6th Open Immunogenicity Congress - Lisbon 2014.

Controlling the rate of false positives in future tests. A Bayesian perspective.

Bruno Boulanger, PhD
Arlenda S.A, Belgium
bruno.boulanger@arlenda.com

Immunogenicity testing

- Antibodies elicited by therapeutic proteins may significantly alter drug safety and efficacy
- Immunogenicity testing is conducted by a multi-tiered approach whereby patient samples are initially screened for the presence of anti-drug antibodies (ADA) in a screening assay
- Samples testing positive for the presence of anti-drug antibodies in the screening assay are subsequently analyzed in a confirmatory assay which characterizes the specificity of the binding response to the drug.
- The objective is to identify ADA^{+} treated patients.
- The question is then $p(ADA^{+} \mid screening^{+})$

The background: Screening Cut point

- It's about the performance of the screening test
- The Screening Cut Point (CP) is determined
  - using a +- reduced number of naïve patients, say 100 patients.
  - using kind of ~"95th percentile" (parametric or not) of observed values
- The aim is to accept 5% false-positive rate (FPR)
- The false-positive rate is deliberately chosen high because
  - It allows to detect low-affinity positive samples
  - the sensitivity of test ($p(CP^+ \mid ADA^+)$ is unknown
- The prevalence or risk - $p(ADA^+)$ - of immunogenicity is unknown
  - By definition, the drug has not yet been evaluated in human !
  - It is in fact the **objective** of the immunogenicity ADA tests

The background:
The role of the confirmatory test

- To confirm the very objective of the immunogenicity testing, ie to confirm a potential ADA^+
  Confirm ADA^+ given CP^+
- The very objective of the immunogenicity testing procedure is

$$p(ADA^+|CP^+)$$

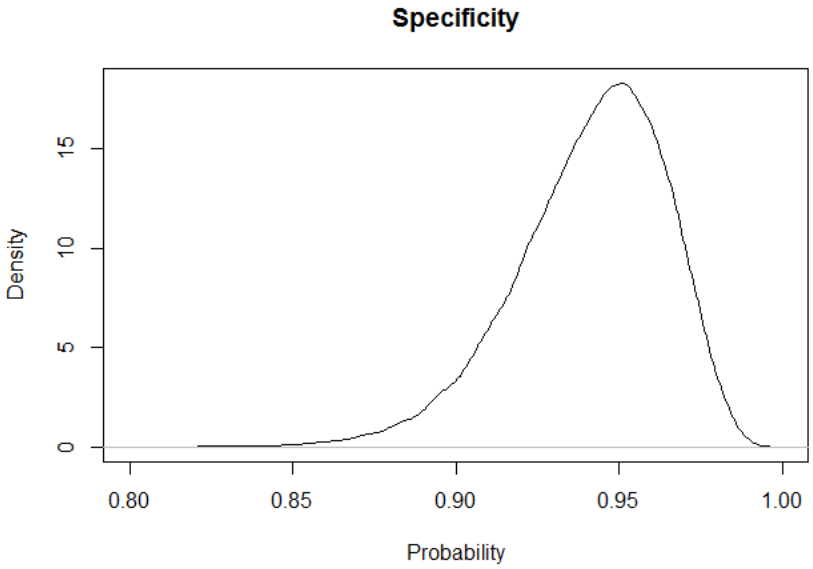
- While the screening cut point of assay is evaluating:

$p(CP^+|ADA^-)$ = False Positive Rate ~ 5% (aim)

$p(CP^-|ADA^-)$ = 95% Specificity of test

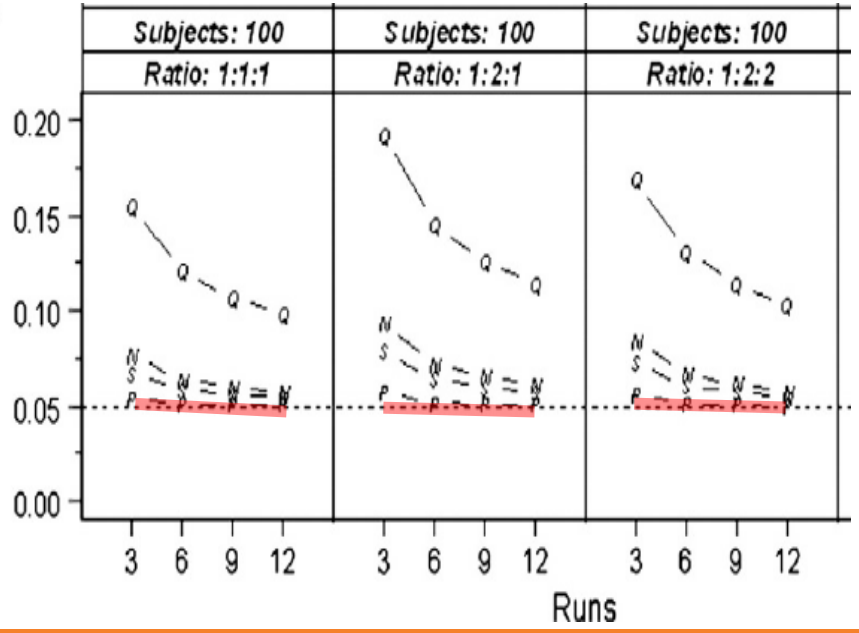
Specificity of screening let's have a closer look

- FPR ~ 1- Specificity = $p(CP^{+}|ADA^{-})$
- Using the 95th percentile on limited sample size to determined the cut-point doesn't not imply that the specificity is exactly 95%.
  - The False Positive Rate (FPR) is not truly 5% either.
  - This is an estimate with uncertainty
  - If based on 100 naïve patients then based on 95 negatives and 5 false positives theory is telling us that the specificity is having a $beta(95+1,5+1)$ distribution
- A priori distribution of Specificity = $beta(N+1, P+1)$



