The Diagnostic Process

Understanding Diagnosis
Defining Valid Process Quality Targets

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Teaching Goals :
This module discusses
our Business = Laboratory Diagnosis

In this module we attempt to properly
“ frame secondary activities ”
- Selection & Implementation of a Valid Method 
    - Logistics
    - Evaluating Test Ability
- Statistical Process Control 

Teaching Goals

Diagnostic Process

- understand " diagnosis " &
  the concepts " relevance & consequence "
- situate laboratory diagnosis
  in the " therapeutic value chain "
- understand " deciding in the face of uncertainty " :
  Bayesian model

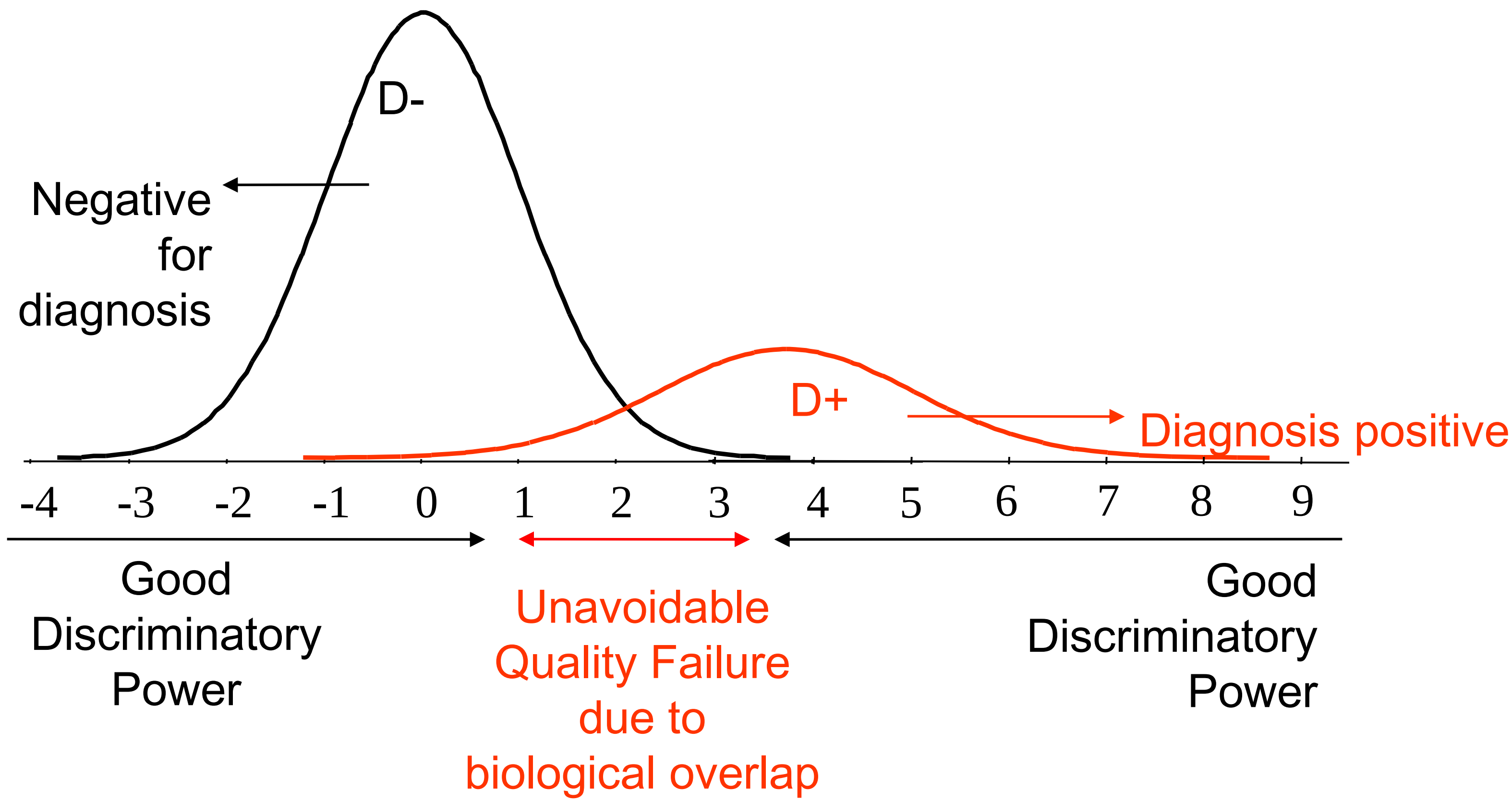
Method Validation

- be able to define " logistic requirements "
- weigh-in analytical characteristics relative to
" operational characteristics of the diagnostic process "

Risk Analysis

- be able to define valid (= appropriate)
  production and analytical " quality targets "
- the latter will be used to design appropriate control procedures
  cfr. separate teaching unit

Intuitive Introduction



What do you do when confronted with a “ Grey Zone ” result ?

- o You do not decide = Certain harm
- o You take a cut-off based decision = On average your patients benefit
- o You request additional tests = **Heuristic Model**

You comply with a “ Minimal Requirement ”

How the Doctor Thinks

After J Groopman

Medical diagnosis
is “ Deciding in the face of Incomplete Knowledge ”

Medical diagnosis 
is not “ to confirm your suspicions ”
but is “ to reduce your doubts ”
and “ not to miss the unexpected ”

Recipe :
Reduce risk by systematic application
of a differential diagnostic algoritm

How to minimize avoidable harm ?

You (have to) accept the Risk & you minimize Adversity
by a more or less Educated Gamble.

→ Bayesian Model

You don't accept the Risk & you minimize Risk
by a more or less successful Problem-Solving Strategy.

→ Heuristics
Differential Diagnosis

These are complementary
& simultaneous processes

Diagnostic Process

Part 1 Operational Definition

What we do when we make a diagnosis

Part 2 Method Validation

Part 3 Diagnostic Ability of a Test

Part 4 Production & Analytical Quality Requirements

Diagnosis = decision making

medical diagnosis = Mental Process

- by its symptoms
- recognize a disease entity
- in order to decide about treatment of a particular patient

} Abstractions

} Concrete

facts
↓
relevant evidence
↓
consequence

Certainty ≈ beyond reasonable doubt ≈ based on Relevant Evidence
(U.S. Federal Rule of Evidence 401)

“ Relevant ” evidence increases the “ likelihood of an appropriate action ”

Facts become relevant evidence, by being consequential

Laboratory Diagnosis: a nested process (1/4)

Physician (
- recognize relevant symptoms
- request the proper test
- **Laboratory** (
  - perform test
  - report result)
- interpret result
- propose treatment to patient)

→ **Test Validation =** *
to assure that the test has all characteristics needed

* Test Validation is discussed in a separate study module 

Laboratory Diagnosis: a nested process (2/4)

Physician (
recognize relevant symptoms
request the proper test
Laboratory (
perform test
report result)
interpret result
propose treatment to patient)

Classically,
Method Validation focuses
on Power of Test
Bayesian Model

Test Ability :
Sensitivity & Specificity

Bayesian Model (1/3)

prior knowledge

about the prevalence of the condition

& about the test ability

= sensitivity & specificity

is converted by

knowledge about the test result

into *posterior predictive power*

= enrichment of the prevalence

in group with a particular test result

Bayesian Model (2/3)

Bayes theorema solves *

P(D+|T+) from P(T+|D+) & P(T+|D-) & P(D+)

Post-test probability | Sensitivity | Specificity | Pre-test prevalence

Likelihood ratio
Test Ability

* The mathematical formalism of the Bayes theorema is discussed in a separate study module 

* In section 3/4 of this unit, we illustrate it in practice

Laboratory Diagnosis: a nested process (3/4)

Patient (
  recognize problem
  select physician
  present symptoms
  Physician (
    recognize relevant symptoms
    request the proper test
    Laboratory (
      perform test
      report result)
    interpret result
    propose treatment to patient)
  comply)

Mental (recognize problem … request the proper test)

Power of Test / Bayesian Model (perform test, report result)

Mental (interpret result … comply)

Brain 2 to Brain 2 (present symptoms … propose treatment to patient)

Brain 1 to Brain 1 (Patient … comply)

Test Ability : Sensitivity & Specificity
is secondary to the mental processes that need to be supported
  Test Request : Menu layout, interactive request, …
  Report : TAT, Format, …

} Lab has to facilitate the best decisions

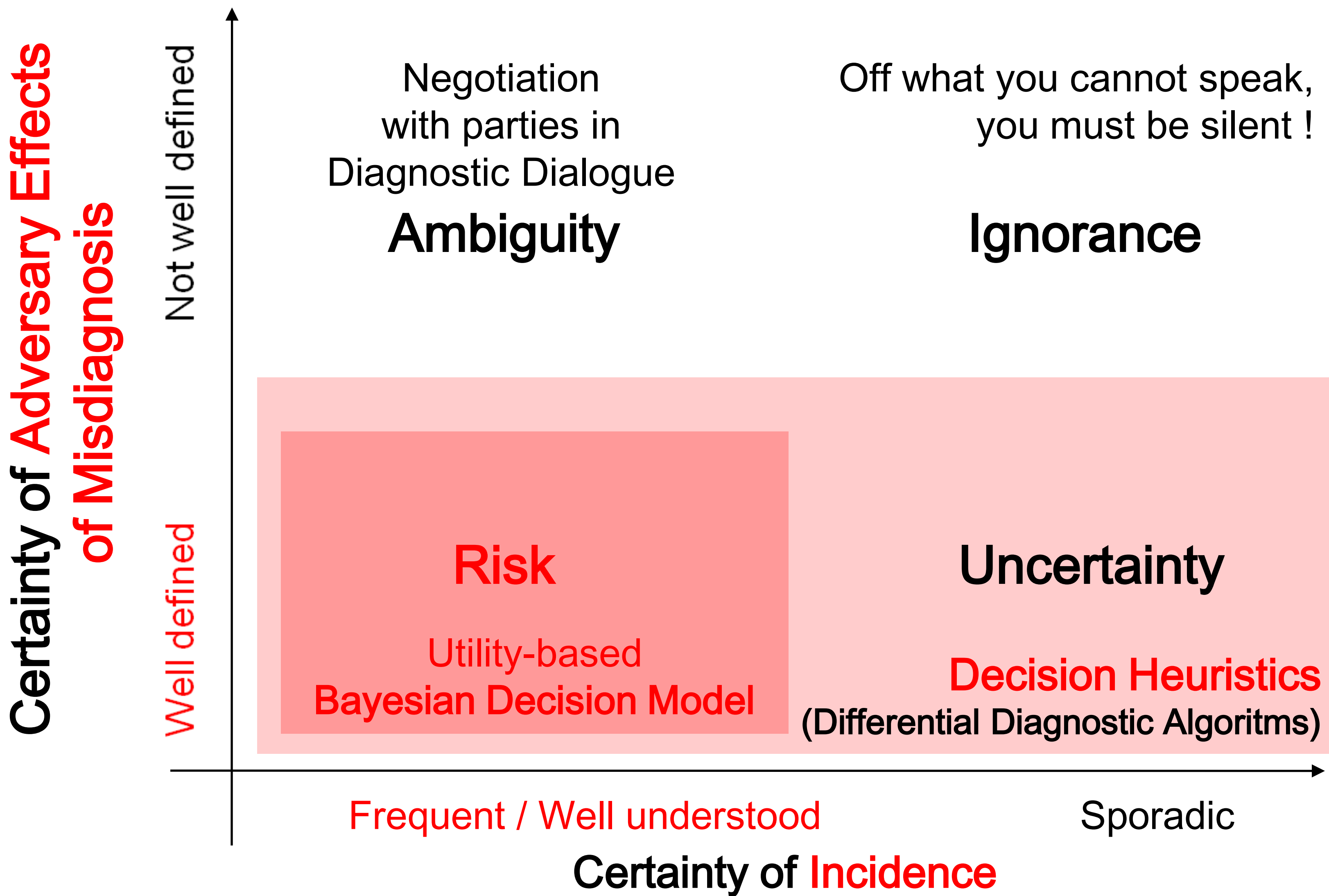
End of the ride: convince your " empowered patient " to do what is best for him

Bayesian Model : revised definition (3/3)

a *considered professional judgement* about
the likelihood of a condition in a patient &
the diagnostic ability of the requested test
is converted by a *learning experience*
i. a. learning that a particular test result was obtained
into *degree of belief* in a given diagnosis

This revised definition articulates with key mental processes

DIAGNOSTIC Actions as function of Uncertainty



After Andy Stirling

Laboratory Diagnosis: a nested process (4/4)

The diagnostic dialogue = a deliberation dialogue

The participants:

- Patient
- Physician
- Laboratory

Typology of the dialogue (After Walton & Krabbe)

- Information / Truth Seeking: etiologic diagnosis
- **Deliberation:** collaboration to decide upon the best action
- Persuasion: compliance with proposal

The lab participates in this deliberation dialogue

Laboratory Diagnosis : Conclusions (1/3)

Patient (
recognize problem
select physician
present symptoms
Physician (
recognize relevant symptoms
request the proper test
Laboratory (
perform test
report result)
interpret result
propose treatment to patient)
comply)

Test Ability : Sensitivity & Specificity
is secondary to the **mental processes**
that need to be supported
Test Request : Menu layout, interactive request, …
Report : Timeliness, Format, …
serves to trigger the best mental decisions

Conclusion 1: Revised Bayesian Model

Conclusion 2: Method Validation = Logistic Optimization

Laboratory Diagnosis : Conclusions (2/3)

Patient (
- recognize problem
- select physician
- present symptoms
- **Physician** (
  - recognize relevant symptoms
  - request the proper test
  - **Laboratory** (
    - perform test
    - report result)
  - interpret result
  - propose treatment to patient)
- comply)

Method Validation = *
to assure that the test has all characteristics needed
for <u>optimum care outcome</u> =
<u>Purposive optimization</u>
- cost-effective care
- compliance in the greatest possible group
- minimize adverse effects

Laboratory Diagnosis : Conclusions (3/3)

Describing the Diagnostic Process purely in terms of a Bayesian Mechanism is an erroneous Reduction

The Diagnostic Process =
Expert Deliberation,
taking into account the known facts,
& reducing uncertainty by a problem solving strategy
= Differential Diagnosis = Decision Heuristics

The lab participates in this Expert Deliberation

Diagnostic Process

Part 1 Operational Definition (what it does, how we do it)

Part 2 Method Validation

Are the " circumstances ",
is the " implementation " of a test
" suited " for its " diagnostic purpose " ?

