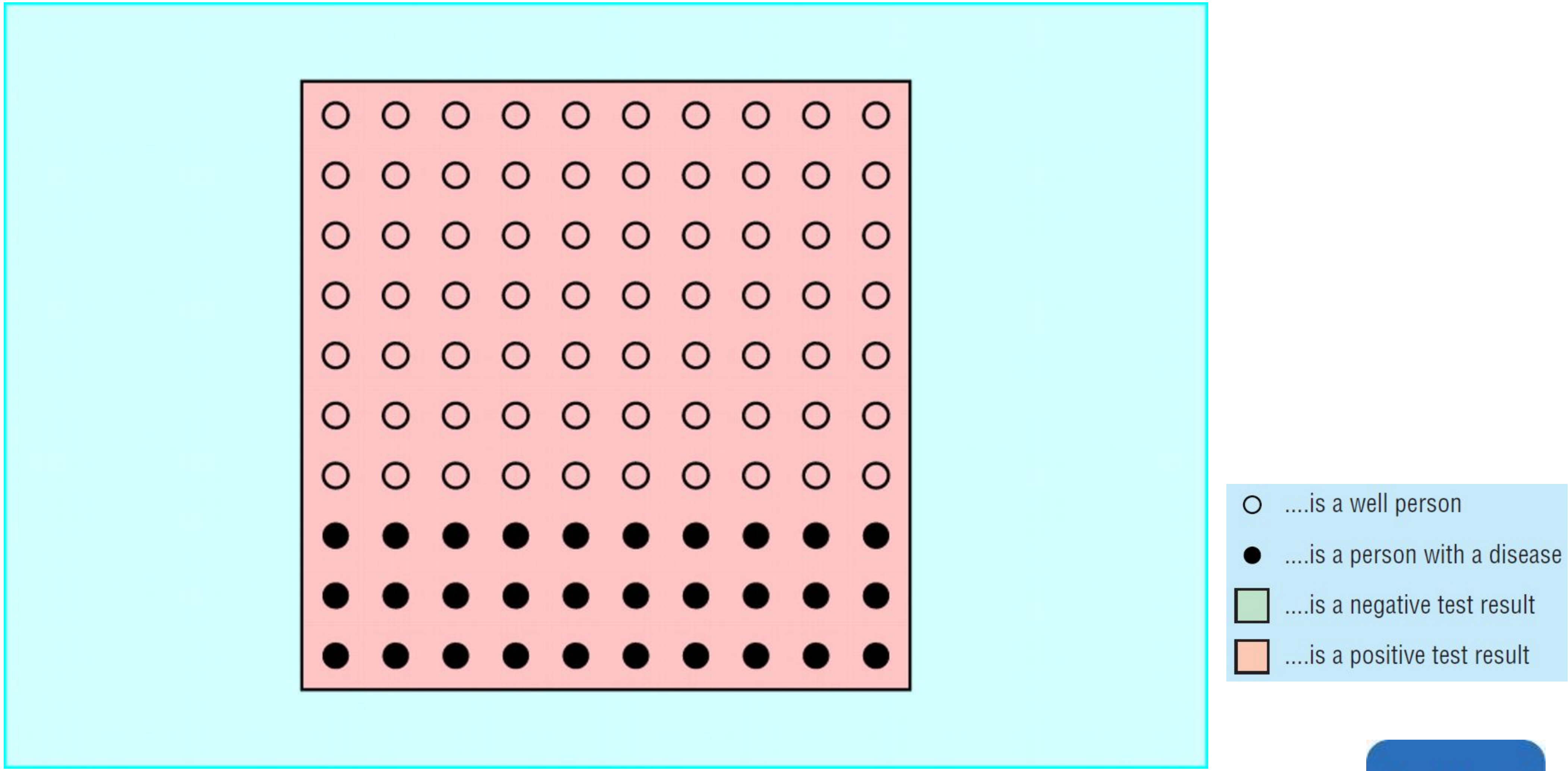
- Define gold standard or reference standard
- Recruit consecutive patients in whom the test is indicated (in whom the disease is suspected)
- Perform gold standard on all, to identify true disease status
- Perform test on all and classify them as test positives or negatives
- Set up 2 x 2 table and compute:
  - Sensitivity
  - Specificity
  - Predictive values