FPR of screening let's have a closer look

- Specificity = $p(CP^{-}|ADA^{-})$, FPR = $p(CP^{+}|ADA^{-})$
- As shown by Hoffman and Berger (2011), the β-expectation Tolerance interval ensures the FPR to be close to 5% in the future given past data on naïve.
- This also assumes that future samples are drawn from a population similar to naïve patients.
- On average, but an uncertainty remains because of limited sample size (<100)
- A good prior is $beta(6,96)$

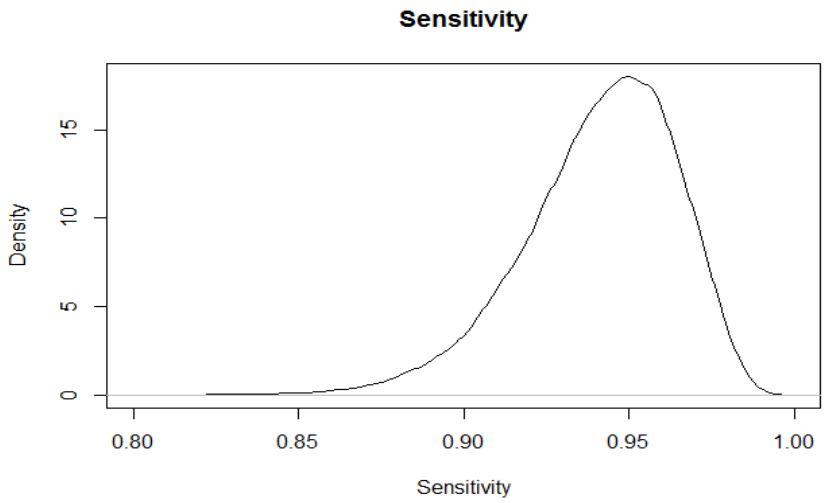


Sensitivity
let's have a closer look

- Sensitivity= $p(CP^{+}|ADA^{+})$
- This is unknown at least at the begin of a development

  ➔ A non-informative could a $beta(1,1)$
  ➔ All values between 0 and 1 are as likely ?
- But a good guess is that most ADA^{+} will provide a CP^{+} signal otherwise everything is falling apart.

  ➔ $beta(96,6)$
- Better than thinking it's a fixed value.



Is this new sample a potential ADA$^+$?

- What is the probability that a sample is ADA$^+$ given the screening results is CP$^+$?

  ➔ $p(ADA^+|CP^+)$

- $$p(ADA^+|CP^+) = \frac{p(CP^+|ADA^+)p(ADA^+)}{p(CP^+|ADA^+)p(ADA^+)+p(CP^+|ADA^-)p(ADA^-)}$$

- $p(CP^+|ADA^+)$ = Sensitivity of test ➔ $beta(96,6)$
- $p(CP^+|ADA^-)$ = 1-Specificity of test ➔ $beta(6,96)$
- $p(ADA^+)$ = Prevalence or risk ➔ $unknown\ in\ fact$

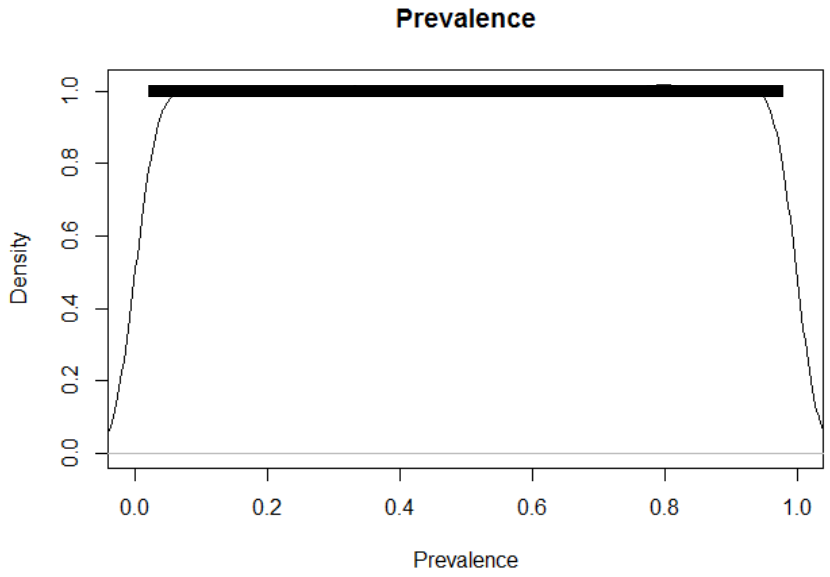
- Note that currently potential ADA$^+$ is based on $p(CP^+|ADA^+)$

Prevalence

- Prevalence= $p(ADA^+)$
- Unknown before starting any trial.
- The Prevalence is the objective in fact
  it's the purpose of the immunogenicity testing approach to evaluate the risk of ADA$^+$ with the new treatment.

- A good prior for

$$p(ADA^+) \sim beta(1,1)$$



Is this first sample a potential ADA^+ ?

