Imperial College London

# Economic Evaluation of an Active TB Diagnostic Test using Decision Trees: A Decision Analytic Approach

Dr Nathan Green

February 9, 2016



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# Section 1

## What and why of economic evaluation



# What is economic evaluation?

- Increasing acceptance that effectiveness information is necessary but not sufficient for decision making.
- Need to explicitly consider costs and opportunity costs of different courses of action.
- Economic methods can contribute to the decision making process.
- Offer a coherent, explicit and theoretically-based approach to:
  - Identifying, measuring and valuing resource use, costs and outcomes.
  - Handling uncertainty.



# What is economic evaluation?

- Economic evaluation: A comparison of alternative diagnostic or treatment options in terms of their costs and outcomes.
  - Costs ($c$): The value of the resources involved in providing treatment and managing side-effects, symptoms and disease-related events.
  - Outcome ($e$): The health effects of the intervention.



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- Decision analysis: Summarise model results in suitable measures. What is the 'best' course of action?



# 4 key components of a health economic evaluation

- Statistical model: Estimate population parameters.
- Economic model: Combine parameters to get averages for cost and outcomes.
- Decision analysis: Summarise model results in suitable measures. What is the 'best' course of action?
- Uncertainty analysis: How does different types of imperfect knowledge affect the results?



# What is economic evaluation?

| Type | Outcome measure |
|---|---|
| Cost-consequence analysis (CCA) | Multiple outcomes reported in disaggregated manner |
| Cost-minimisation analysis (CMA) | None (evidence or assumption of equivalent outcomes) |
| Cost-effectiveness analysis (CEA) | Natural units (e.g. life years, cases detected) |
| Cost-utility analysis (CUA) | QALYs (longevity and quality of life) |
| Cost-benefit analysis (CBA) | Monetary valuation |



# What is economic evaluation?

- Comparative methodology: Interested in incremental costs and outcomes- multivariate results.
  Can summarise population economic averages in a 'cost per outcome' ratio using

**Definition**

Incremental Cost-Effectiveness Ratio (ICER)

$$\frac{\Delta C}{\Delta E} = \frac{C_{new} - C_{old}}{E_{new} - E_{old}}$$

where $C = \mathbb{E}[c|\theta]$ and $E = \mathbb{E}[e|\theta]$.



## Subsection 1

# RCTs



# Where can we get good evidence about cost-effectiveness?

- A good source is randomised controlled trials (RCT):
  - Unbiased estimates of treatment effects
  - Can collect outcome and resource use information prospectively
  - Obtain patient-specific data
- So why use a model to conduct an economic analysis then?



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  - May be unsuitable for population interventions
  - May not compare all the relevant alternatives
  - Trial duration may not be long enough
  - We may be interested in long-term/lifetime costs and effects



# RCTs: Patients may not be representative

- Trials tend to provide evidence specific to a particular setting or group of patients, and this may not represent patients commonly seen in clinical practice or reflect the requirements for the particular decision problem being posed.
- If there is a need to generalise to other settings or patient sub-groups, additional modelling of the trial baseline risks and resource usage informed by other sources may be required to make the results generalisable.



# RCTs might not compare all the relevant alternatives

- Economic evaluation is a comparative methodology for assessing the value of one course of action compared to another (or range of options).
- A randomized trial may provide evidence on two or three options, but is unlikely to be able to provide evidence on all the relevant options available.



# Information in studies may have to be combined

- A single trial is unlikely to provide all the information required, and it might be necessary to combine evidence from a range of sources.
- Important to scrutinise evidence for its applicability to the evaluation being undertaken.
- In the case of economic evaluation this means evidence on resource utilisation, unit costs, effectiveness and quality of life.
- The range of sources may include trials but also cohort studies, surveys or patient records, expert opinion.
- Decision models can provide an organizing framework within which these different types of data can be synthesised.



# RCTs might not encompass time horizon

- The appropriate time period for the purpose of an economic evaluation is the time period that is long enough to capture in full the differences in resource use, unit costs and benefits between the alternative options being evaluated.
- Often, as is the case for interventions for chronic disease, this requires a time horizon that captures the patients lifetime.
- Trials rarely provide evidence over the lifetime of all patients (except in cases of interventions for terminal illness).
- There is therefore a need to extrapolate beyond the trial evidence, and decision models can provide a vehicle to extrapolate evidence from trials to a longer, more appropriate, time horizon.



# Decision analysis

Decision analysis (DA) is an explicit quantitative approach to decision making under uncertainty.

- Mathematical representation of a series of possible events that flow from a set of alternative options being evaluated.
- DA compares at least two alternatives.
- The likelihood of each event is expressed as probability.
- Each event has associated values/outcomes.
- DA is based on the concept of expected value (EV).
  - For a given option, EV is the sum of the values of each event weighted by the probability of the event.



# Section 2

## Decision Trees



# Steps in constructing and analysing Decision Trees

A decision tree is a visual representation of a decision analysis:

- Structure the tree



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# Steps in constructing and analysing Decision Trees

A decision tree is a visual representation of a decision analysis:

- Structure the tree
- Estimate probabilities
- Estimate payoffs (assign values to costs and outcomes)
- Analyse the tree
  - Evaluate the tree
  - Explore uncertainty



# Structuring the Decision Tree

A decision tree is made up of nodes, branches and outcomes

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# Structuring the Decision Tree

A decision tree is made up of nodes, branches and outcomes

- Nodes:
  - Decision node (square): Describes the problem. Deterministic choice.
  - Chance node (circle): Represents the point at which several possible events can occur.
  - Terminal node (triangle): Represents the end of a tree with a payoff attached.