Imagine a hypothetical population (some with disease and others without)



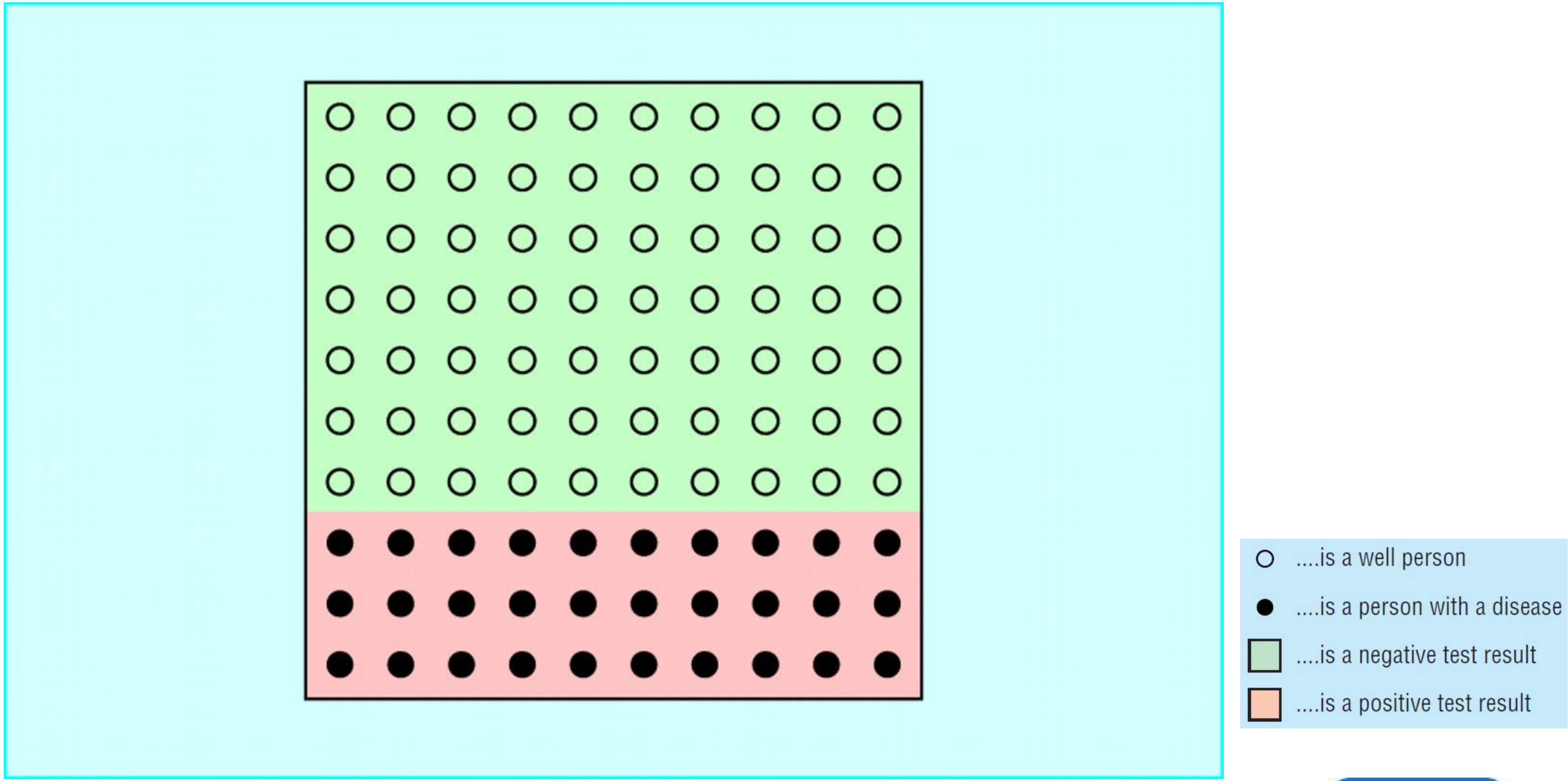
Loong T BMJ 2003;327:716-719

If a test was positive in everyone, what would you make of this test?