- Assume first patient, measure is > CP (CP^+)
  - fixed specificity/sensitivity ➔ 0.95 and 0.95
  - Unknown prevalence ➔ say 0.5

- $p(ADA^+|CP^+) = \frac{p(CP^+|ADA^+)p(ADA^+)}{p(CP^+|ADA^+)p(ADA^+)+p(CP^+|ADA^-)p(ADA^-)}$

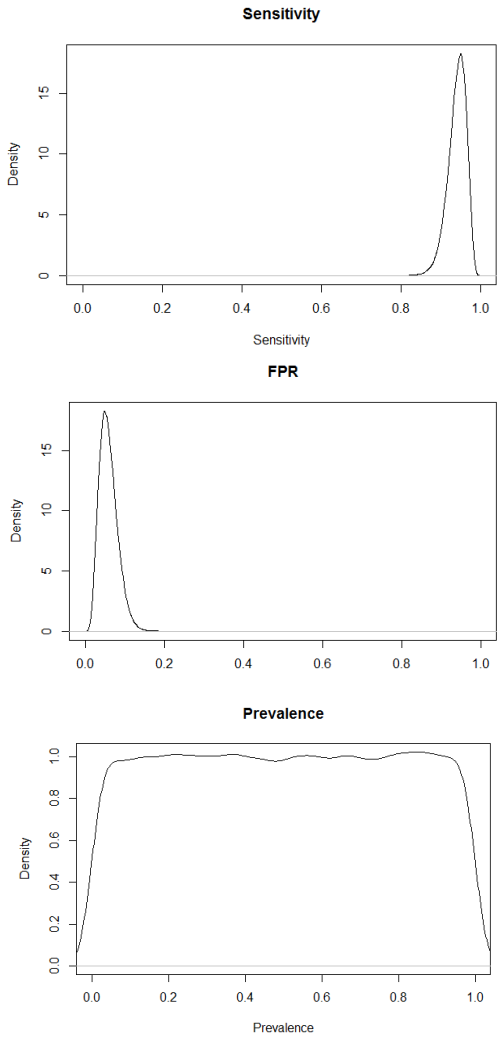
- $p(ADA^+|CP^+) = \frac{0.95 \,.\, 0.5}{0.95 \,.0.5+0.05 \,.\, 0.5} = \; 0.95$
- This seems to imply that $p(CP^+|ADA^+) = p(ADA^+|CP^+)$!
- Maybe the underlying idea behind the FPR choice.
- This is only true when prevalence $p(ADA^+)$ is unknown !

Is this 101th sample a potential ADA^+ ?

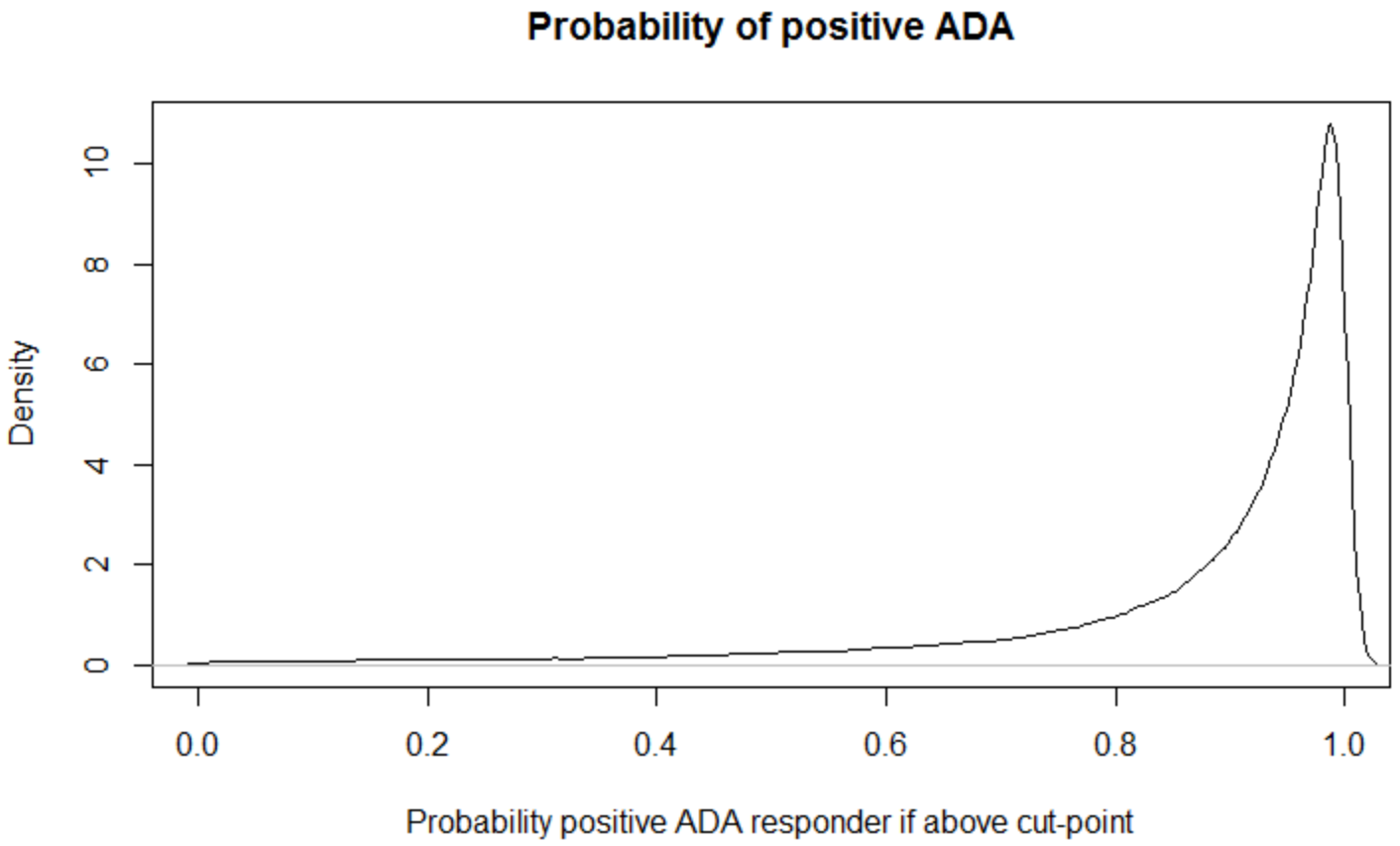
- Assume 100 patients already tested, 2/100 have been confirmed as ADA^+, 98/100 as ADA^-
- The 101th patient is > CP (CP^+)
  - fixed specificity/sensitivity ➔ 0.95 and 0.95
  - A priori prevalence ➔ estimated as 0.02
- $$p(ADA^+|CP^+) = \frac{p(CP^+|ADA^+)p(ADA^+)}{p(CP^+|ADA^+)p(ADA^+)+p(CP^+|ADA^-)p(ADA^-)}$$
- $$p(ADA^+|CP^+) = \frac{0.95 \times 0.02}{0.95 \times 0.02+0.05 \times 0.98} = 0.28$$
- There is little chance to be confirmed as ADA^+
- Now $p(ADA^+|CP^+) \ll p(CP^+|ADA^+)$