# Structuring the Decision Tree

- Branches issuing from a chance node represent possible events patients may experience at that point in the tree.
- Branch probabilities represent the likelihood of each event.
- The sequence of chance nodes from left to right usually follows the sequence of events.
- The events stemming from a chance node must be mutually exclusive and probabilities should sum to 1.



# Advantages of Decision Trees

- They enable the economic question to be structured in a meaningful and visual manner.



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- They enable the economic question to be structured in a meaningful and visual manner.
- They allow data informing the model parameters to be assimilated and, where appropriate, synthesised.
- They are relatively simple to undertake and suitable for:
  - Diseases that occur only once.
  - Decisions about acute care.
  - Decisions with short time frames.



# Limitations of Decision Trees

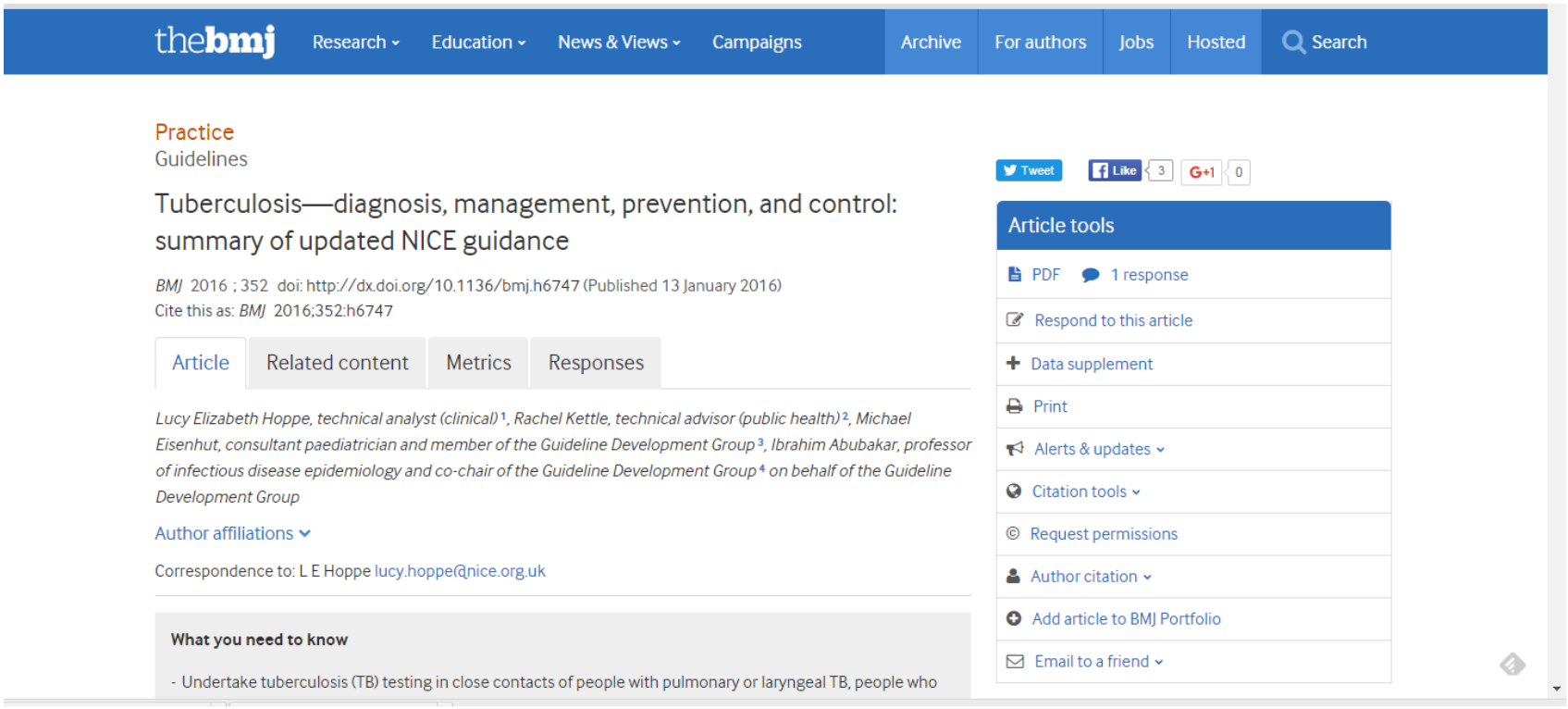
- They do not explicitly account for passage of time:
  - Passage of time accounted for by outcome measure.
  - Limited ability to account for long term outcomes.



# Limitations of Decision Trees

- They do not explicitly account for passage of time:
  - Passage of time accounted for by outcome measure.
  - Limited ability to account for long term outcomes.
- Possible to add branches but results in a complex model.
- Other modelling techniques can handle repeated events better.
- Structure of tree only allows for one-way progression of patient through model: Not movement back and forth between states.
- Decision trees can still be useful as a sub-model.