Part 3 Diagnostic ability of a test

Part 4 Production & Analytical Quality Requirements

Part 2a/4

Method Validation

The right perspective :
support the decision process

Method Validation = Optimizing the Decision Process

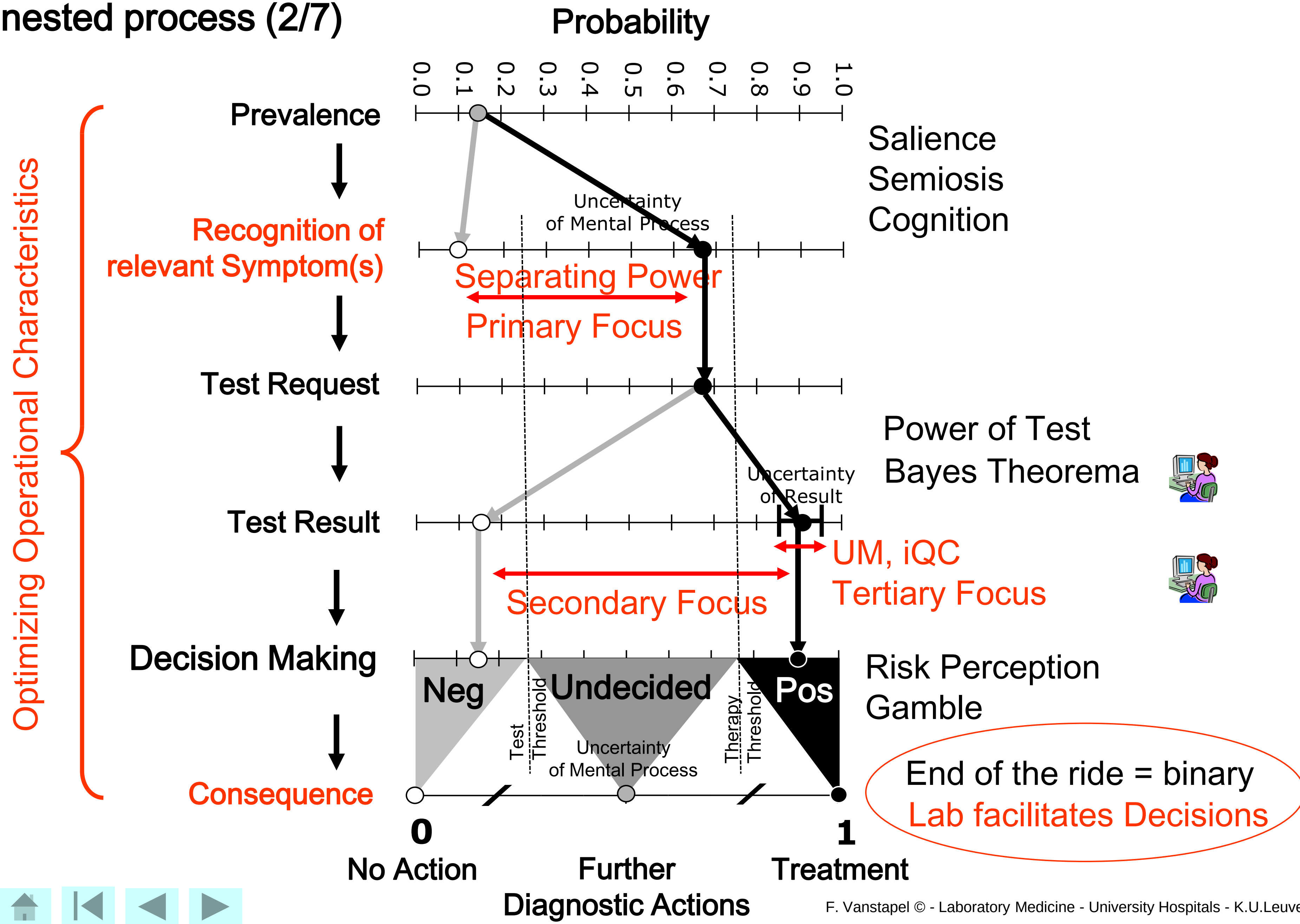
Bayesian Model : Operational Characteristics (1/7)

1. value delivered by a particular diagnostic act depends on
   - its position in the sequence of diagnostic acts
   - the therapeutic relevance of the result

2. the diagnostic process articulates with mental processes

3. operational characteristics refer to the
   increment in the degree of belief in a given diagnosis
   = reduction in uncertainty of interpretation

Laboratory Diagnosis : nested process (2/7)



Bayesian Model : Operational Characteristics (3/7)

getting into the head of Dr. John Malkovich
becoming mental

You are 80% certain of your diagnosis

- ○ You request a sensitive test — neg result rules out
- ○ You request a specific test — pos result rules in
- ○ You do no further testing

Bayesian Model : Operational Characteristics (3/7)

getting into the head of Dr. John Malkovich
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You are 80% certain of your diagnosis

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- ○ You do no further testing

You are 80% certain of your diagnosis

- ○ You treat all of your patients
- ○ You treat all of your patients with 80% of the recommended dosis — of course not
- ○ You treat 80% of the patients randomly selected — result ± conf. interval ?

How can you have answered !
Which **risk** were you negotiating ?

Bayesian Model : Operational Characteristics (4/7)

1. value of obtaining a test result depends on
   - the “ sequence ” of diagnostic acts
   - the therapeutic “ relevance ” = “ consequences ”

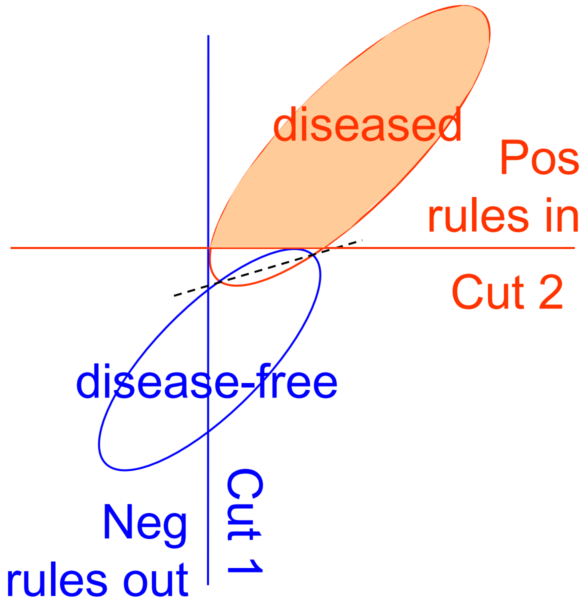
2. degree of belief in a given diagnosis is
   “ seldom absolute ” = “ uncertainty ”

3. the communicating mental processes
   in their own right are statistical in nature :
   - geared at negotiating risk 
   - allow to make on average the best decision
   - at a price of accepting wrong decisions

Bayesian Model : Operational Characteristics (5/7)

I don't want to take risk. I want more then ..% certainty !

- You request a sensitive test — neg result rules out
- You request a specific test — pos result rules in



Thermodynamic principle :

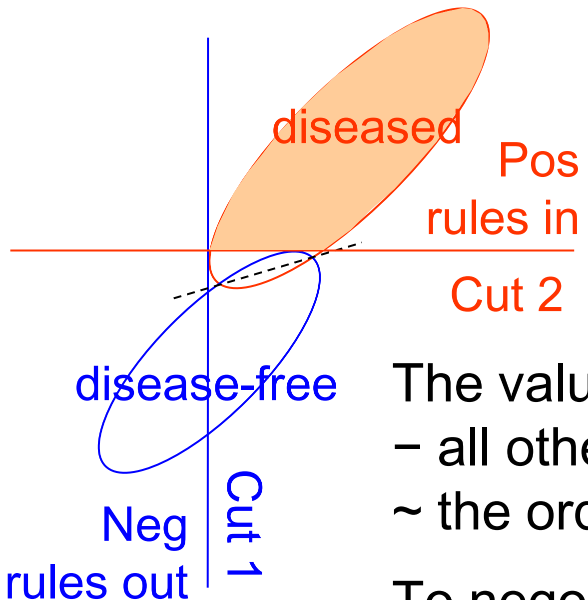
The increment in " certainty "

= greater " purity " of the resulting sample

is at the cost of " yield "

= " cases lost " on the altar of truth and certainty

Bayesian Model : Operational Characteristics (6/7)



Even when results are produced in tandem, at one time they are simultaneously available for interpretation

The value of a test is determined by
− all other available information
~ the order in which results are released

To negotiate the uncertainty of interpretation (see later : the confidence on likelihood ratio's), the clinician will evaluate the validity of test results
- internal **consistency** with previous results
- **external consistency** with the body of knowledge

In order to come to a decision the corresponding mental process is geared at
- neglecting inconsistent results
- overvaluing confirmatory evidence

Bayesian Model : Operational Characteristics (7/7)

The concept of “ Therapeutic Freedom ”
recognizes the primacy of mental processes involved

- salience & semiosis allow us to operate amid a flood of inputs
- by reducing (perceived) uncertainty,
  we reduce (perceived) risk
- thus we trade in yield for certainty
  we tend to overvalue certainty and
  to neglect the price we pay
- we tend to ask for redundant confirmation
  we selectively “ overvalue ” either the pro’s or the contra’s
  to reinforce our decisions
  to pacify ourselves
- we make a(n informed) gamble, take a risk & decide
- these mental processes are **necessary to be able to operate**
  but **are inherently “ biased ” = prone to “ mistakes ”**

Decision making = what it is all about = a mental process

How Doctors Think (J. Groopman)

- → Pattern recognition
- → Decide in the face of Uncertainty

RISK TAKING versus RISK ADVERSION

CONFIDENCE versus AMBIGUITY

GESTALT versus DECONSTRUCTION

↓

R) Methodical approach

gain in error variability

reduction in uncertainty

broadened sensitivity

find unexpected but relevant features

Part 2b/4

Method Validation

The right methodology :

systematic process optimization

Method validation is treated in greater detail in a separate teaching unit 

Method Validation

Is the test implementation suited for its diagnostic purpose ?

1. Logistic requirements

What are the " circumstances " of the diagnostic act ?

Are service level & needs of the care program(s) matched ?

2. Risk management

Which minimal requirements / key performance characteristics need to be guaranteed ?

3 Which outcome Which factors key to performance have to be **controlled** by a process-centred approach ?

1-3 is an obligate order

the answer to the next question
depends on the answer to the former

Method Validation

Requirements of laboratory test

- Relevant
- Accurate
- Timely
- Accessible
- Understandable
- Comparable
- Coherent
- Complete
- Right price / costs

= purposive

= fit for purpose

List on the left is borrowed from governmental census agencies

- it applies to any "diagnostic" process
- it will return in the teaching unit on (statistical) process control 

Specs / targets
cfr. method validation file 

Method Validation

Logistic requirements of laboratory test

- Relevant	: position / function in care algorithm(s) ?
- Accurate	: sampling design
- Timely	: timing / TAT with respect to care program(s)
- Accessible	: test request / reporting of results & conclusions
- Understandable	: cumulative reports / reference & decision limits
- Comparable	: over methods / time frames
- Coherent	: with other tests & procedures
- Complete	: identification of lacking / censored data
- Right price/costs	: low financial & user burden to patients & medical staff

(non exhaustive list)

Method Validation

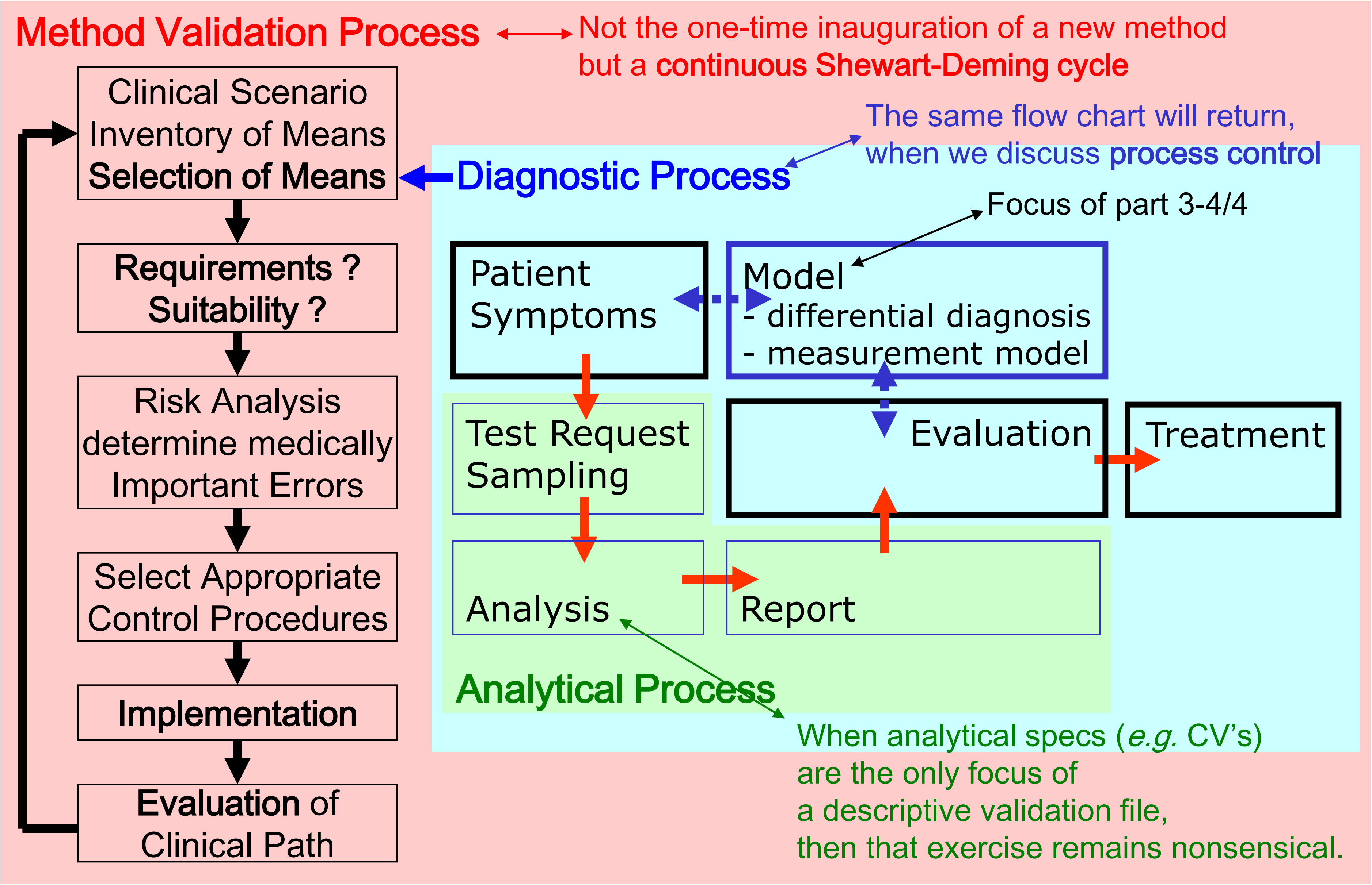
Analytical requirements of laboratory test

- Relevant	:
- Accurate	: data processing / analytical traceability
- Timely	:
- Accessible	:
- Understandable	: traceability to the applicable clinical studies
- Comparable	: commutability over methods / time frames
- Coherent	: diagnostic specificity of measurement
- Complete	:
- Right price/costs	:

(non exhaustive list)

This list is far shorter than the former &
these analytical requirements can only be specified
when knowing the circumstances (*cfr*. logistics) of the diagnostic scenario

METHOD VALIDATION: PROCESS FLOW CHART



Method Validation : Conclusions

“ No barking up the wrong tree ”

Primary focus shall be

Valid Logistic Implementation of the Test

- by Business Project Management Techniques

Secondary focus will be

Defining & maintaining Valid Analytical Specs

- to optimize the diagnostic process served
- as a framework for

(statistical) Control of the Analytical Process 

These questions can only be answered

by examining the specific clinical scenario’s

Valid Logistic Implementation

What are critical area's amenable to improvement ?