But all are guesses with uncertainty

- At the beginning one can assume:
- $p(CP^+|ADA^+)$ = Sensitivity of test
  ➔ $beta(96,6)$
- $p(CP^+|ADA^-)$ = 1-Specificity of test
  = FPR
  ➔ $beta(6,96)$
- $p(ADA^+)$ = Prevalence or risk
  = Unknown
  ➔ $beta(1,1)$

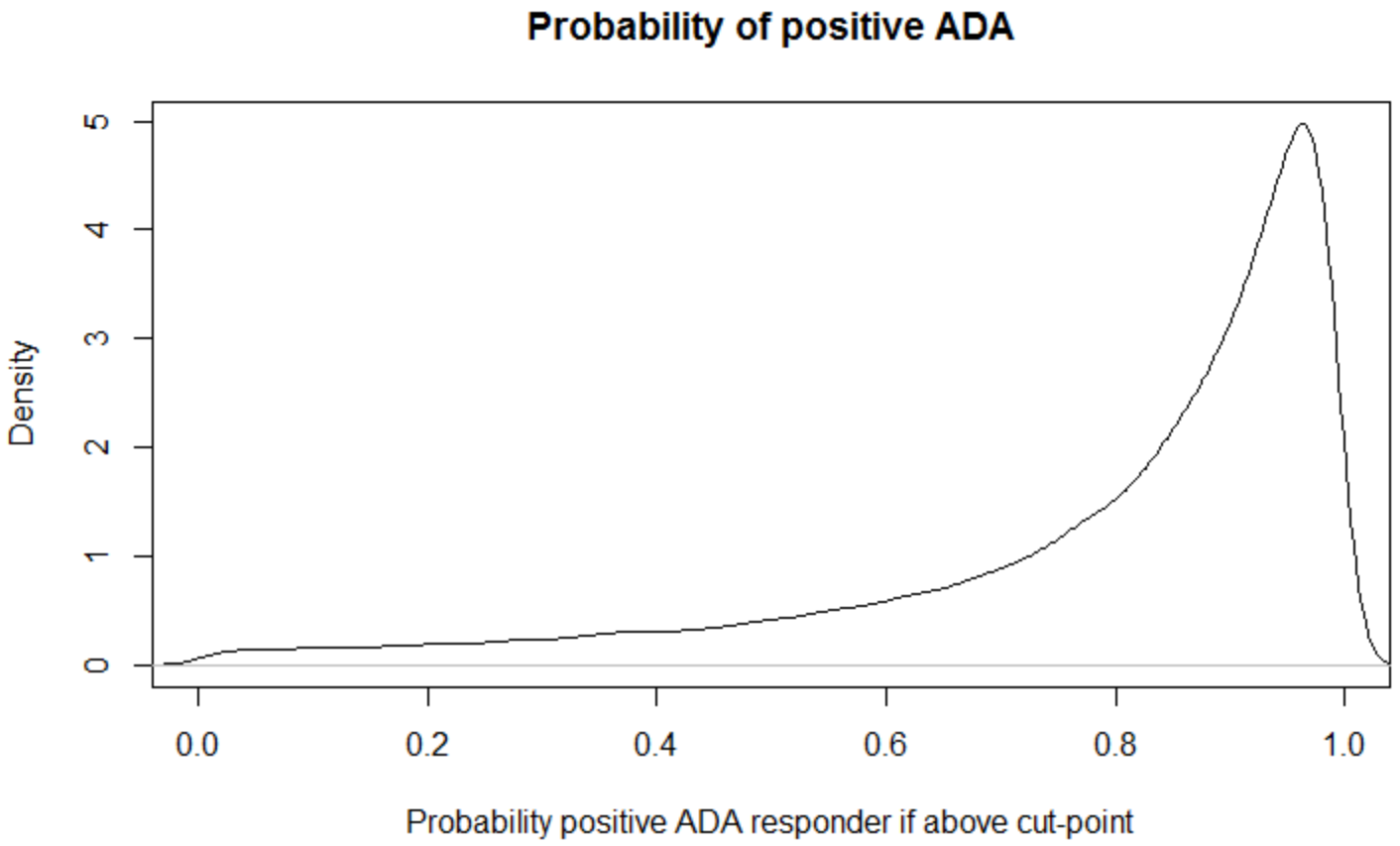