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Practice
Guidelines

# Tuberculosis—diagnosis, management, prevention, and control: summary of updated NICE guidance

*BMJ* 2016 ; 352 doi: http://dx.doi.org/10.1136/bmj.h6747 (Published 13 January 2016)
Cite this as: *BMJ* 2016;352:h6747

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*Lucy Elizabeth Hoppe, technical analyst (clinical)[1], Rachel Kettle, technical advisor (public health)[2], Michael Eisenhut, consultant paediatrician and member of the Guideline Development Group[3], Ibrahim Abubakar, professor of infectious disease epidemiology and co-chair of the Guideline Development Group[4] on behalf of the Guideline Development Group*

Author affiliations

Correspondence to: L E Hoppe lucy.hoppe@nice.org.uk

**What you need to know**

- Undertake tuberculosis (TB) testing in close contacts of people with pulmonary or laryngeal TB, people who

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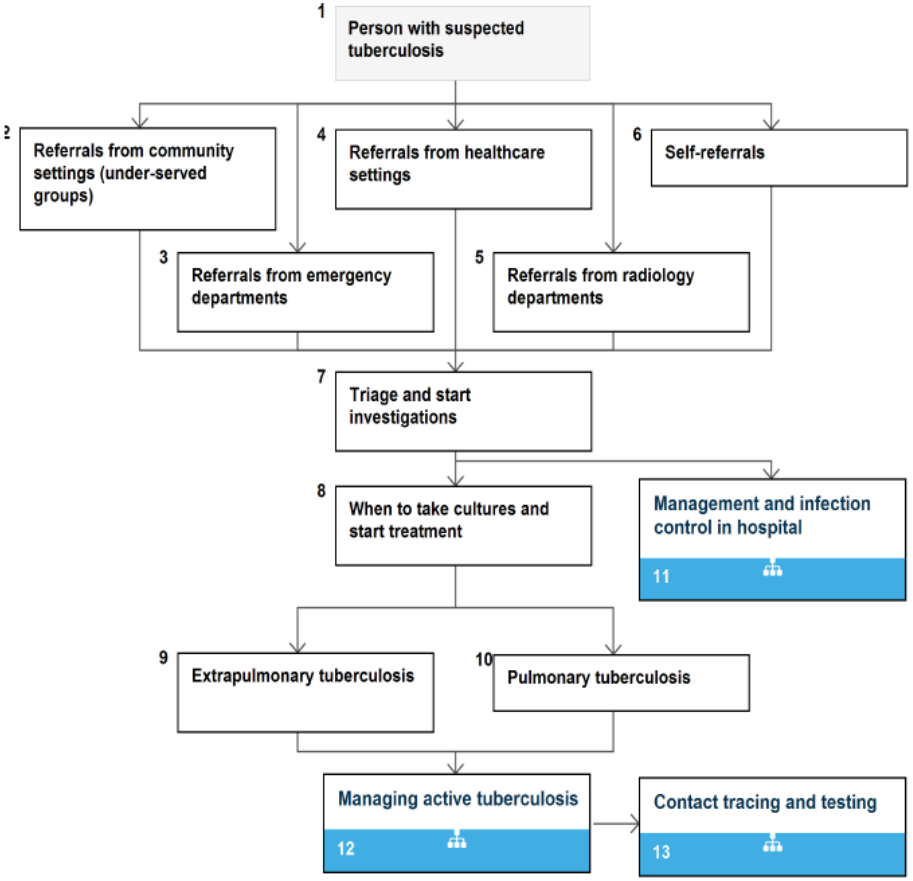
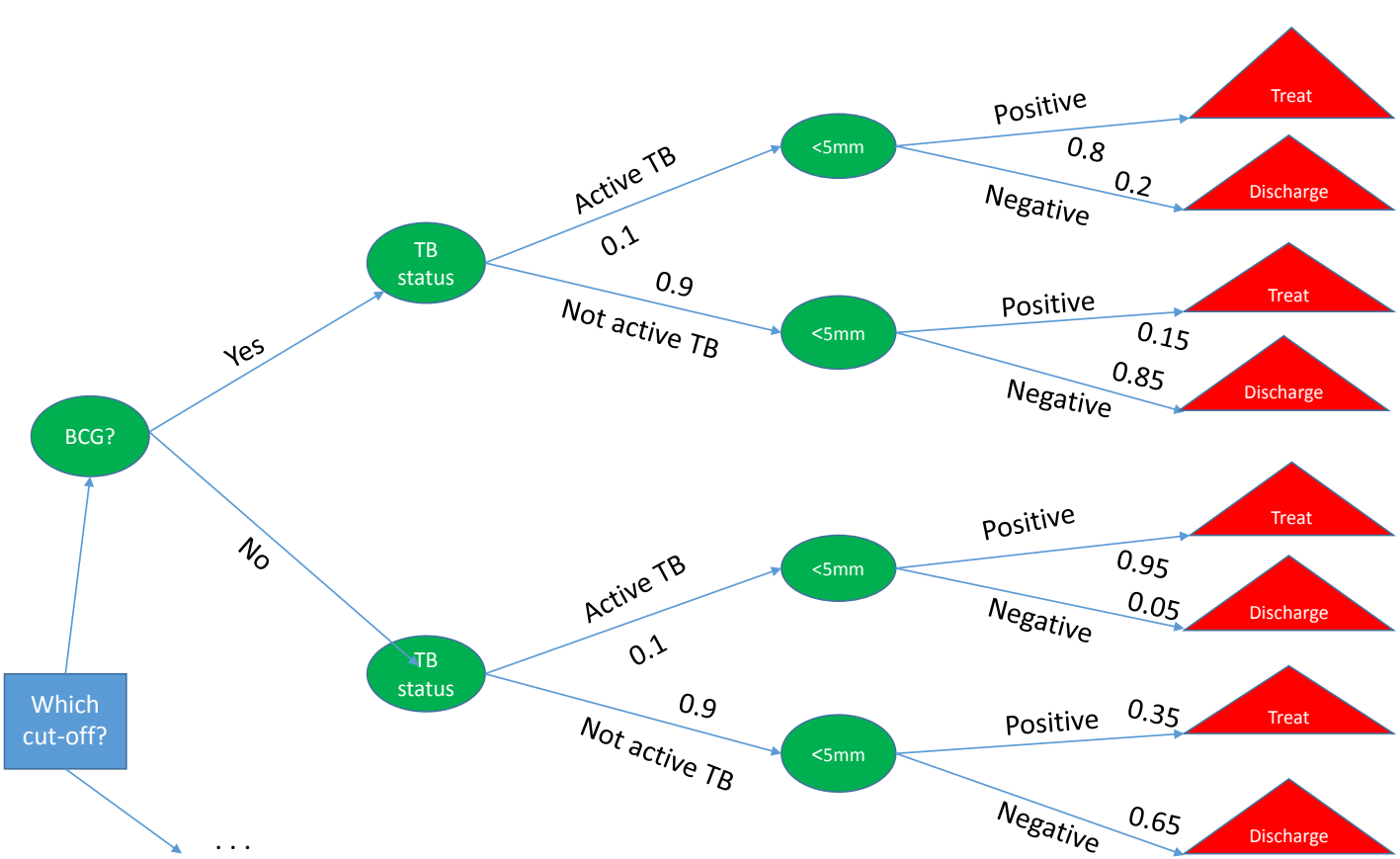
# NICE suspected TB pathway