Joint Commission of Accreditation of Healthcare Organizations (JCAHO)
National Patient Safety Goals (NPSG) 2006

Laboratory-related goals

NPSG #1: **Accuracy of Patient & Sample Identification**

NPSG #2: **Effectiveness of Communication among Caregivers**

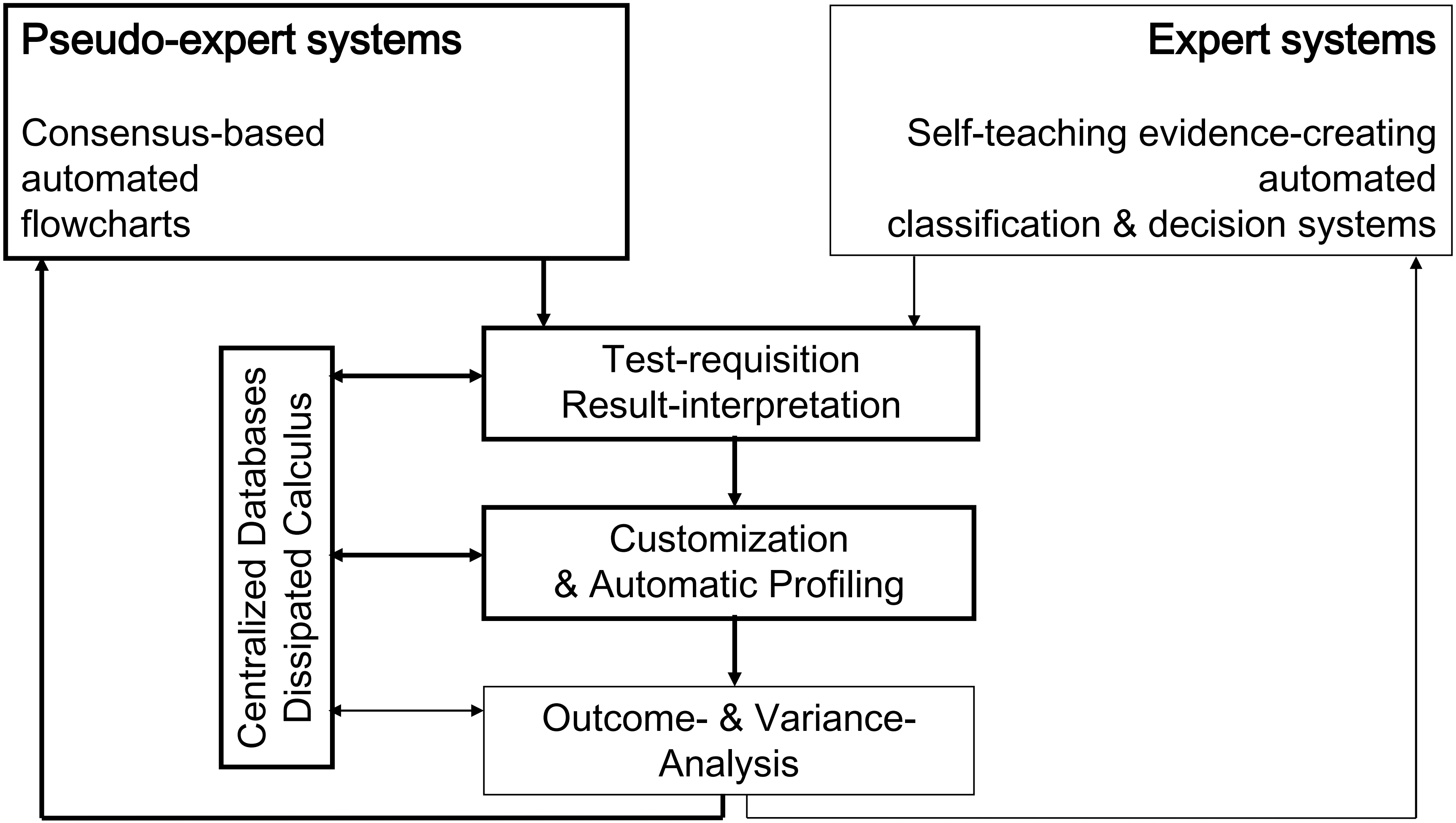
- 2.a. read-back verification
- 2.b. unambiguous acronyms
- 2.c. timeliness of critical results

NPSG #4: **Universal Protocols**

Method Validation : Questions to ask

- Which benchmarks to develop and maintain procedures ?
- What are best practices ?
- How to document your critical activities and track your progress ?
- How to reduce miscommunication ?

New Developments : the new information technology age



Diagnostic Process

Part 1 Operational Definition (what it does, how we do it)

Part 2 Method Validation

Part 3 Diagnostic ability of a lab test

How good is the test
at discriminating diagnostic alternatives ?

Part 4 Production & Analytical Quality Requirements

Validating Method Ability

At the end of your method validation, you will have to answer *i.a.* these “ relevant = consequential ” questions :

- Will I report categorically or quantitatively ?
- Which reference- / decision-limits will I use ?
- Which analytical specs have to be guaranteed ?

Discover in what follows
how the answers to the above questions depend on
the interplay of

- specific clinical scenario’s
- the measurement model
- the bayesian model

Part 3a/4

Diagnostic Ability of your Test

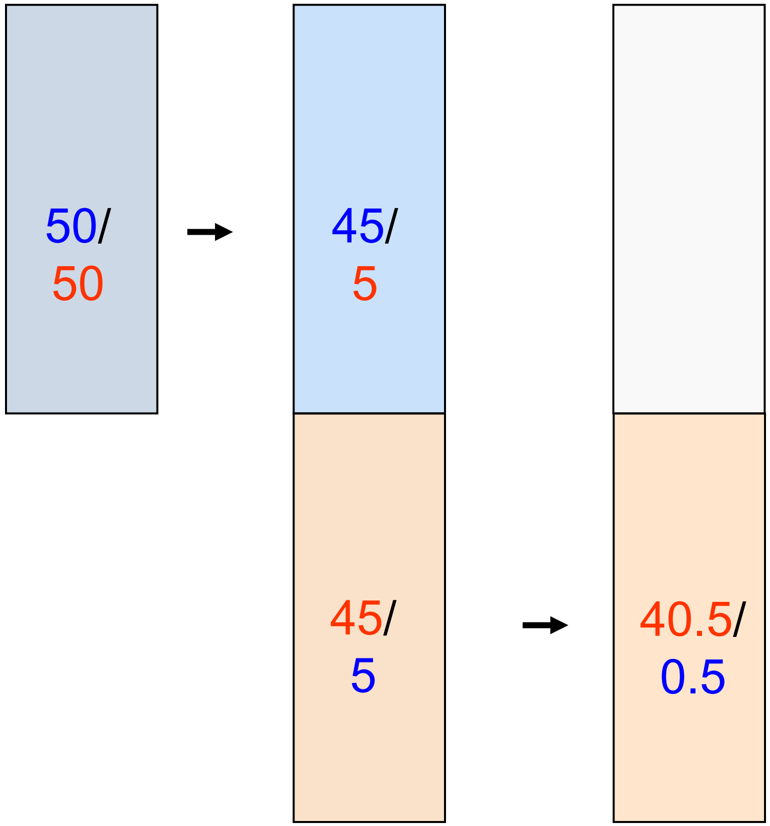
about sensitivity, specificity, likelihood ratio's, and the like

Diagnostic Ability
Understanding the Separating Power of your Test

Intuitive Intro

To be read together with unit on Bayes theorema 

Extraction / Purification in a 2-phase system



Mixture → Extraction → Wash

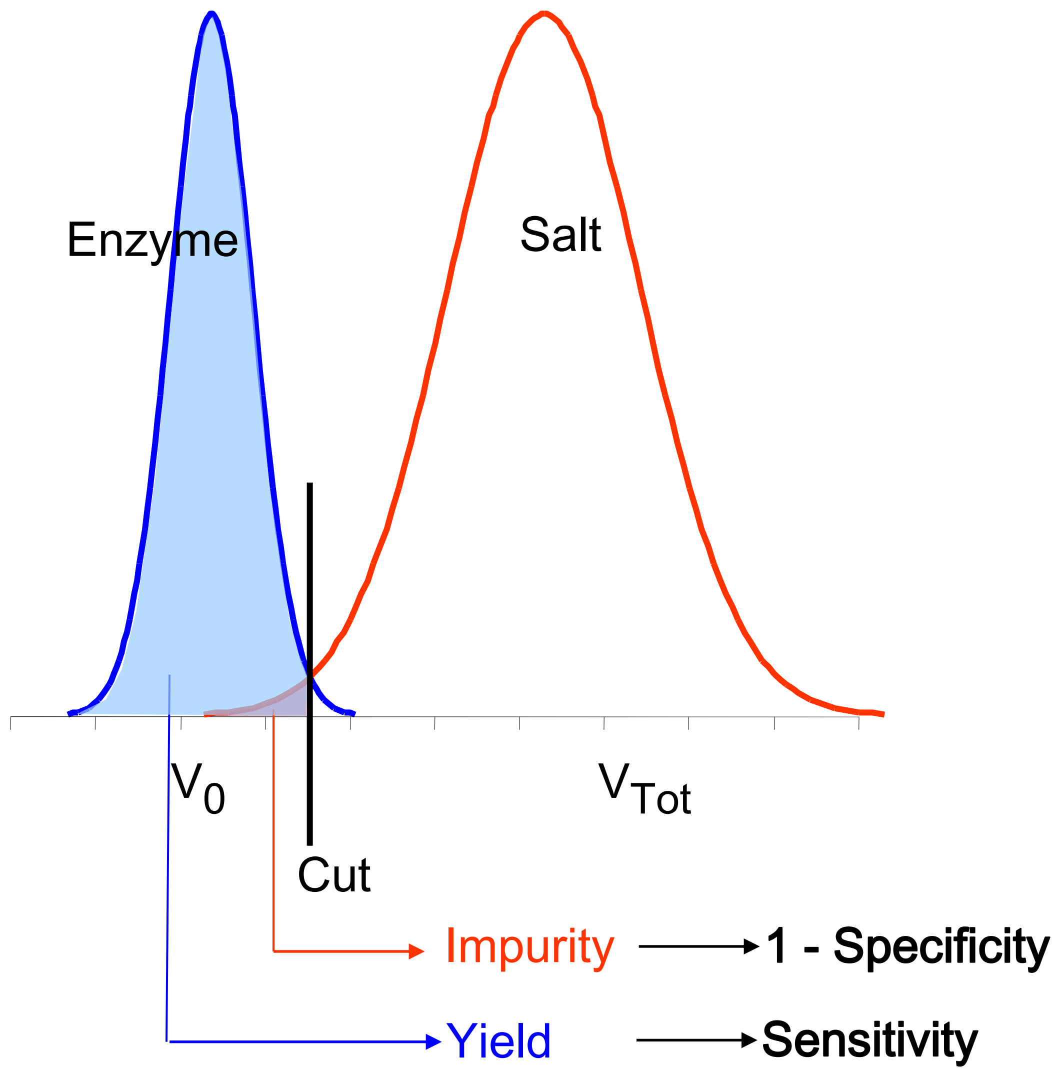
Clinical Case-mix → Triage → Post-triage Certainty

The separating power
is determined by the “ partition coëfficients ”
equivalent to “ likelihood ratio’s ”