FPR ~ 0.05 Sensitivity ~ 0.95
unknown prevalence, before starting

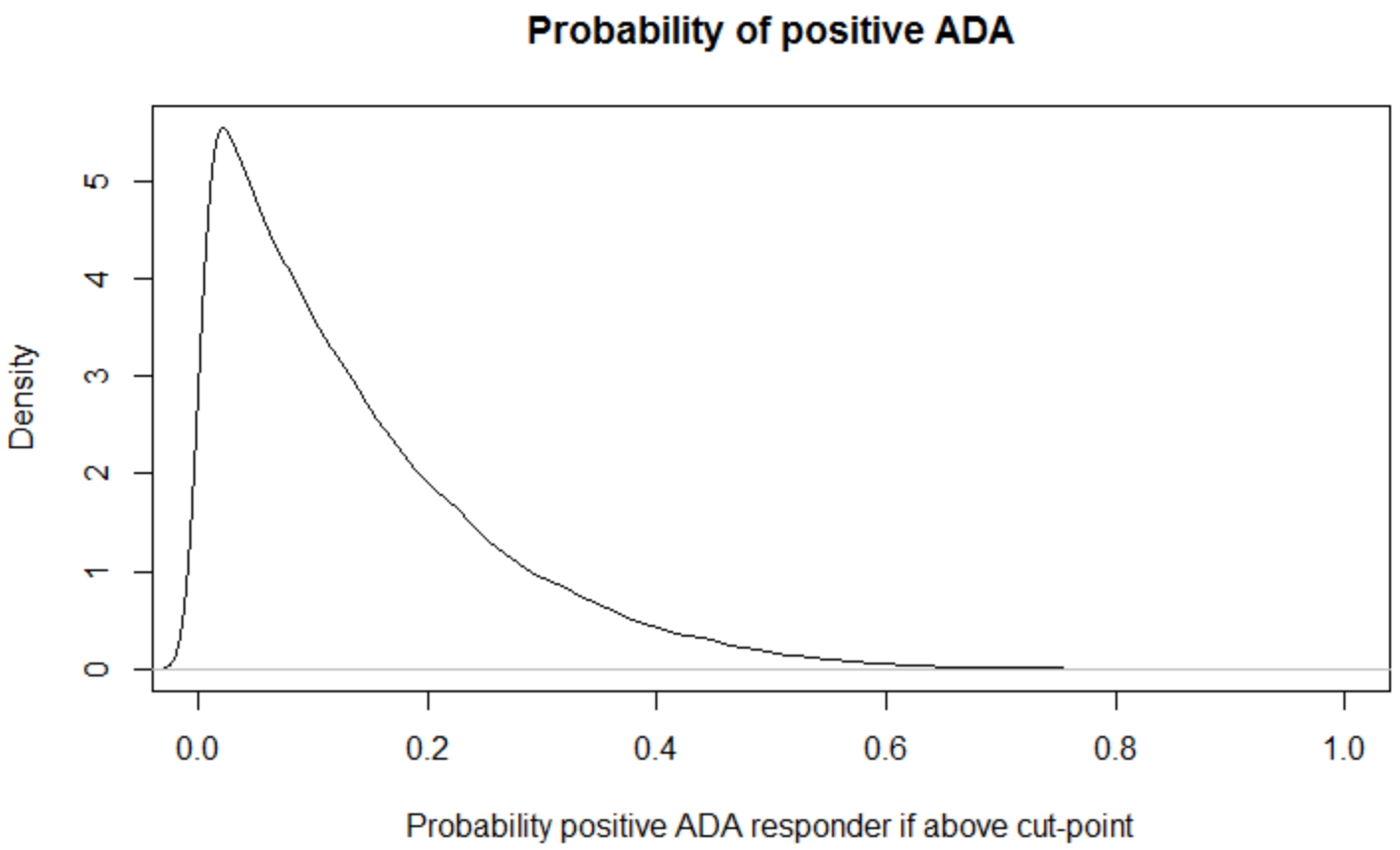


This is the intended performance: ~ 5% chance to be a FPR

FPR ~ 0.05 Sensitivity ~ 0.95
1/0 patient confirmed negative



FPR ~ 0.05 Sensitivity ~ 0.95
100/0 patients confirmed negative