# Simple decision tree example: New TST guidelines




| cost | utility |
|---|---|
| £60 | 50 |
| £10 | -100 |
| £60 | -10 |
| £10 | 0 |
| £70 | 50 |
| £20 | -100 |
| £70 | -10 |
| £20 | 0 |

# Analysing Decision Trees

- The decision tree is averaged-out and 'folded-back' to get the expected payoffs for each strategy.
- Estimated separately as the sum of products of the probability of events and their payoffs i.e. weighted average of the outcome values.
- Cost-effectiveness analysis: Strongly and extendedly dominated strategies removed and ICERs estimated.



# Combined probabilities for each branch

If probability of BCG is 0.1 (c.f. NHS Immunisation Statistics, England 2012-13) then

$$
\begin{aligned}
p_1 &= 0.1 \times 0.1 \times 0.8 = 0.008 \\
p_2 &= 0.1 \times 0.1 \times 0.2 = 0.002 \\
p_3 &= 0.1 \times 0.9 \times 0.15 = 0.0135 \\
p_4 &= 0.1 \times 0.9 \times 0.85 = 0.0765 \\
p_5 &= 0.9 \times 0.1 \times 0.95 = 0.0855 \\
p_6 &= 0.9 \times 0.1 \times 0.05 = 0.0045 \\
p_7 &= 0.9 \times 0.9 \times 0.35 = 0.2835 \\
p_8 &= 0.9 \times 0.9 \times 0.65 = 0.5265
\end{aligned}
$$



# Expected cost and health impact

- Cost:

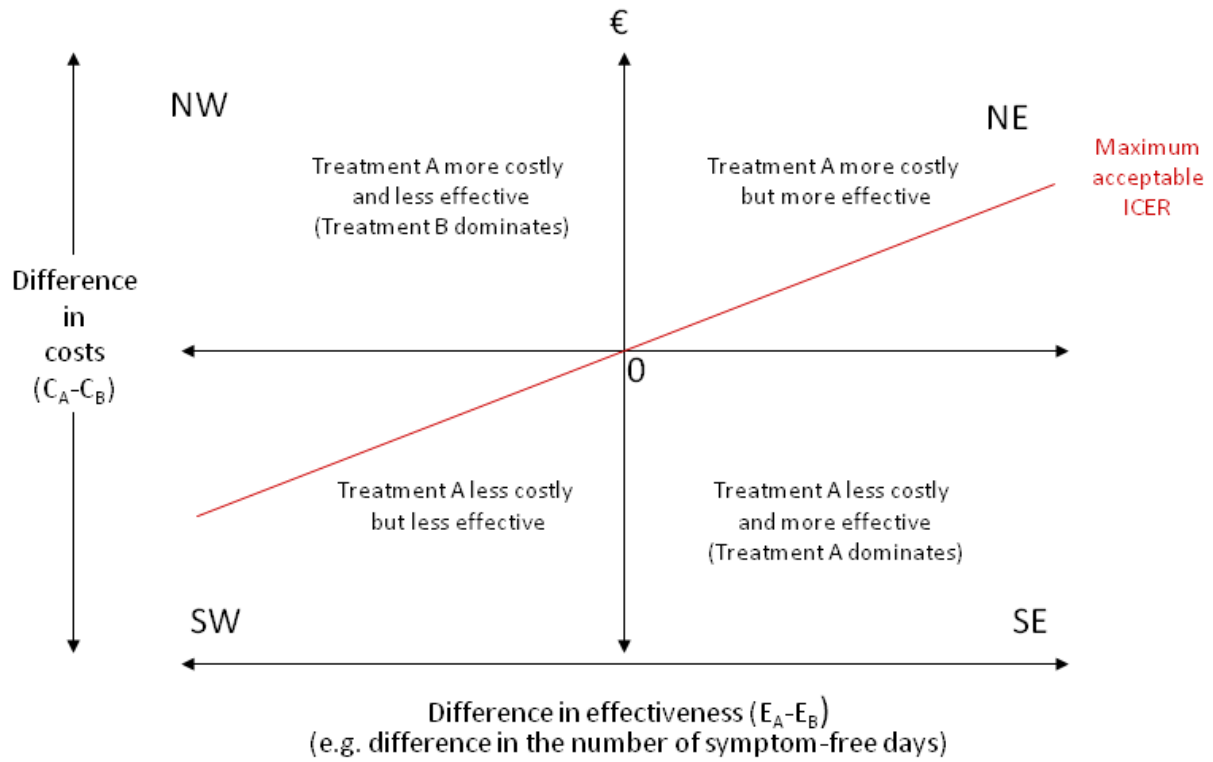
$$0.008 \times 60 + 0.003 \times 10 + 0.0135 \times 60 + 0.0765 \times 10$$
$$+0.0855 \times 70 + 0.0045 \times 20 + 0.2835 \times 70 + 0.5265 \times 20$$
$$= 38.535$$