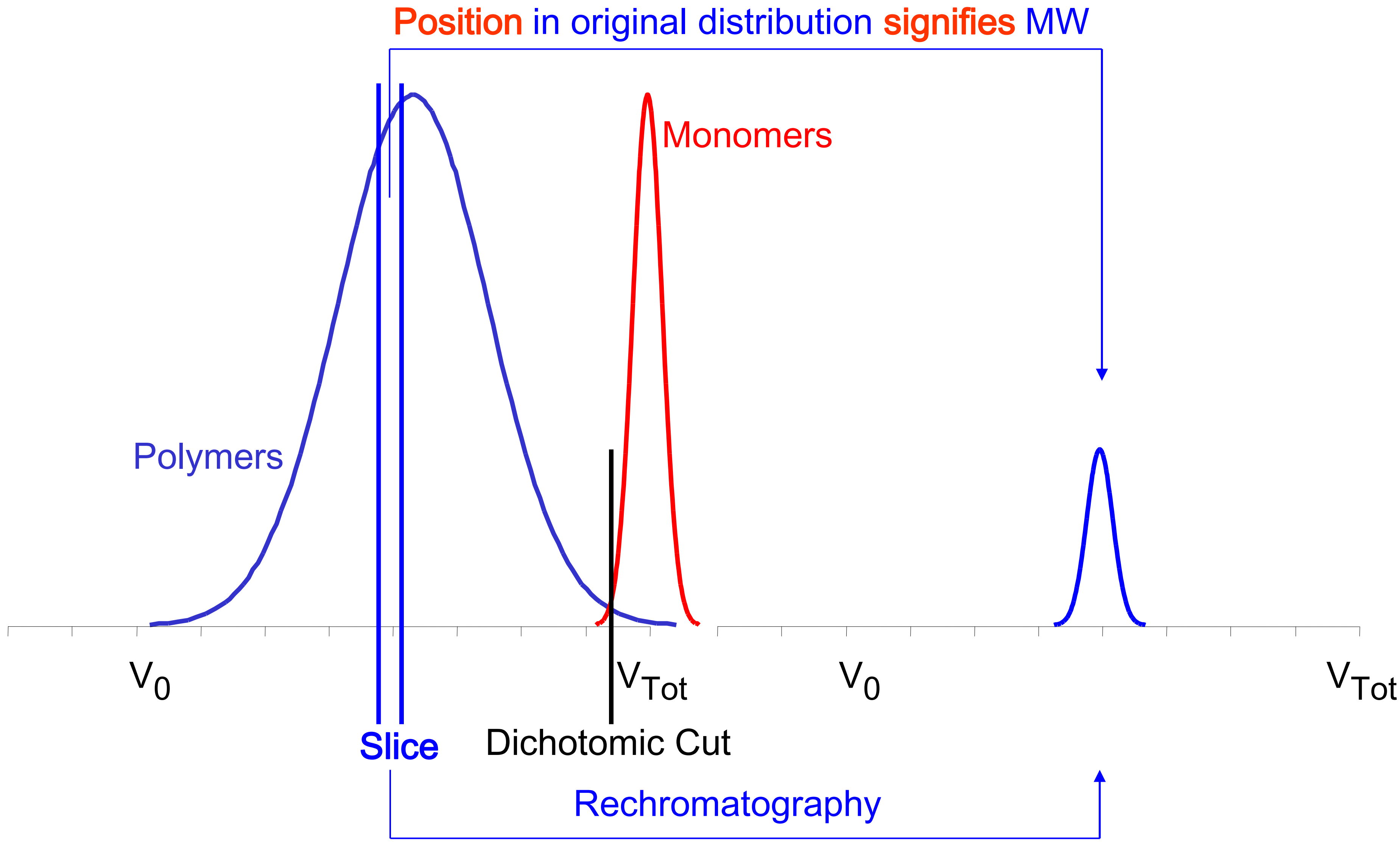
Each step
increases the “ enrichment ”
equivalent to “ predictive power ”

The increase in “ purity ”
is at the expense of “ yield ”
equivalent to “ sensitivity ”

Gelfiltration : Desalting a $(NH_4)_2SO_4$ enzyme preparation



Gelfitration : Fractionating a polymer mixture

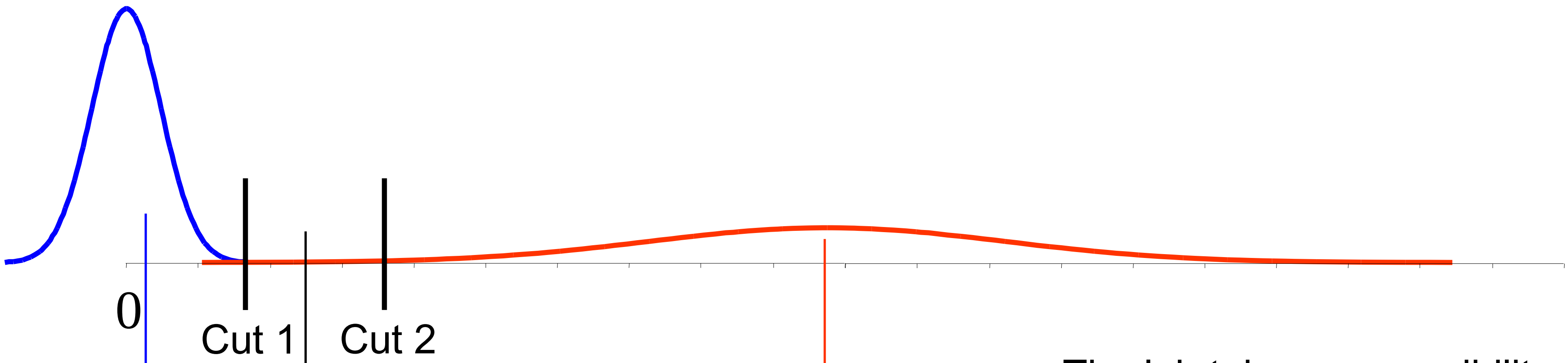


Diagnostic Ability
Separating Power of your Test

Categorical & Quantitative
Test Responses
and their Bayesian Interpretation

Scenario 1 : Categorical Report

The raw data



Negative

Gray Zone
sensitivity/specificity pay-off

Positive

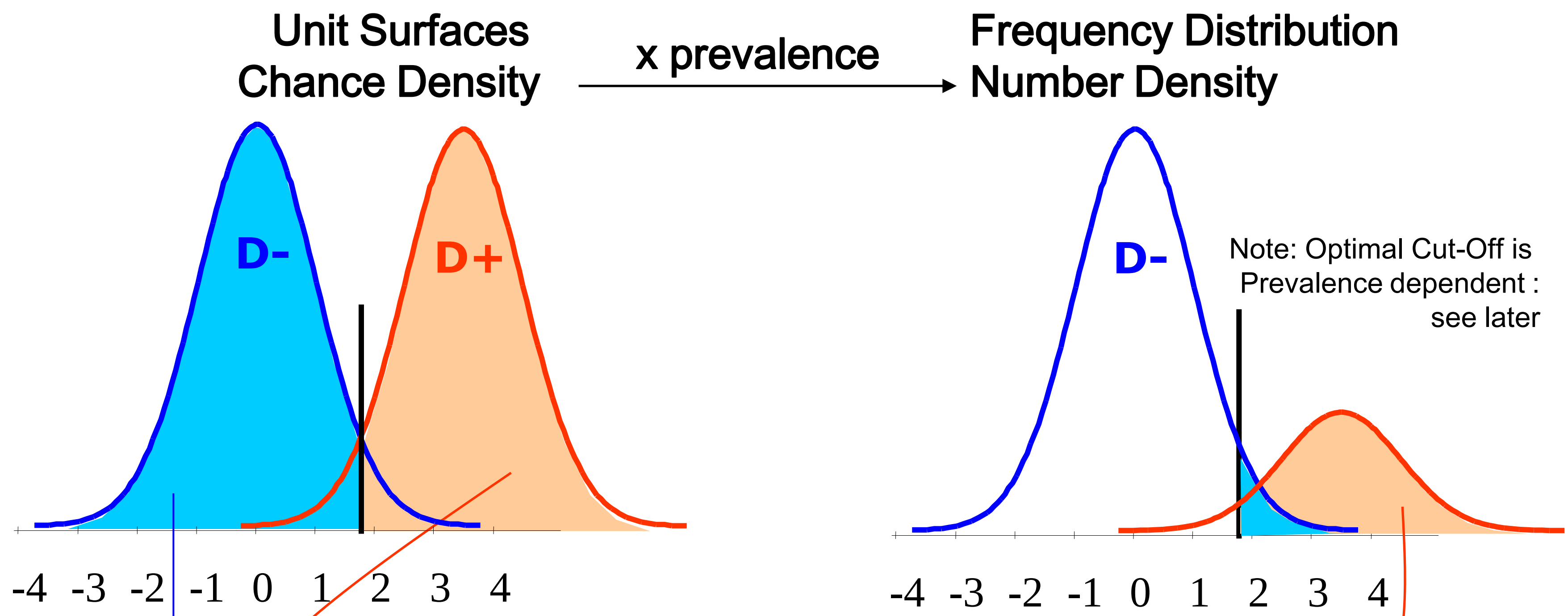
The lab takes responsibility
for the interpretation
Report = Categorical

Bayesian Evaluation of Results

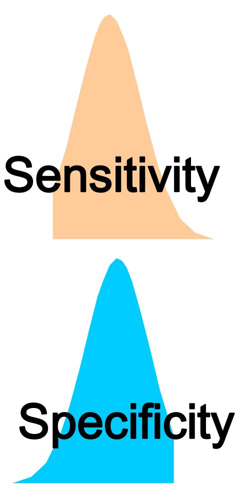
- Categorical classification derived from measurement of a continuous variable
- Sensitivity and Specificity are large for any particular value
  = Risk for misclassification is small
- The interpretation & treatment
  does not depend on the actual value of the underlying measurand

Diagnosis = with respect to a cut-off value

Scenario 1 : Interpretation of Categorical Result

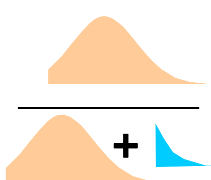


Bayesian Evaluation of Results



	Pre-test prevalence	
	$P(D^+)$	$P(D^-)$
$P(T^+\|D^+)$	$P(T^+\|D^+)\ P(D^+)$	$[1 - P(T^-\|D^-)]\ P(D^-)$
$P(T^-\|D^-)$		$P(T^-\|D^-)\ P(D^-)$

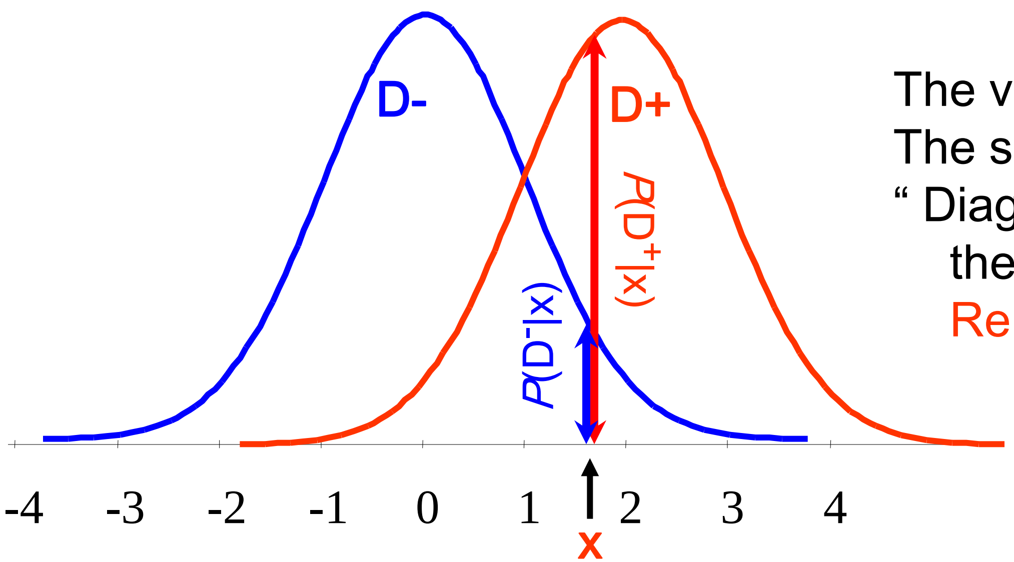
$P(D^+|T^+)$



For calculus see unit: Bayes theorema

Scenario 2 : Quantitative Report

The raw data



The value refers to a measured quantity.
The size of the quantity carries significance :
" Diagnostic certainty " is function of
the observed value, x.
Report = Quantitative

Bayesian Evaluation of Results

cfr. Index of individuality
Minimum change value

The size of the quantity carries significance

- The value found is ~ reproducibly located in the overall distribution
- Sensitivity and Specificity are suboptimal for a range of values
- Risk for misclassification is large due to biological overlap
- The interpretation / treatment
  depends on the actual value of the measurand

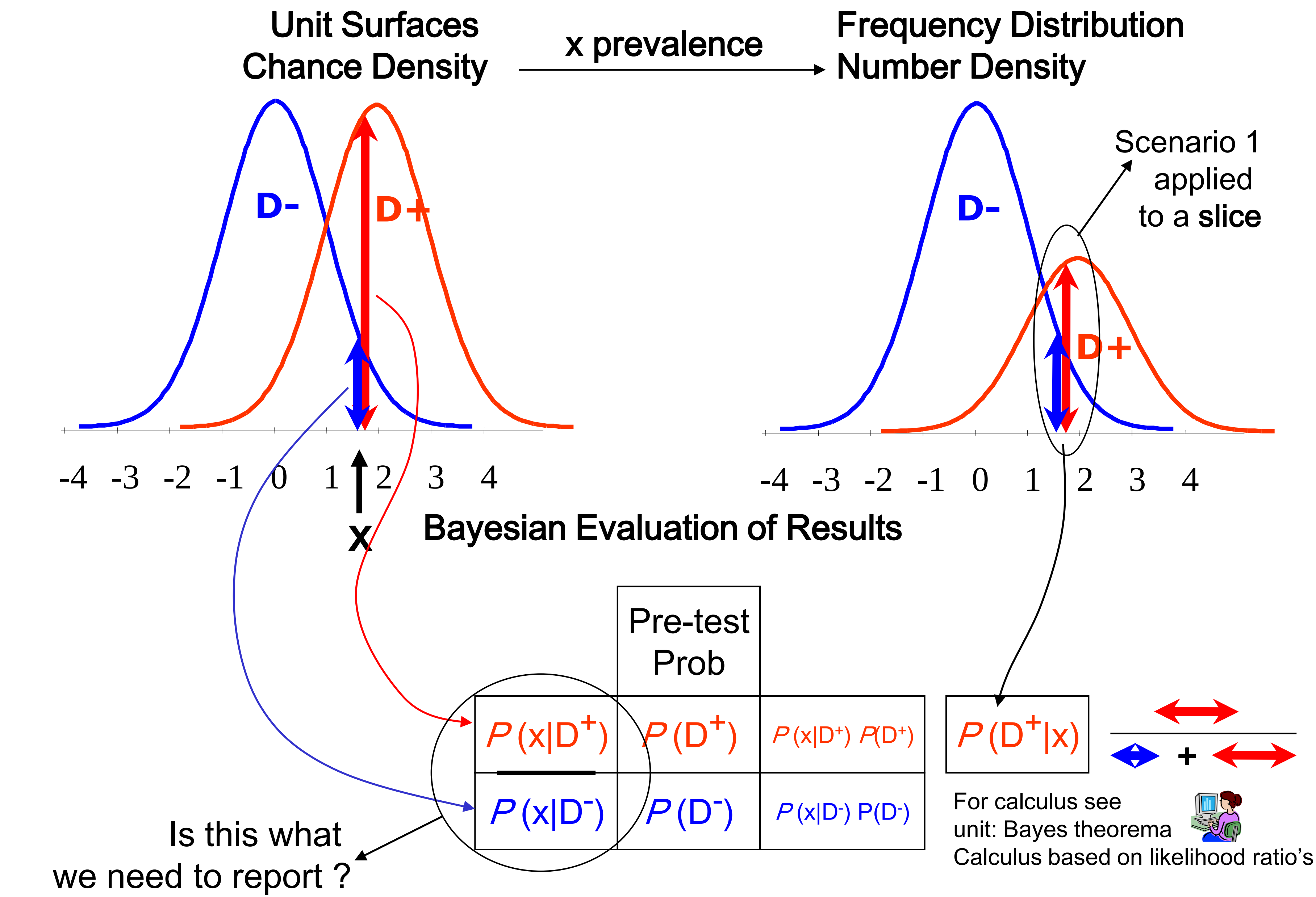
Diagnosis ⟶ $P(D+|x)$

Quantitative Report

Quantitative reporting
implies that the quantity carries significance

CAVE: When the quantity does not carry significance, quantitative reporting can be a cause of over-interpretation & inappropriate decisions

Scenario 2 : Interpretation of Quantitative Result



How to report how “ diagnostic ” a quantitative result is ?