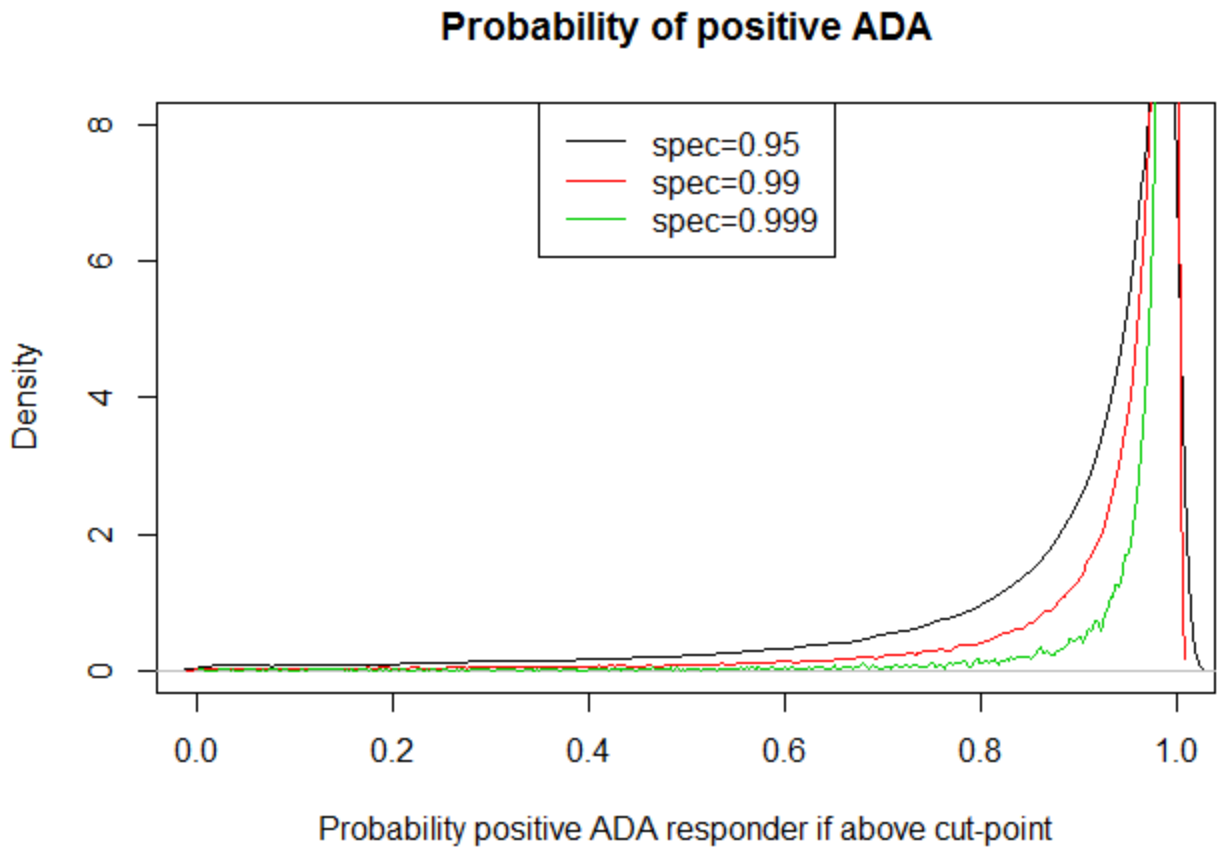
What's going on ?

- The lower the prevalence the higher the probability a potential ADA+ to be a False Positive.
- When the prevalence appears to be low –hopefully- confirmatory tests are busy testing samples likely to be negative ADA-

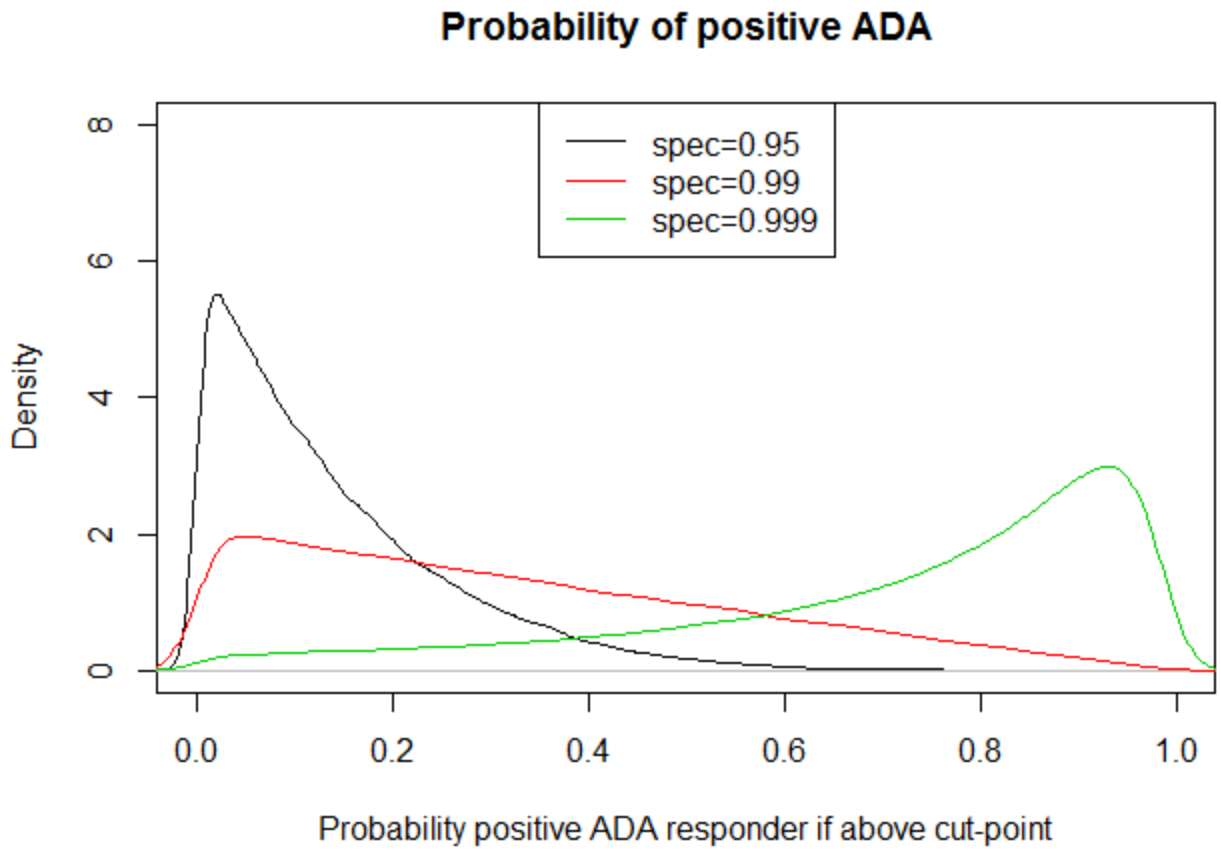
Solution ?