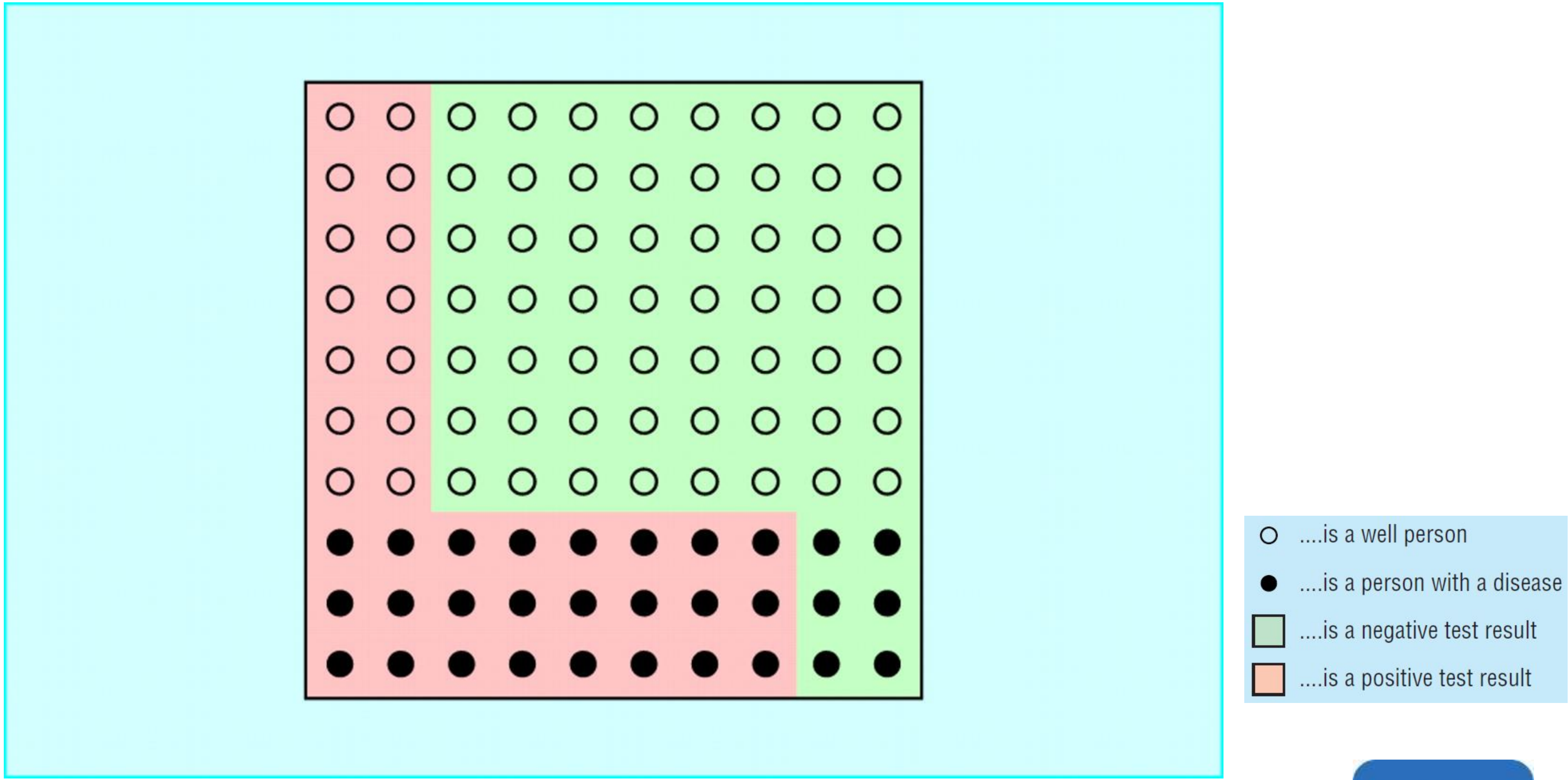
Loong T BMJ 2003;327:716-719

What about this scenario?