How to report how " diagnostic " a quantitative result is ?

	Pre-test Odds		Post-test Odds	
$\frac{P(x\|D^+)}{P(x\|D^-)}$	x $\frac{P(D^+)}{P(D^-)}$	=	$\frac{P(x\|D^+)\ P(D^+)}{[1 - P(x\|D^-)]\ P(D^-)}$	$P(D^+\|x)$

1. Positive Likelihood Ratio :

as a means for reporting the position of a result, x in the " **universum** of possible results " ? → **Answer = NO**

In most cases, diagnosis remains a mental process in the head of the clinician

- Is your " teaching sample " matched to your " actual clinical case-mix " ?
  Are the available data relevant ? : Answer = almost never
  (reported studies : usually matched controls, balanced design) *
- Does user of the result know what likelihood-ratio's stand for ?
  Probably not : non-linear parameter, referring to artificial **1/1 prevalence**
- " Interpretation " stems from
  " straight-forward " multiplication with " pre-test odds ".
  Which " pre-test odds ", which " differential diagnosis " ?

* This study design is for good reasons

How to report how " diagnostic " a quantitative result is ?

2. Keep it simple : " Distance " from " reference "

- fraction of average of " normal " reference x / X_{Ref}
- z-score $(x- X_{Ref}) / S_{Ref}$
- times upper limit of reference range $x / (X_{Ref} + k\ S_{Ref})$
- …

common practice in metabolics & in rare diseases,
where a small control sample is analyzed
in parallel with the clinical sample
as a means of calibration & quality control
the above parameters can be reported without reference values
since that information is included in the reported derived parameter

3. Keep it super-simple : report "value" with "reference or decision limits"

Undoubtedly, that is the minimum that you need.

But is it that simple ?

Are cut-offs prevalence- / differential-diagnosis-independent ?

How does the physician / the patient interpret results near the cut-off ?

Read the next episode …

Part 3b/4

Diagnostic Ability

Minimizing Costs of Misclassification

Diagnostic Ability
Costs of Misclassification

Inventory of Costs

Production Costs

Costs of the Test
- Equipment and Materials
- Personnel (training, and production)
- Reporting
- Overheads

Costs of Appraisal of Conformity
- Validation of the Test
- Internal Quality Control (iQC)
  - Costs of materials & testing
  - Cost of evaluation
  - Costs of scrap and rework
  - Costs of false positives & false negatives
- External Quality Evaluation (eQE)
  - Costs of the service
  - Costs of performing the test
  - Costs of eQE-administration
  - Costs of false positives & false negatives

↑

~ Fixed Costs

Costs of Quality Failure

Costs of false positive iQC
- Internal / External
  - Superfluous Work-up
  - Wasted time and anxiety

Costs of false positive diagnosis
- Internal / External
  - Superfluous Work-up
  - Burden and anxiety

Costs of false negative diagnosis
- Internal / External
  - Superfluous Work-up
  - Missed benefits

↑

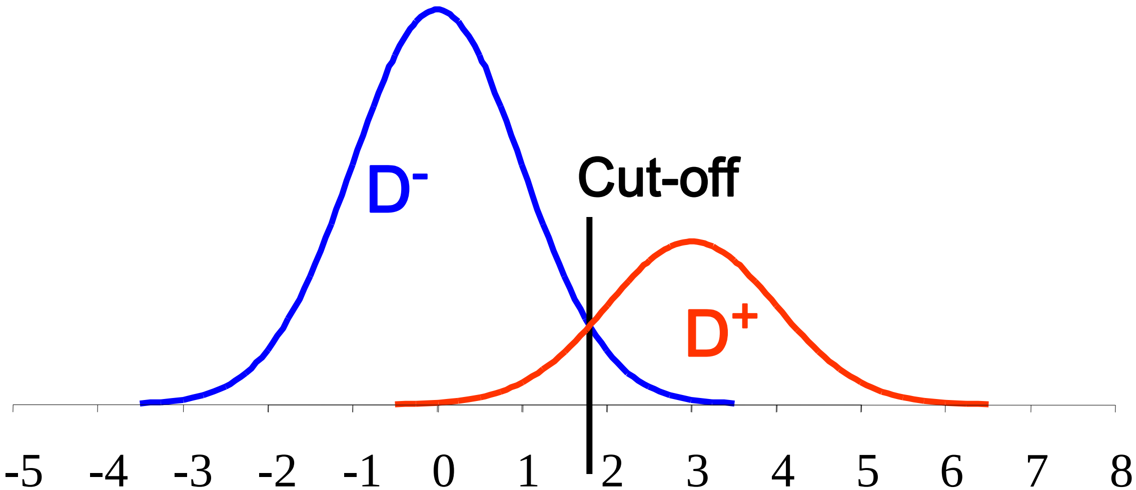
Minimize adverse effects

$fpr \times cost_{fp} + fnr \times cost_{fn}$

Diagnostic Ability
Costs of Misclassification

Power Curves
or
seek the minimum of adverse effects

Minimize adverse effects fpr x $cost_{fp}$ + fnr x $cost_{fn}$



fpr x $cost_{fp}$ = (1 - Specificity) x (1 - Prevalence) x $cost_{fp}$

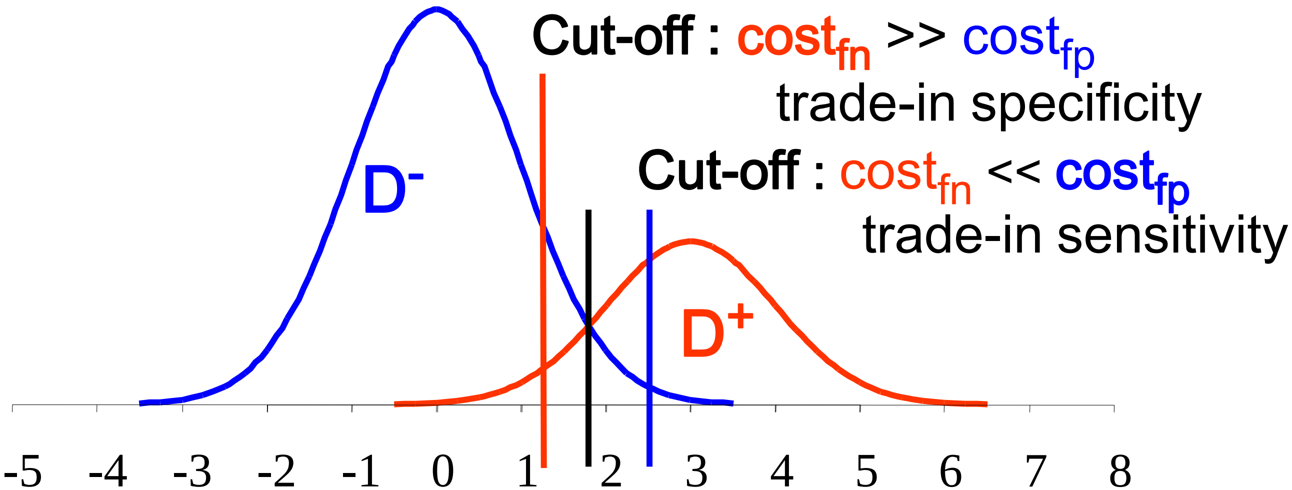
fnr x $cost_{fn}$ = (1 - Sensitivity) x Prevalence x $cost_{fn}$

ROC-curve

Optimize TRUTH → delivers Cut-off

However our business is not the truth, but the best outcome

Minimize adverse effects $fpr \times cost_{fp} + fnr \times cost_{fn}$



$fpr \times cost_{fp}$ = (1 - Specificity) x (1 - Prevalence) x $cost_{fp}$

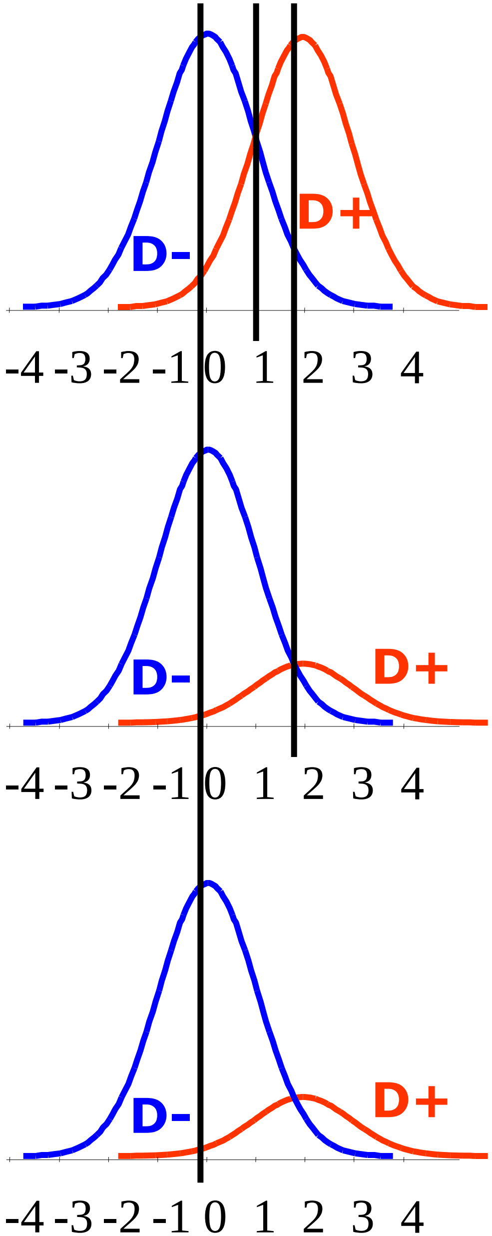
$fnr \times cost_{fn}$ = (1 - Sensitivity) x Prevalence x $cost_{fn}$

Optimize TRUTH

Maximize PROFIT
= Minimize Adverse OUTCOME
(purposive clinical optimization)

→ delivers best Cut-off

Why cut-offs not always do the job for you



ROC-analysis :

cut-off from sensitivity-specificity data

= not prevalence-weighted = irrelevant

Prevalence – weighted :

cut-off maximizes TRUTH

= not purpose-weighted

But do you know the pre-test odds ?

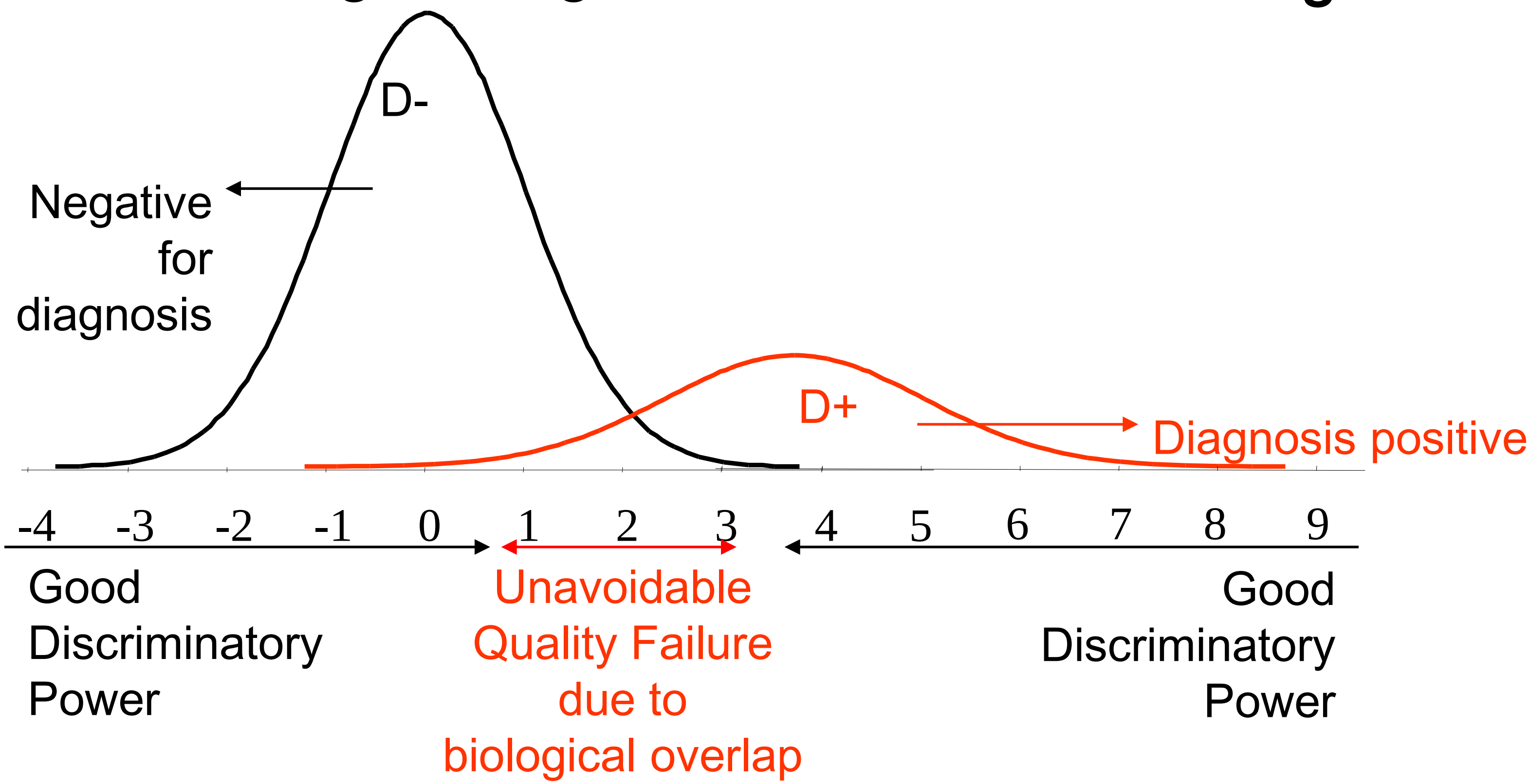
Prevalence * Value – weighted

cut-off maximizes **OUTCOME**

And what about our professional credo :

“ you shall NOT HARM ” ?