- Should the decision to go in confirmatory test be based on
$$p(ADA^+|CP^+)$$
- Should the Specificity or 1-FPR be adapted to observed prevalence?
$$p(CP^+|ADA^-) = 0.05 \text{ -> } 0.01 \text{ -> } 0.001 \text{ ?}$$

Specificity =0.95 - 0.99 - 0.999
Assuming sensitivity is 0.95
0/0 patients confirmed negative



Specificity =0.95 - 0.99 - 0.999
Assuming sensitivity is 0.95 (ie 95/5)
100/100 patients confirmed negative

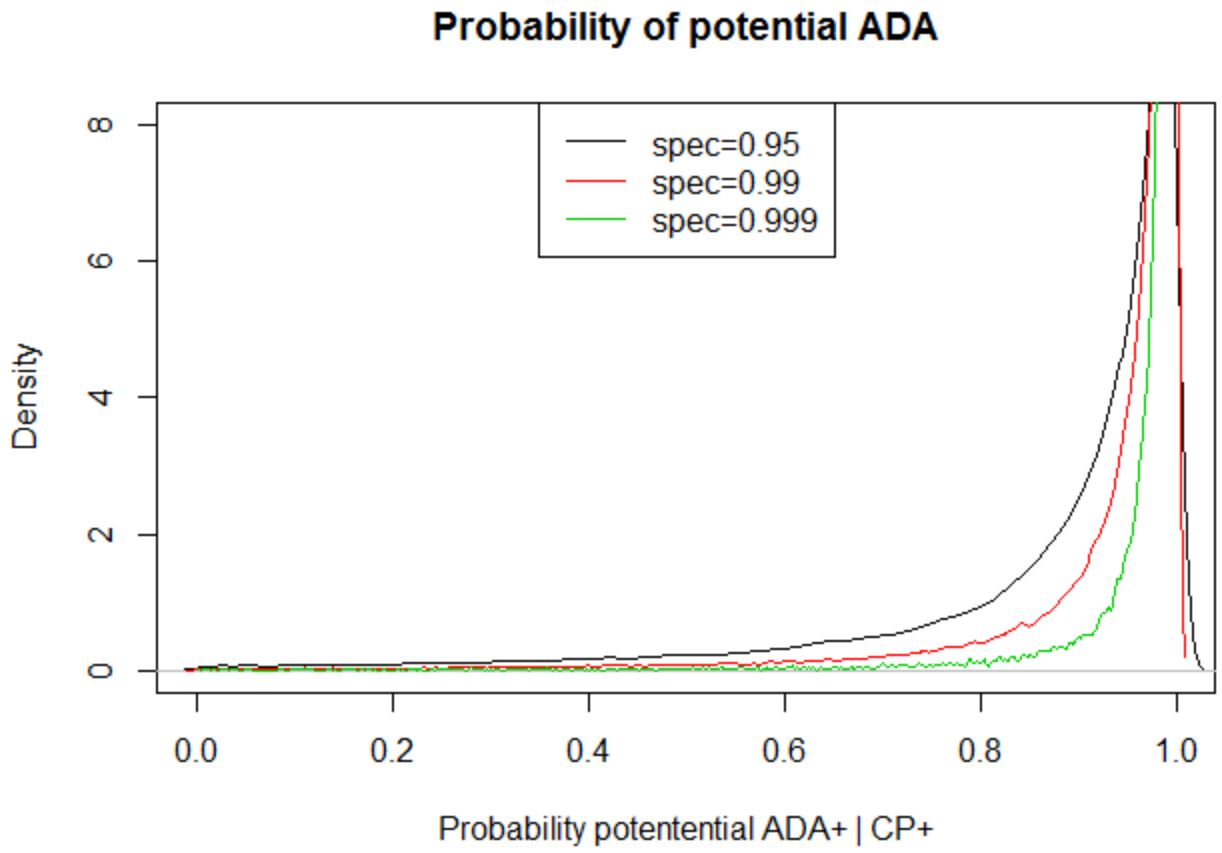


What's does that means?