- Health:

$$0.008 \times 50 + 0.003 \times (-100) + 0.0135 \times (-10) + 0.0765 \times 0$$
$$+0.0855 \times 50 + 0.0045 \times (-100) + 0.2835 \times (-10) + 0.5265 \times 0$$
$$= 0.955$$



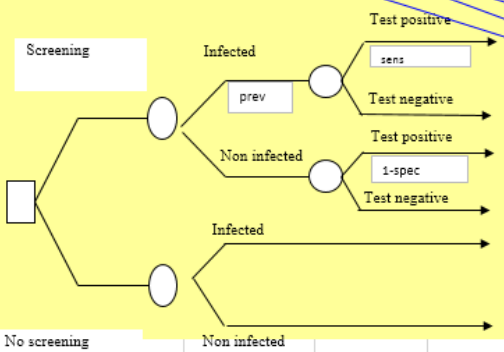
# The incremental cost-effectiveness plane of treatments A and B.



| Paramete | Value | | |
|---|---|---|---|
| Sensitivity | 0.9 | Cost of screening | 10 |
| Specificity | 0.9 | Cost of treatment | 100 |
| Prevalence | 0.1 | Cost of treatment l | 200 |

| Outcome | Cost ($) | Utility |
|---|---|---|
| True positive | 110 | 0.48 |
| False negative | 210 | 0.45 |
| False positive | 110 | 0.79 |
| True negative | 10 | 0.94 |
| Infected | 200 | 0.45 |
| Non infected | 0 | 0.94 |

1
2
3
4




**Screening option**

| | | |
|---|---|---|
| probability true positive | sens*prev | 0.09 |
| probability false negative | (1-sens)*prev | 0.01 |
| probability true negative | spec*(1-prev) | 0.81 |
| probability false positive | (1-spec)*(1-prev) | 0.09 |

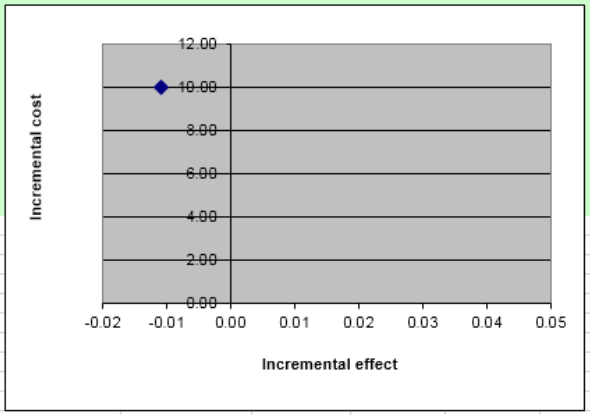
**Costs**

| | |
|---|---|
| True positive | 9.9 |
| False negative | 2.1 |
| True negative | 8.1 |
| False positive | 9.9 |