You dislike gambling ? What about an honest gamble ?



What do you do when confronted with a “ Grey Zone ” result ?

- o You do not decide = Certain harm
- o You take a cut-off based decision = On average your patients benefit
- o You request additional tests = You honor the “trust of your patient”

Are you aware of the “Opportunity Cost” ?

Diagnostic Power of a Test : Conclusions

Provided that you know the pre-test odds
you can define **cut-off values**
Provided that you know the spectrum of cases
you can report **likelihood ratio's**

In most situations, the lab knows
neither the pre-test odds,
nor the spectrum of cases,
nor the differential diagnostic question.

While the concepts are simple and form a useful framework,
their real-life application is not necessarily straight-forward.

The reduction of the Diagnostic Process
to a purely Bayesian Process is unwarranted.
Of what one cannot speak, one must be silent.

Diagnostic Process

Part 1 Operational Definition (what it does, how we do it)
Part 2 Method Validation
Part 3 Diagnostic Ability of a Test
Part 4 Production & Analytical Quality Requirements

What are the requirements
for maintaining optimum diagnostic ability ?

Step 0 : Purposive Method Validation
Define requirements
fit for purpose

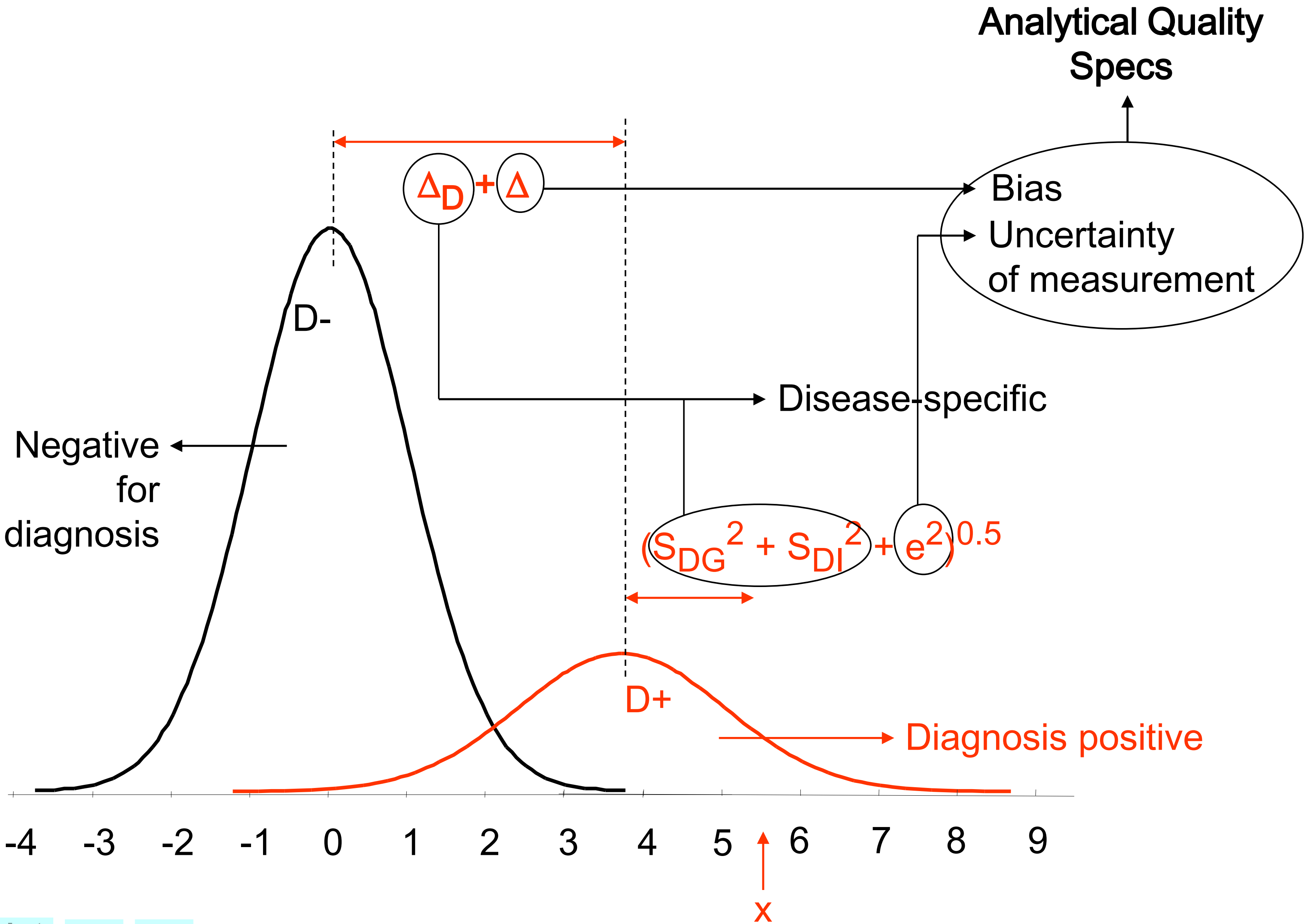
Step 1 : Measurement & Reporting
- uncertainty of measurement 
- pre- & post-analytical steps

Step 2 : Interpretation of Results

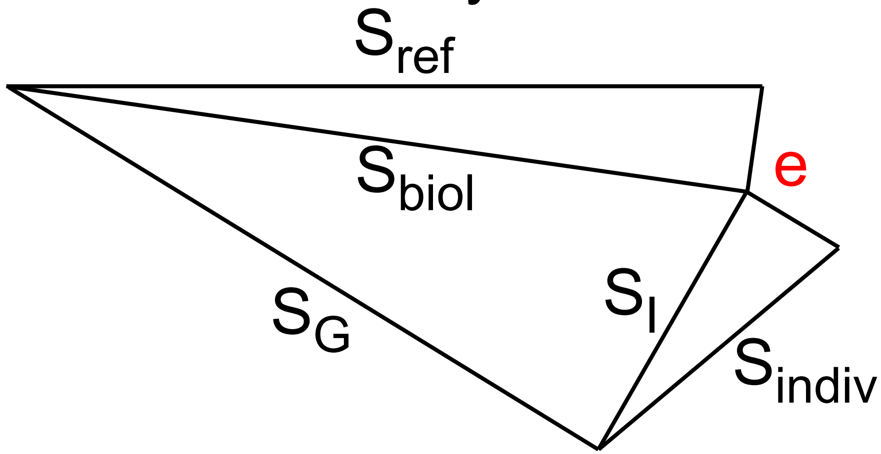
How to report how " certain " you are " about a value " ?

Does the answer come from
your estimate of the Uncertainty of Measurement ?

The measurement model



Effect of uncertainty of measurement



Pythagorean rule :

- random error adds destructively
- effect of e is typically small to the extent that it may become irrelevant

Test-drive our simulator

$$S_{biol} = (S_G^2 + S_I^2)^{0.5}$$

- S_I: intra-individual variance
- S_G: (inter-individual) group variance
- S_{biol}: intrinsic biological variance

$$S_{ref} = (S_{biol}^2 + e^2)^{0.5}$$

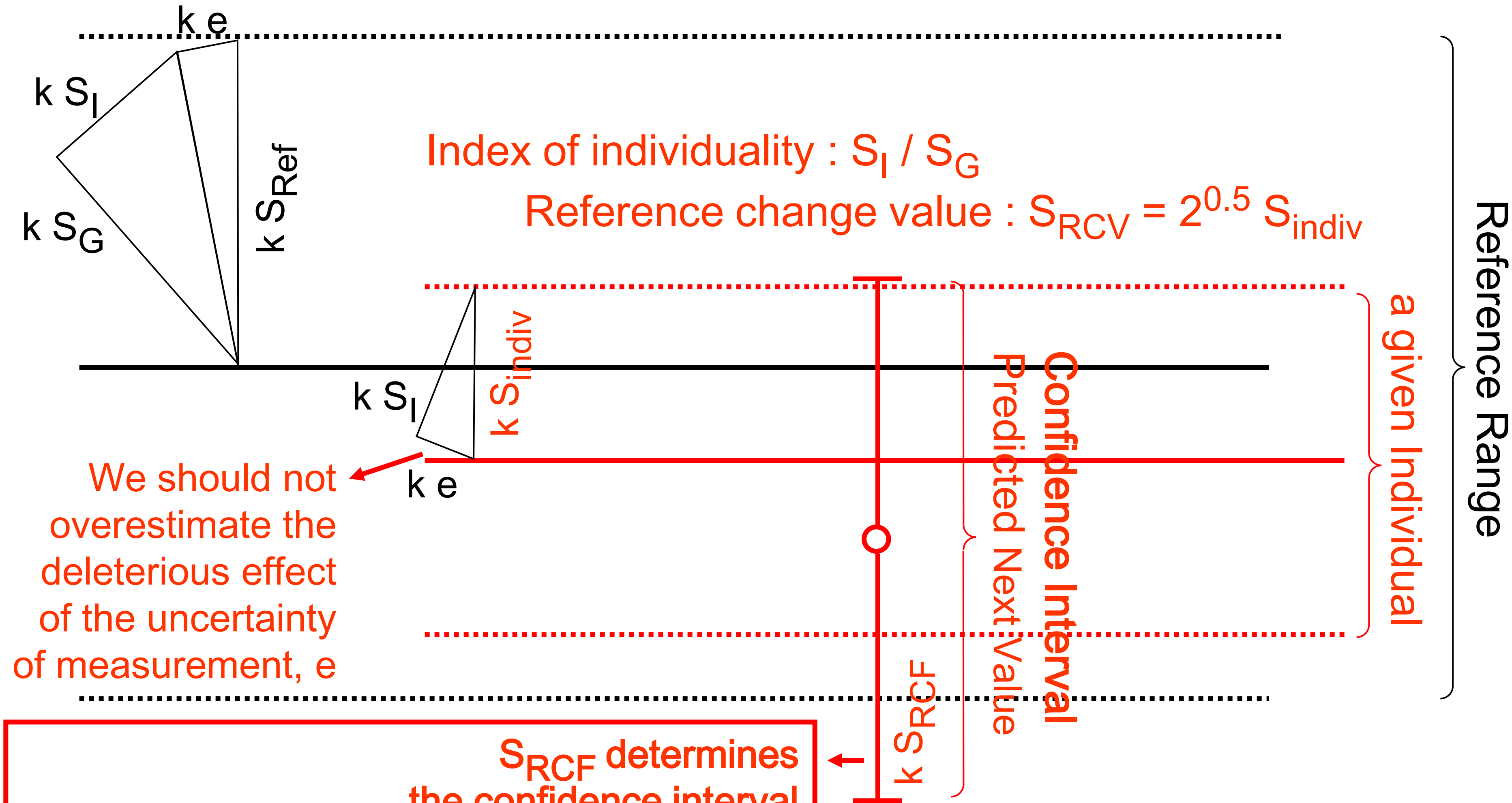
- e: Unavoidable uncertainty of measurement