Loong T BMJ 2003;327:716-719

In reality, most tests will produce these sorts of results



Loong T BMJ 2003;327:716-719

Let us now quantify test accuracy

- Diagnostic 2 X 2 table:

	Disease +	Disease -
Test +	True Positive	False Positive
Test -	False Negative	True Negative

Sensitivity [true positive rate]

	Disease present	Disease absent
Test positive	True positives	False positives
Test negative	False negative	True negatives

The proportion of patients with disease who test positive = P(T+|D+) = TP / (TP+FN)

Specificity [true negative rate]

	Disease present	Disease absent
Test positive	True positives	False positives
Test negative	False negative	True negatives

The proportion of patients without disease who test negative: P(T-|D-) = TN / (TN + FP).

Predictive value of a positive test

	Disease present	Disease absent
Test positive	True positives	False positives
Test negative	False negative	True negatives

Proportion of patients with positive tests who have disease = P(D+|T+) = TP / (TP+FP)

Predictive value of a negative test

	Disease present	Disease absent
Test positive	True positives	False positives
Test negative	False negative	True negatives

Proportion of patients with negative tests who do not have disease = P(D-|T-) = TN / (TN+FN)

Example: Antibody test for Covid-19

Clinical Chemistry

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Article Contents

Abstract

Author notes

Supplementary data

ACCEPTED MANUSCRIPT

Clinical Performance of Two SARS-CoV-2 Serologic Assays FREE

Mei San Tang, Karl G Hock, Nicole M Logsdon, Jennifer E Hayes, Ann M Gronowski, Neil W Anderson, Christopher W Farnsworth Author Notes

Clinical Chemistry, hvaa120, https://doi.org/10.1093/clinchem/hvaa120

Published: 13 May 2020 **Article history** ▾

103 specimens from 48 patients with PCR confirmed SARS-CoV-2 infections and 153 control specimens were analyzed using SARS-CoV-2 serologic assays by Abbott and EUROIMMUN (EI).

https://academic.oup.com/clinchem/advance-article/doi/10.1093/clinchem/hvaa120/5836557

EUROIMMUN TEST

Gold Standard

Antibody test		PCR+ Covid cases	Pre-2019 negative controls	
	Positive	41	3	44
	Negative	7	47	54
		48	50	98

Sensitivity = 85%
Specificity = 94%

Pos Predictive Value = 93%
Neg Predictive Value = 87%

Disease prevalence in this study ~50% (48 / 98)

What happens when we use this test to measure sero-prevalence?

- Let’s imagine the population prevalence is is modest (e.g. 30%)
  - If 1000 people were tested in this population, with the 85% sensitivity and 94% specificity we have for Euroimmun test, we should get this 2x2 table:

		Disease +	Disease -	
Antibody test	+	255	42	297
	-	45	658	703
		300	700	1000

Pos Predictive Value = 86% (less than 93% when prevalence was 50%)
Neg Predictive Value = 94%

What happens when we use this test to measure sero-prevalence?

- Let's imagine the population prevalence is low (e.g. 2%)
  - If 1000 people were tested in this population, with the 85% sensitivity and 94% specificity we have for Euroimmun test, we should get this 2x2 table:

		Disease		
		+	-	
Antibody test	+	17	59	76
	-	3	921	924
		20	980	1000

Pos Predictive Value = 22% (for 1 true positive, there will be nearly 4 false-positives)
Neg Predictive Value = ~100%

Sources of bias in diagnostic studies

- Bias due to an inappropriate reference standard
- Spectrum bias
- Verification (work-up) bias
  - Partial verification bias
  - Differential verification bias
- Review bias (lack of blinding)
- Incorporation bias

Take home messages

- Diagnostic tests are not perfect & need to be validated carefully before use
- Diagnostic and screening tests are very different and should not be confused
- Doctors and patients need to understand that all tests have their inherent error (i.e. false positives and false negatives)
- Tests should always be interpreted in context (hospital use vs prevalence surveys)
- Tests should be avoided unless there is a clear indication