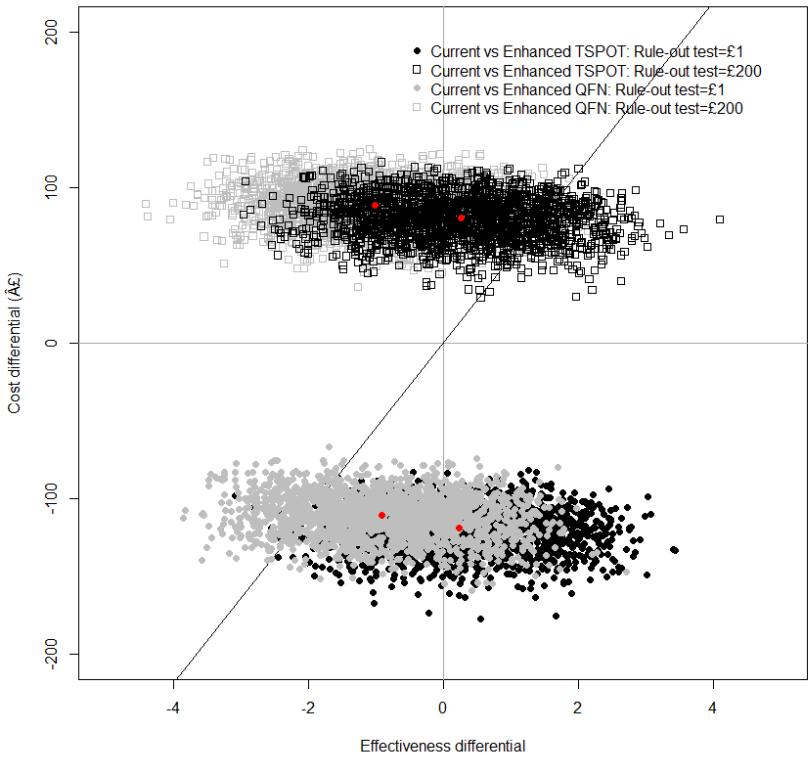
**Utilities**

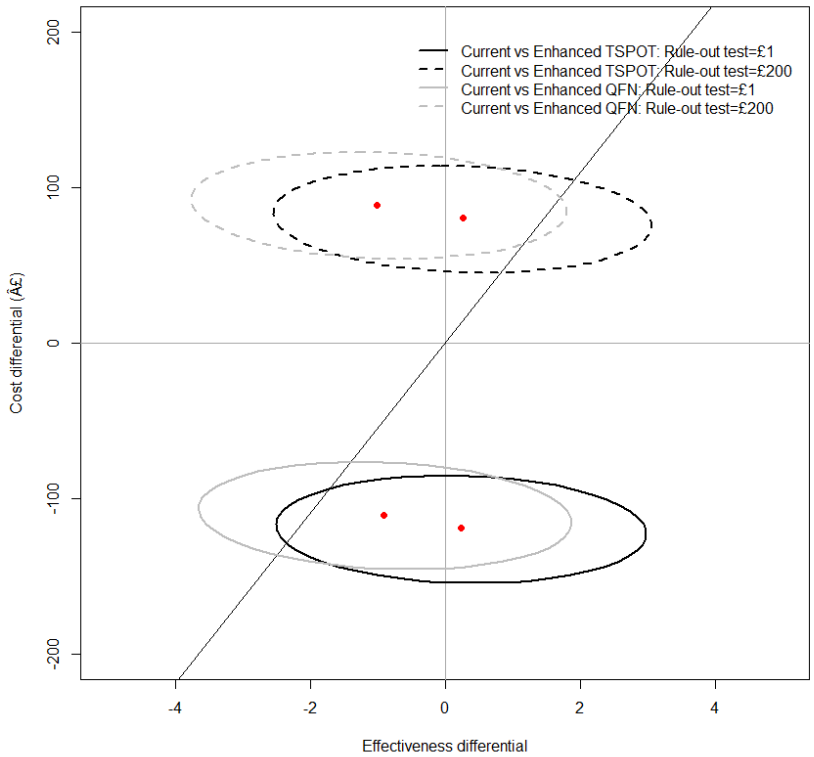
| | |
|---|---|
| True positive | 0.0432 |
| False negative | 0.0045 |
| True negative | 0.7614 |
| False positive | 0.0711 |

| Strategy | Cost | Effect | Incremental cost | Incremental effect | Incremental CE |
|---|---|---|---|---|---|
| No screening | 20.00 | 0.89 | | | |
| Screening | 30.00 | 0.88 | 10.00 | -0.01 | -925.93 |



# Example simulated output



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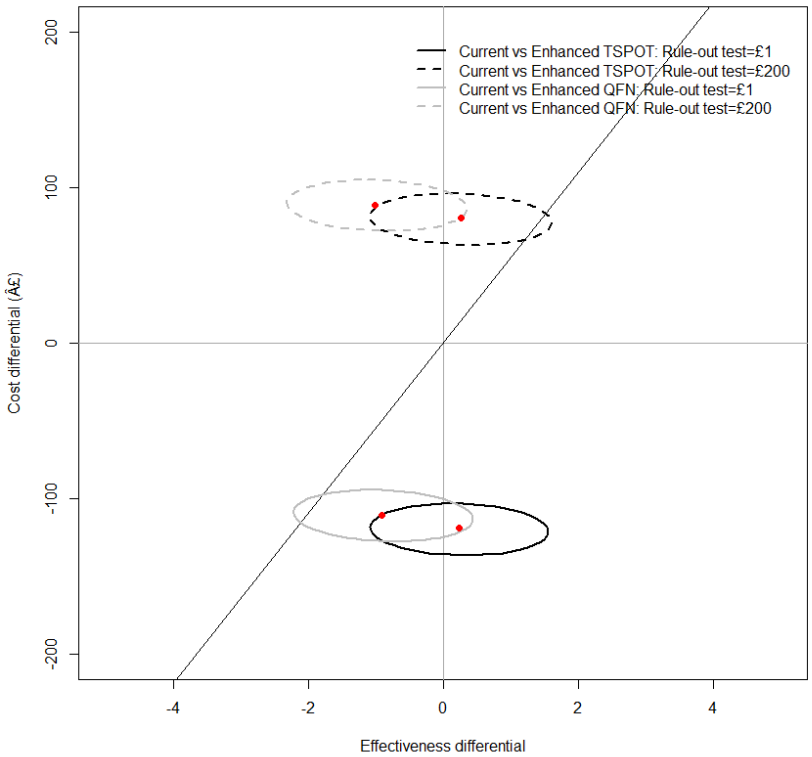