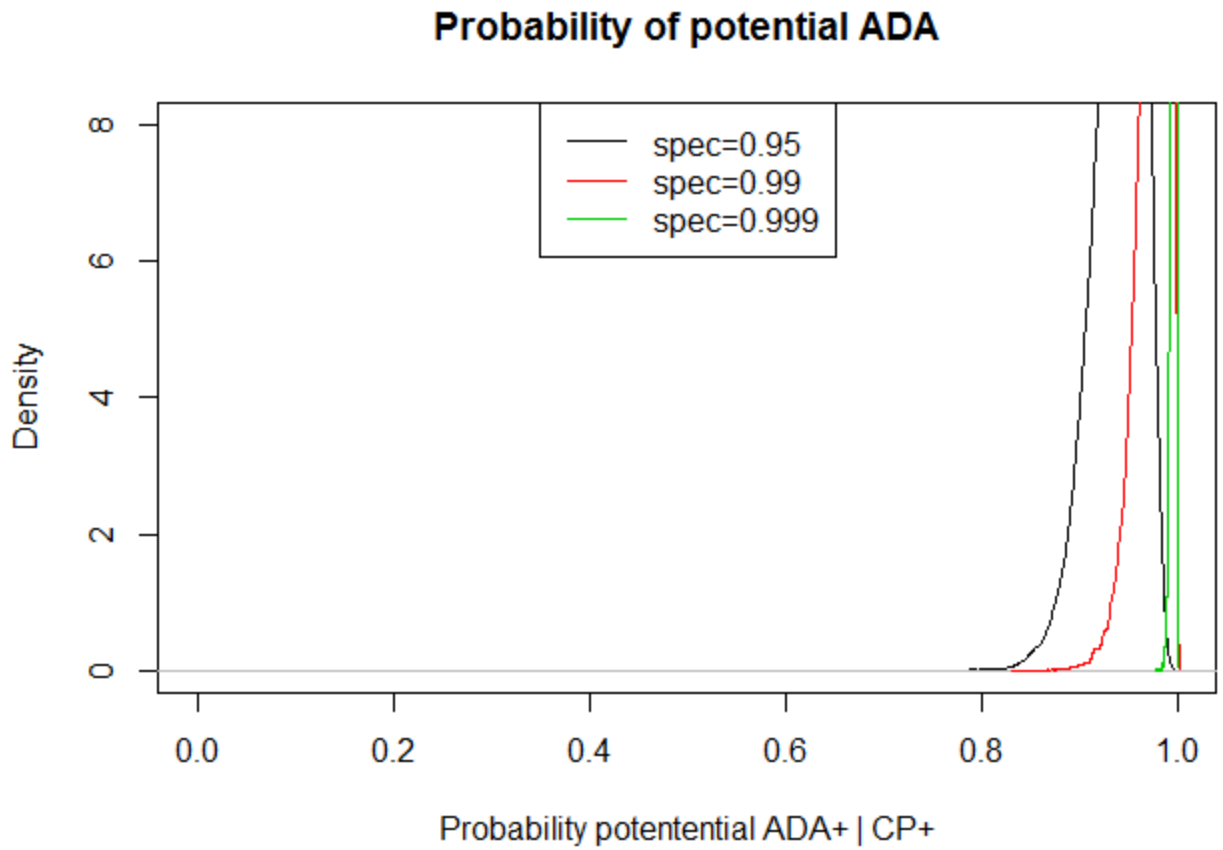
- When the risk of $p(ADA^+)$ is **unknown**, then the FPR is about the 5% aimed
- When the risk of $p(ADA^+)$ is **known / estimated** to be low, then the $p(ADA^+|CP^+)$ is becoming low and the rate of false positive is becoming very large.
- Increasing progressively the Specificity with estimated prevalence $p(CP^+|ADA^-)$ = 0.05 -> 0.01 -> 0.001 allows to keep the $p(ADA^+|CP^+)$ close to the original intended levels.

- ➔ When the risk of $p(ADA^+)$ is **known / estimated** to be medium, then what is happening with $p(ADA^+|CP^+)$?.

Specificity =0.95 - 0.99 - 0.999
Assuming sensitivity is 0.95
0/0 patients confirmed negative

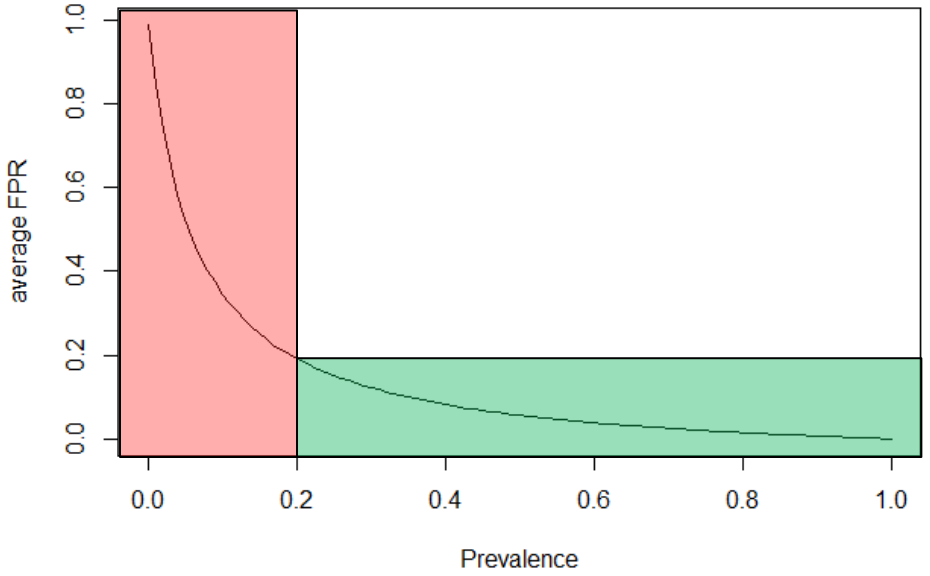


Specificity =0.95 - 0.99 - 0.999
Assuming sensitivity is 0.95 (ie 95/5)
50/100 patients confirmed negative



What's does that means?

- When the risk of $p(ADA^+)$ is >20%,
  - ➔ the FPR is remaining around the intended 5%.
  - ➔ Using $p(CP^+|ADA^+)$ -as currently done- instead of $p(ADA^+|CP^+)$ will give about the same outcome.
- When $p(ADA^+)$ is smaller than 20%, then it's recommended to shift to the adequate decision rule: $p(ADA^+|CP^+)$



Conclusions

- The intended decision rule is in fact $p(ADA^+|CP^+)$
- When Prevalence is unknown and response of ADA+ is unknown, the current CP decision rule $p(CP^+|ADA^+) \sim p(ADA^+|CP^+)$
  - This is good news
- When information about Prevalence is available, then

  $p(CP^+|ADA^+) \sim p(ADA^+|CP^+)$ when $p(ADA^+)$ is >20%

  $p(ADA^+|CP^+)$ is preferred when $p(ADA^+)$ is <20%
- Using the Prediction interval or β-expectation interval for the CP determination is recommended to achieve intended FPR

  .

  ➔ β-expectation interval is based on $\mathrm{E}[p(CP^+|ADA^+)\,|data] \geq 5\%$

Arlenda
Modeling Your Drug Development

bruno@arlenda.com

THANK YOU