- S_{ref}: apparent population variance

$$S_{indiv} = (S_I^2 + e^2)^{0.5}$$

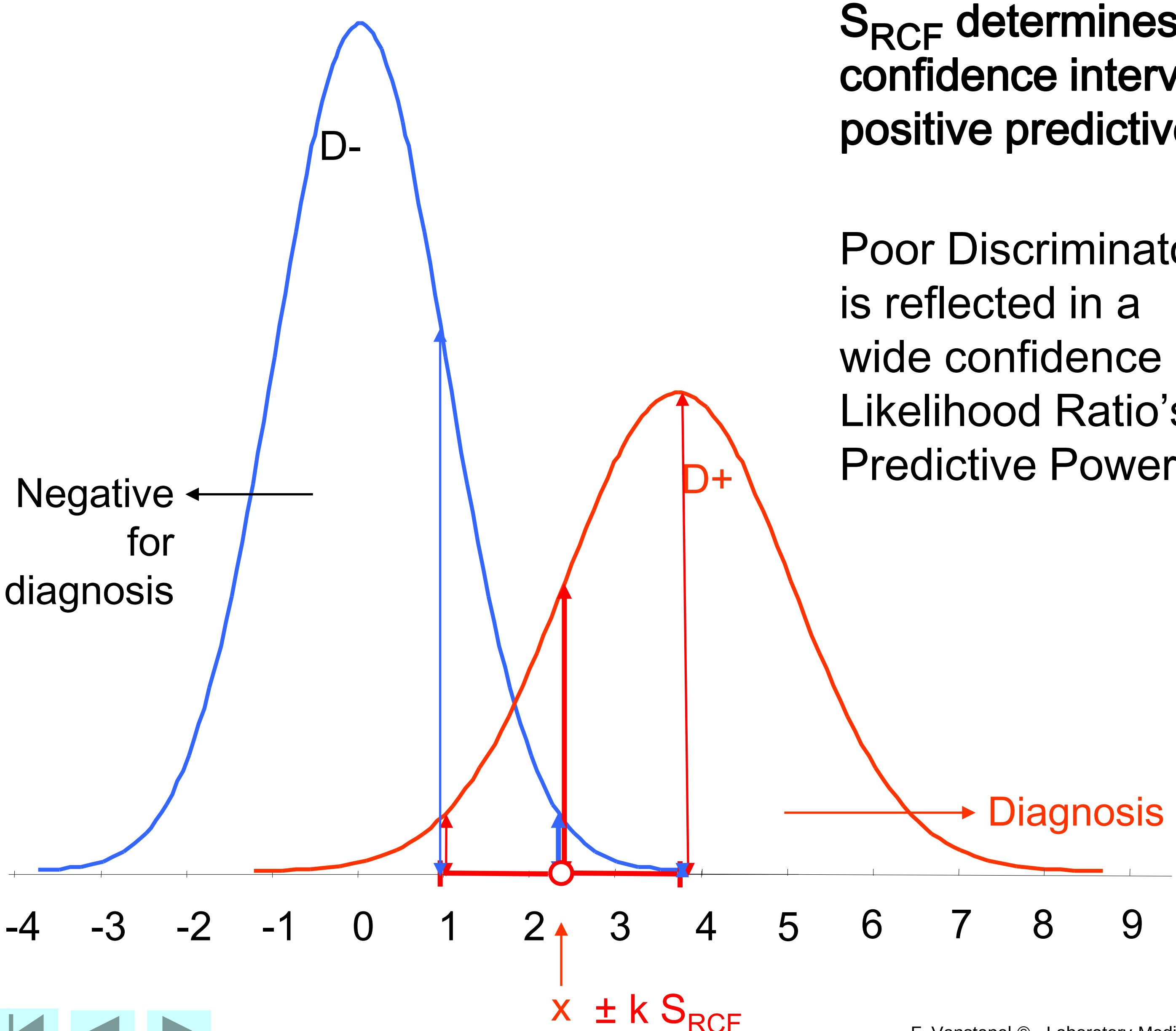
- S_{indiv}: apparent individual variance

How to report how “ certain ” you are “ about the value ” ?
“ Reference change value, k S_{RCF} ”



S_{RCF} determines the confidence interval on likelihood ratio’s for an individual result

The measurement model



S_{RCF} determines confidence interval on positive predictive value

Poor Discriminatory Power is reflected in a wide confidence interval for Likelihood Ratio's & Predictive Power

How to report how " certain " you are " about a value " ?

Your estimate of the Uncertainty of Measurement
is the right answer to the wrong question !

The right question is :
How certain are you of the " interpretation " ?

How to report how " stable a patient " is ?

Uncertainty of Measurement is ~ irrelevant

1. Confidence intervals : not ± k e, but ± k $2^{0.5}$ S_{indiv}

for reporting the uncertainty = confidence about repeat measurements ?

- Is your patient sick ? Do you know the pathology-specific S_{ID} ?

Answer : S_{ID} almost never known,
& dependent on differential diagnostic question
which generally is not known by the lab

To walk this path, provide interactive facilities to user of data

2. Cumulative (graphical) reports

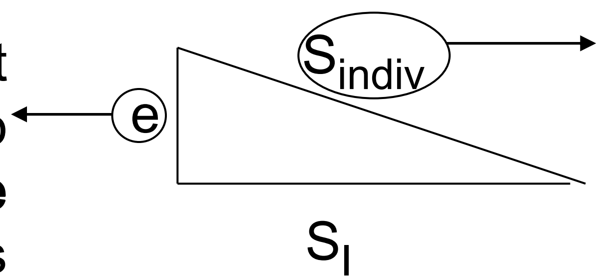
- Only indicated for tests which are frequently repeated for a diagnostic purpose
  but these are the tests where the above question is relevant
- Repeat measurements are then not overconsumption, but the only way to negotiate uncertainty about the interpretation of a first result
- The user of the data teaches himself
  - variability within an individual patient, to be correlated with known clinical history
  - multiple patients and events as a teaching data base

Diagnosis is a mental process

Evaluation of consistency of results

To negotiate the uncertainty of interpretation
the clinician will request additional or follow-up tests to evaluate
- the internal consistency with previous results
- the external consistency with the body of knowledge

A **repeat** measurement
by the lab
on the **same sample**
for decision-prone results
is **irrelevant**



A **repeat** measurement
on a **new sample**
compresses the confidence interval with
$1 - 1 / 2^{0.5}$ = **29%**
provided that you rely
on the average of results

Step 0 : Purposive Method Validation
Define requirements
fit for purpose

Step 1 : Measurement & Reporting
- uncertainty of measurement
- pre- & post-analytical steps

Step 2 : Interpretation of Results

Method Validation

Logistic requirements of pre- and post-analytical steps

- Relevant :
- Accurate : sampling and conditioning, patient ID, …
- Timely : timing / TAT with respect to care program(s)
- Accessible : test request / reporting of results & conclusions
- Understandable : cumulative reports / reference & decision limits
- Comparable :
- Coherent :
- Complete : identification of lacking / censored data
- Right price/costs : low financial / user burden to patients / medical staff

(non exhaustive list)

These items are important : to maximize benefit / to prevent errors 
For any particular test, you have to ask :

“ Are the general procedures, that I rely on, adequate ? ”

Step 0 : Purposive Validation
Define requirements
fit for purpose

Step 1 : Measurement and Reporting

Step 2 : Interpretation of Results
The diagnostic scenario determines requirements with respect to diagnostic ability & analytical quality

Diagnostic Scenario's are defined by their " therapeutic consequences & diagnostic intent "

Diagnostic Scenario's	**Intent**
Screening Case Finding	Low-cost detection of treatable conditions with low-prevalence
Differential Diagnosis	Confirm / Disprove
Staging	Classify in a continuum
Follow-up	Evaluate expected changes

Diagnostic Scenario's are defined by the nature of the " prior knowledge "

Diagnostic Scenario's	**Bayes Prior Knowledge**
Screening Case Finding	Prevalence
Differential Diagnosis	Professional Judgement
Staging Follow-up	H_0 , H_1 & Statistical Inference

Diagnostic Scenario's depend on test(s) with " necessary characteristics "

Diagnostic Scenario's	**Test Characteristics**
Screening Case Finding Differential Diagnosis	Good diagnostic ability = separating power
Staging	Low S_{RCF} & Low bias
Follow-up	Good analytical reproducibility

These are the clinical scenario's
where **Control** of the **Analytical Process** is most relevant 
Main issue: **commutability in time and across the walls of the lab and institutions**

Step 0 : Purposive Validation
Different diagnostic Scenario’s
translate into appropriate analytical specs

Step 1 : Measurement

Step 2 : Interpretation of Results

In the unit on statistical process control,
we elaborate on how to guarantee these specs

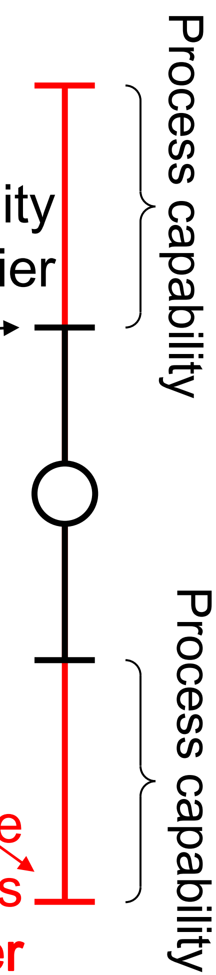
An observation free of uncertainty is impossible

“ How much uncertainty can you tolerate ? ”

1. Production capability
   = the best you can guarantee
2. European guide line
   = desirable quality goals
3. What the diagnostic scenario tolerates
   = the least you must guarantee

best attainable quality
= min error frontier

better then this may be
lost opportunity costs
= max error frontier



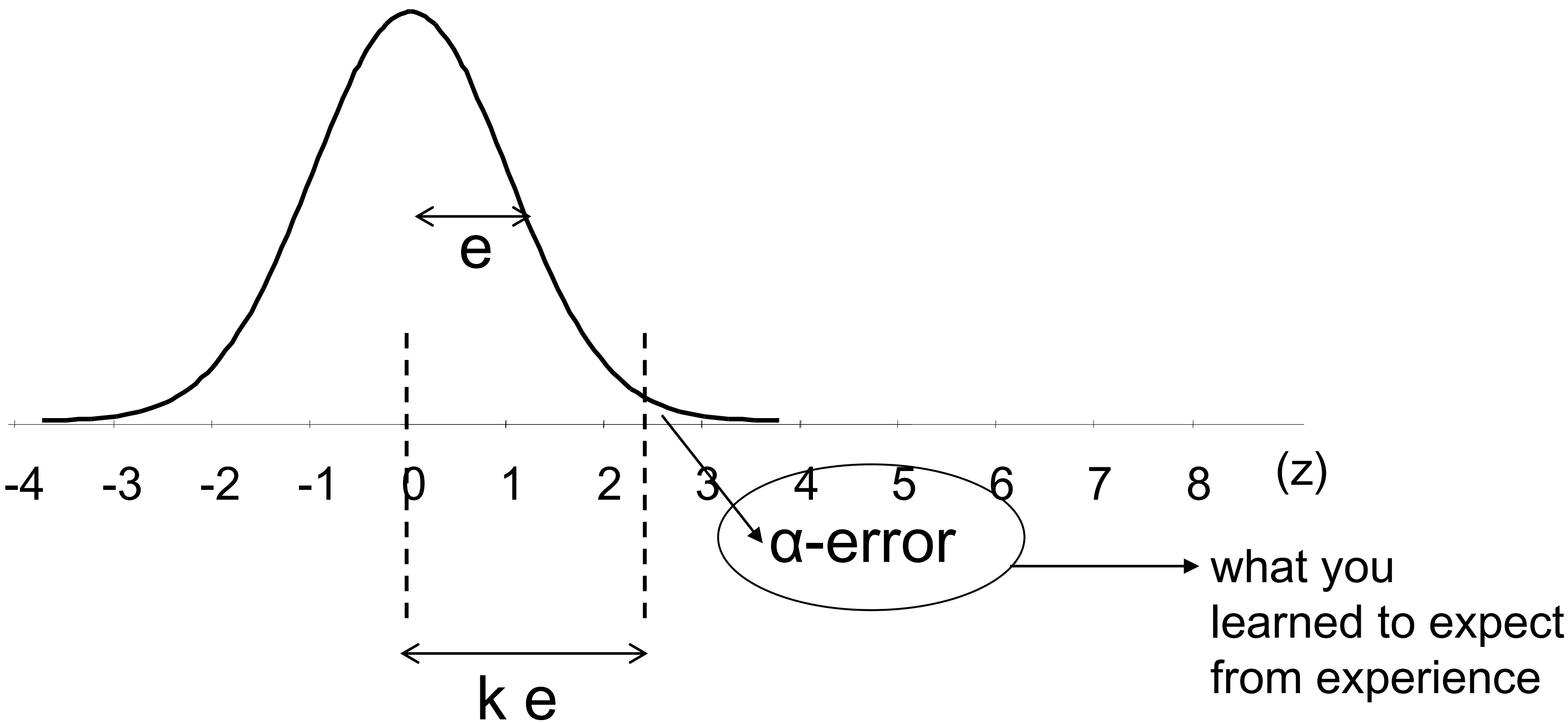
“ How much uncertainty can you tolerate ? ”

1. Production capability :
   don’t promise what you can’t guarantee
2. European guide line :
   desirable quality goals
3. What the diagnostic scenario tolerates :
   as much as is wise to invest in

Attainable quality = best possible quality (1/2)

e : uncertainty of measurement

k e : change is detectable

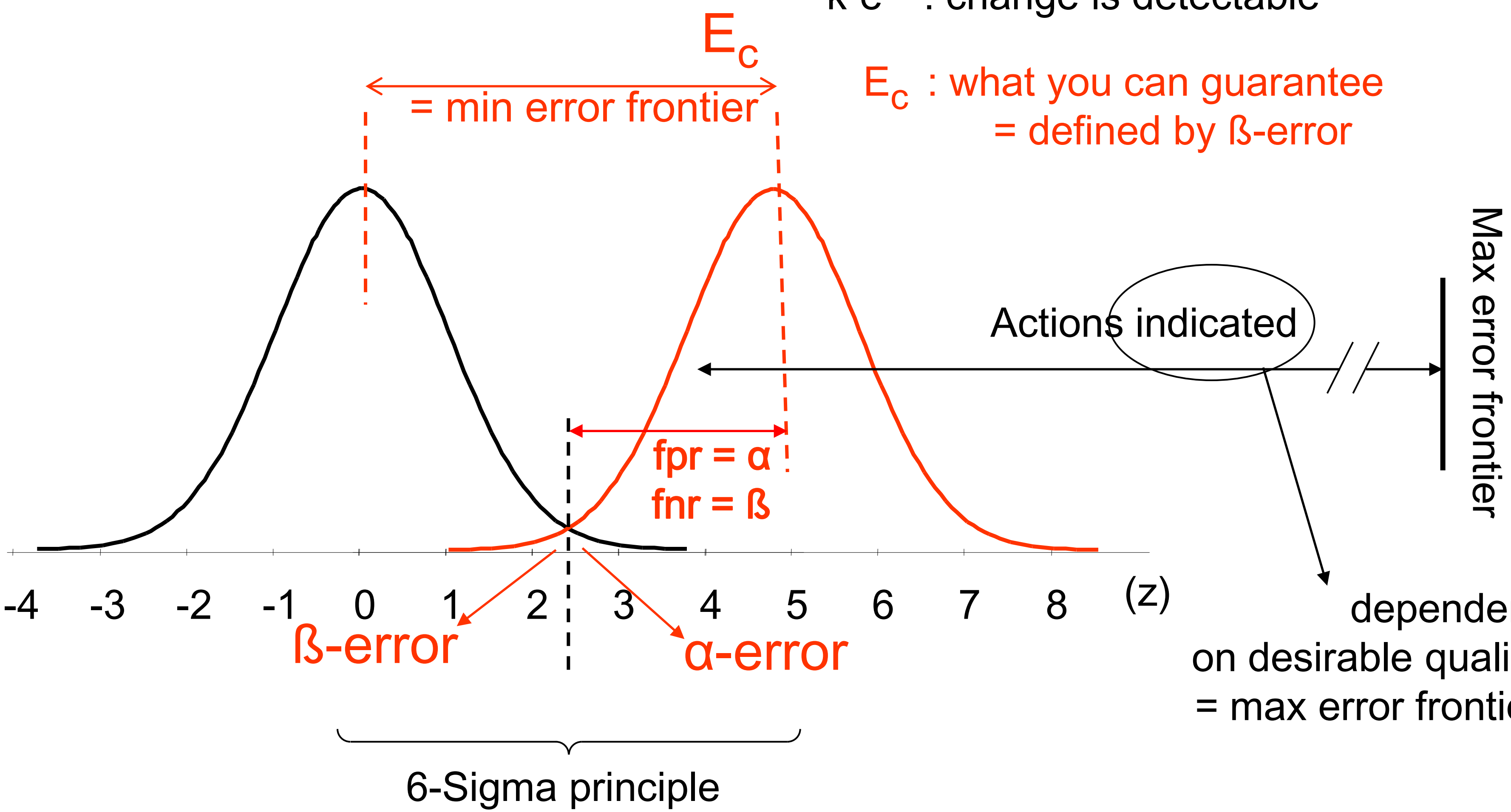


Attainable quality = limit costs of quality control (2/2)