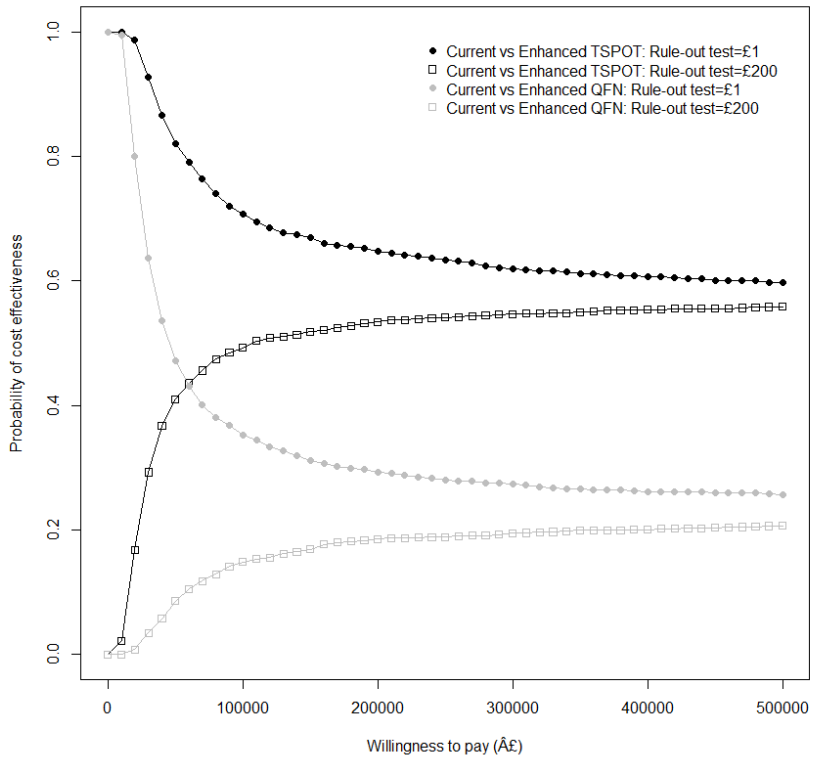

# Section 3

## Exploring test performance component



# Fundamental classification statistics

- True positive (TP): Number of correct predicted positives.



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- False positive (FP): Number of incorrect predicted positives. Equivalent with Type I error.



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- True positive (TP): Number of correct predicted positives.
- True negative (TN): Number of correct predicted negatived.
- False positive (FP): Number of incorrect predicted positives. Equivalent with Type I error.
- False negative (FN): Number of incorrect predicted negatives. Equivalent with Type II error.



# Contingency tables

| | | **True diagnosis** | | |
|---|---|---|---|---|
| | | **p** | **n** | **Total** |
| **Test diagnosis** | **p′** | True Positive | False Positive | P′ |
| | **n′** | False Negative | True Negative | N′ |
| | **Total** | P | N | |

# Contingency table summary statistics

- Sensitivity $= p(T|D) = \frac{TP}{TP+FN} = \frac{TP}{P}$



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- False discovery rate (FDR) $= 1 - PPV = p(D^c|T) = \frac{FP}{TP+FP}$



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- False discovery rate (FDR) $= 1 - PPV = p(D^c|T) = \frac{FP}{TP+FP}$
- Negative predictive value (NPV) $= p(D^c|T^c) = \frac{TN}{FN+TN}$
- False omission rate (FOR) $=$ 1-NPV $= p(D|T^c) = \frac{FN}{FN+TN}$
- Accuracy $= \frac{TP+TN}{M}$



# Contingency table summary statistics

Notice that the PPV and NPV depend on the prevalence. We can alternatively compute them using:

- PPV $=$

$$\frac{\textit{sensitivity} \times \textit{prevalence}}{\textit{sensitivity} \times \textit{prevalence} + (1 - \textit{specificity}) \times (1 - \textit{prevalence})}$$

- NPV $=$

$$\frac{\textit{specificity} \times (1 - \textit{prevalence})}{(1 - \textit{sensitivity}) \times \textit{prevalence} + \textit{specificity} \times (1 - \textit{prevalence})}$$



# How to compare the performance of diagnostic tests?

- Dichotomous test (only 2 results)



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  - Likelihood ratios
  - Sensitivity specificity, PPV, NPV



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  - Odds ratios
  - Likelihood ratios
  - Sensitivity specificity, PPV, NPV
- Multilevel level ($>$ 2 results)
  - Receiver operating characteristic curve (ROC)



Subsection 1

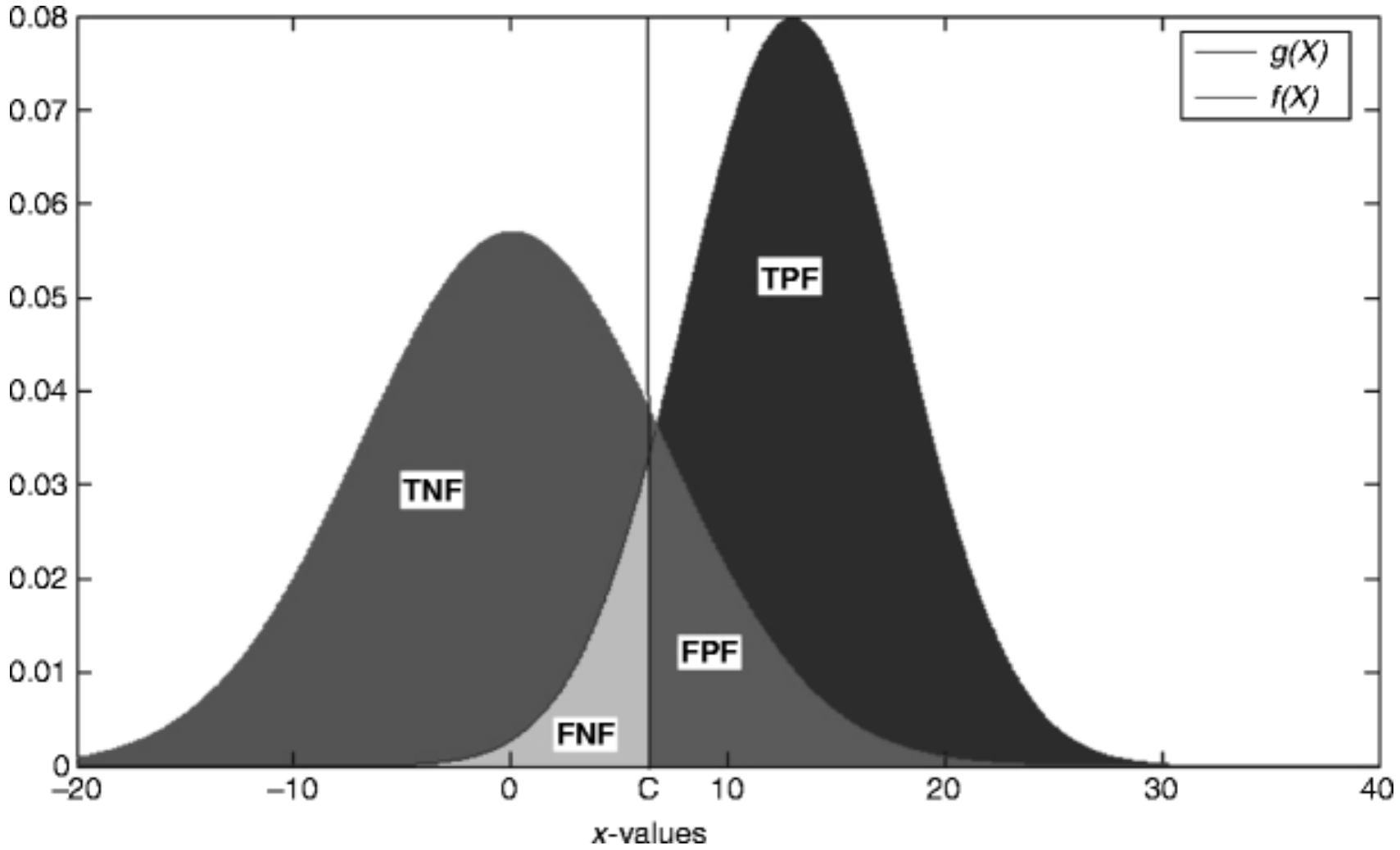
## ROC curves



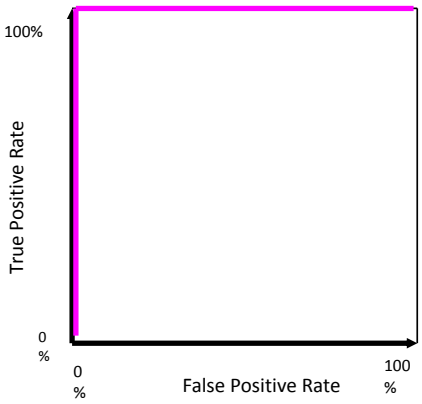
# Receiver operating characteristic curves (ROC)

- TP rate (sensitivity) on vertical axis and FP rate (1-specificity) on horizontal, for varying classification threshold
- Illustrates the trade-off between sensitivity and specificity
- A single curve summary of the information in the cumulative distribution functions of the scores of the two classes.
- c.f. *ROC Curves for Continuous Data*, Krzanowski and Hand (2009).



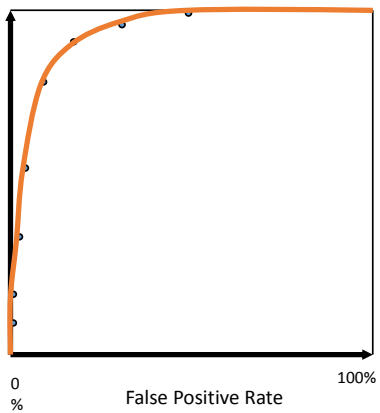

0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
g(X)
f(X)
TPF
TNF
FPF
FNF
–20
–10
0
C
10
20
30
40
x-values

Best Test:

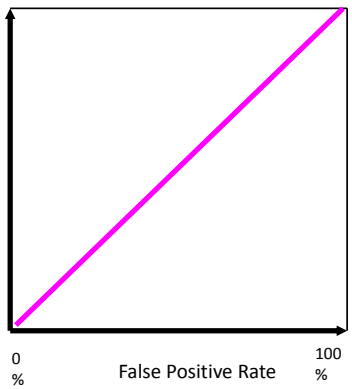



The distributions don't overlap at all

A good test:




Worst test:




The distributions overlap completely

# End