e : uncertainty of measurement

k e : change is detectable

E_c : what you can guarantee
= defined by ß-error

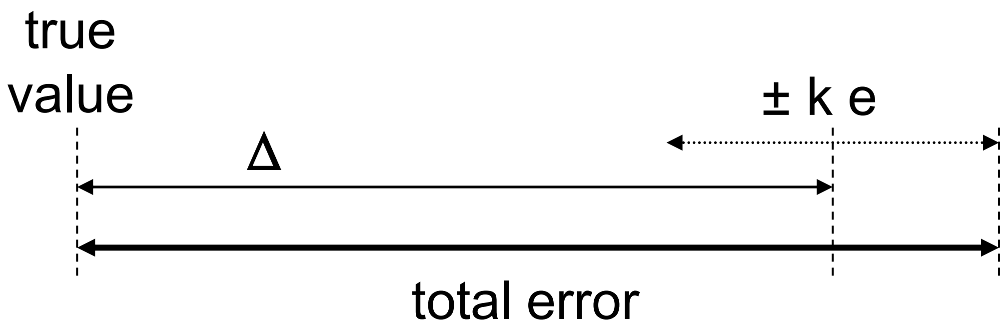


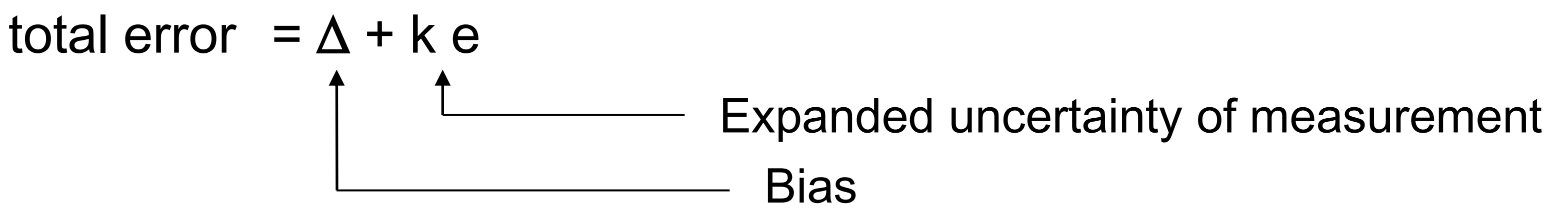
dependent
on desirable quality
= max error frontier

“ How much uncertainty can you tolerate ? ”

1. Production capability :
   don’t promise what you can’t guarantee
2. European guide line :
   desirable quality goals
3. What the diagnostic scenario tolerates :
   as much as is wise to invest in

Total error concept



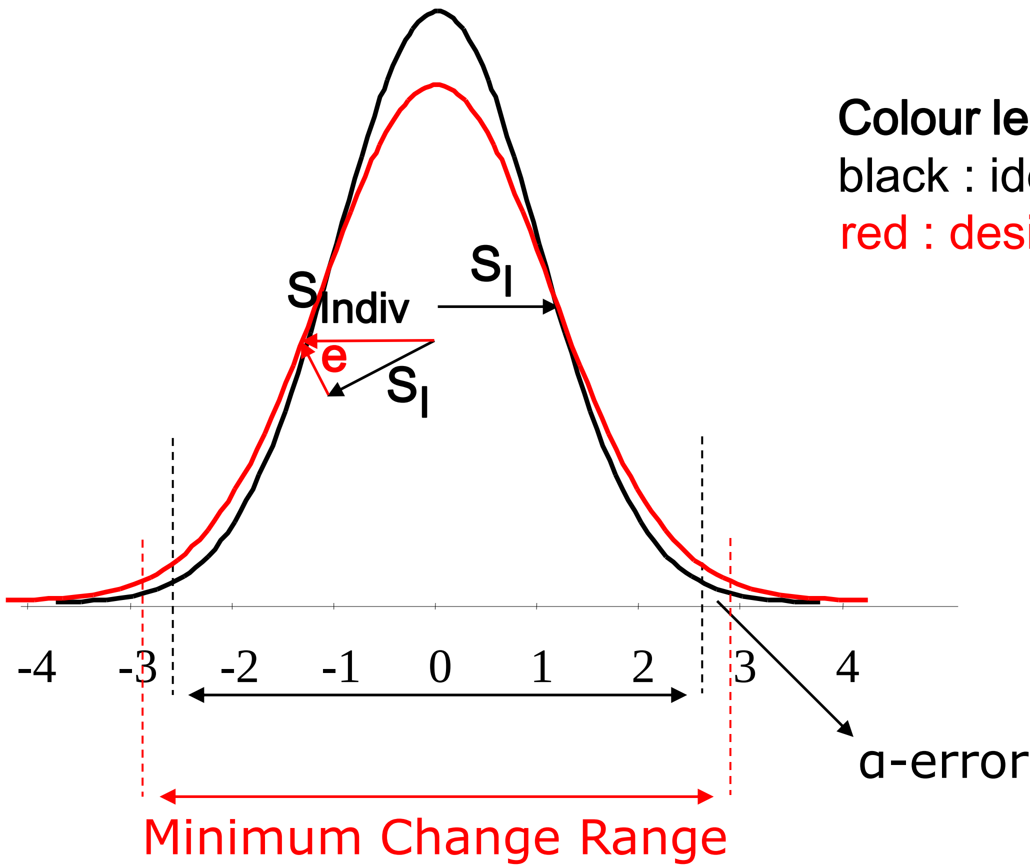


However,

- At best, your method is traceable and gives the best estimate for the truth
  whence Δ = 0 ± the epistemic uncertainty
- At worst, bias exists,
  but Δ remains unknown, till it is uncovered,
  and by that fact ends to exist

European Guideline (1/3)

Scand J Clin Lab Invest 59:491-500 (1999)



Colour legend

black : ideal error-free world

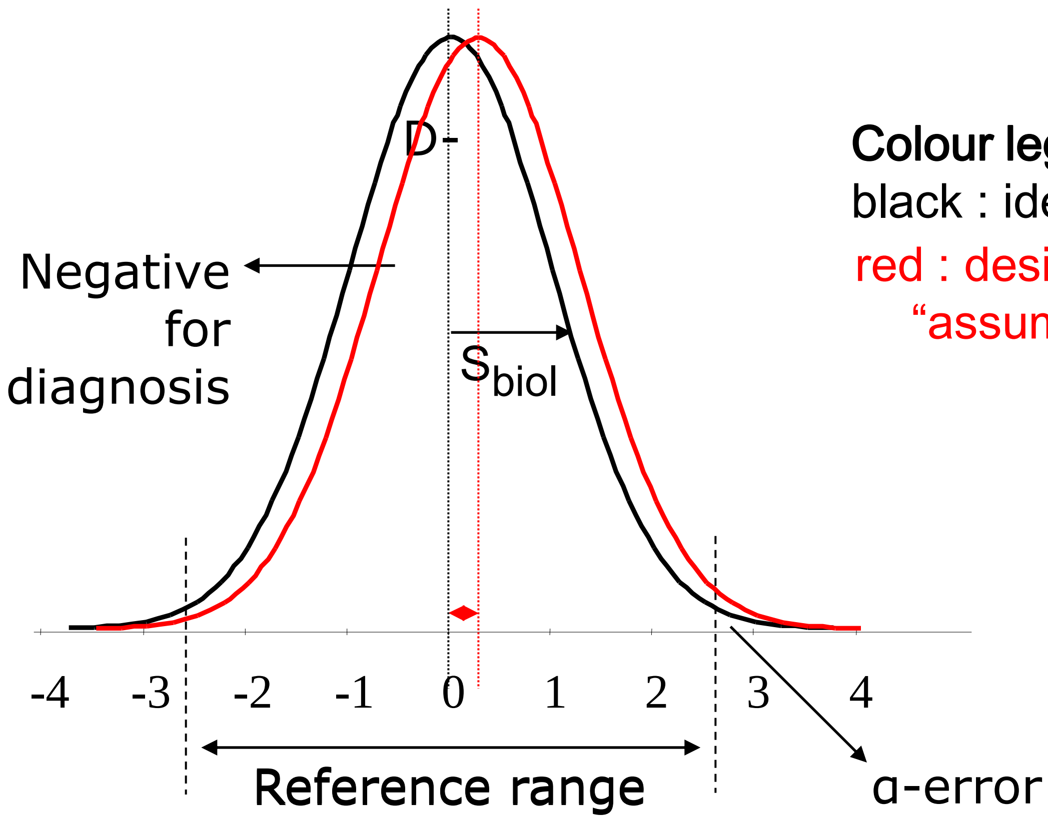
red : desirable error frontier

Target 1 : optimize recognition of " **individuals** "

$e < 0.5\ S_I \longrightarrow S_{I,eff} = (S_I^2 + 0.5\ S_I^2)^{0.5}$

$1.11\ S_I$

European Guideline (2/3)



Colour legend

black : ideal error-free world

red : desirable bias frontier "assuming that you can estimate it"

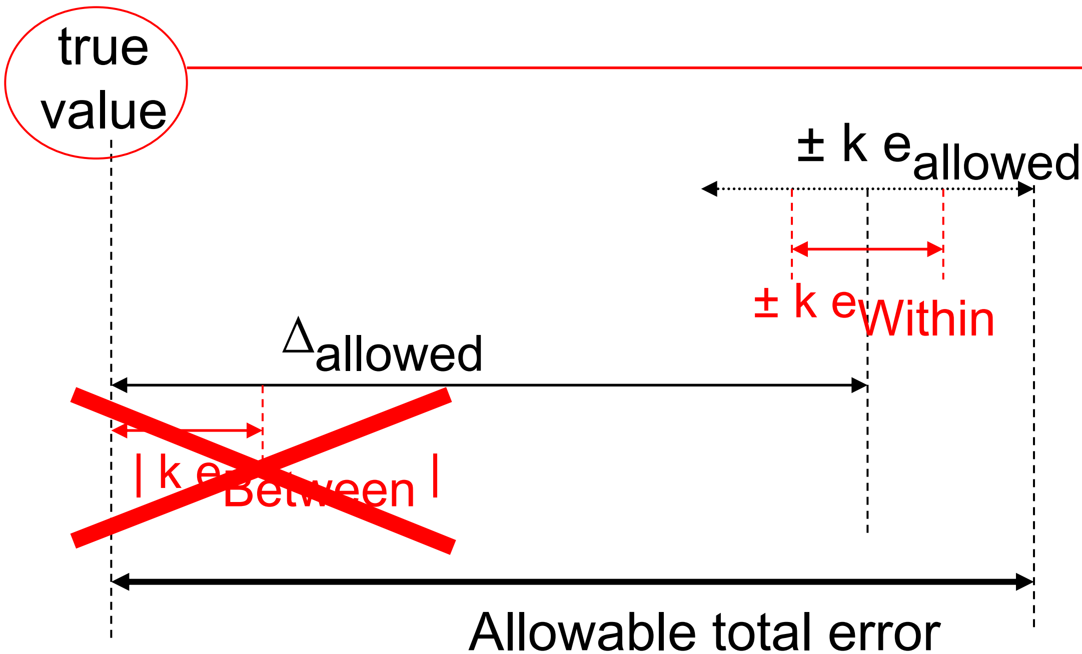
Target 2 : minimize miss-classification of " normals "

$$\Delta < 0.25\ (S_I^2 + S_G^2)^{0.5} = 0.25\ S_{biol}$$

European Guideline (3/3)

Target 3 : Desirable frontier for Total Error (TE)

TE < Δ + k e with k = 1.65 or 2.33



Known ?

Can you predict the sign ?
If the answer is no,
then this is **random error !**

Analytical specs of your actual method

$e^2_{Tot} = e^2_{Within} + e^2_{Between}$

- $e^2_{Between}$: Variance from calibrations, reagent batches, …
- e^2_{Within}: Short-term analytical variance
- e^2_{Tot}: Long-term total variance

“ How much uncertainty can you tolerate ? ”

1. Production capability :
   don’t promise what you can’t guarantee
2. European guide line :
   desirable quality goals ?
3. What the diagnostic scenario tolerates :
   as much as is wise to invest in

Relevance of European Guideline ? Scand J Clin Lab Invest 59:491-500 (1999)	Diagnostic Scenario: Staging	Monitoring	Screening Case-finding Diagnosis
Target 1 recognize " individuals " $e < 0.5\ S_I$		**~ relevant** minimum change value	
Target 2 correctly classify " normals " $\Delta < 0.25\ (S_I^2 + S_G^2)^{0.5}$			
Target 3 frontier for Total Error (TE) $TE < \Delta + k\ e$ with $k = 1.65$ or 2.33	**relevant**		**~ irrelevant** depends on separating power not on certainty of distribution of normals

Risk analysis 

Step 1 : Analysis of uncertainty of measurement

Step 2 : Analysis of medically important errors

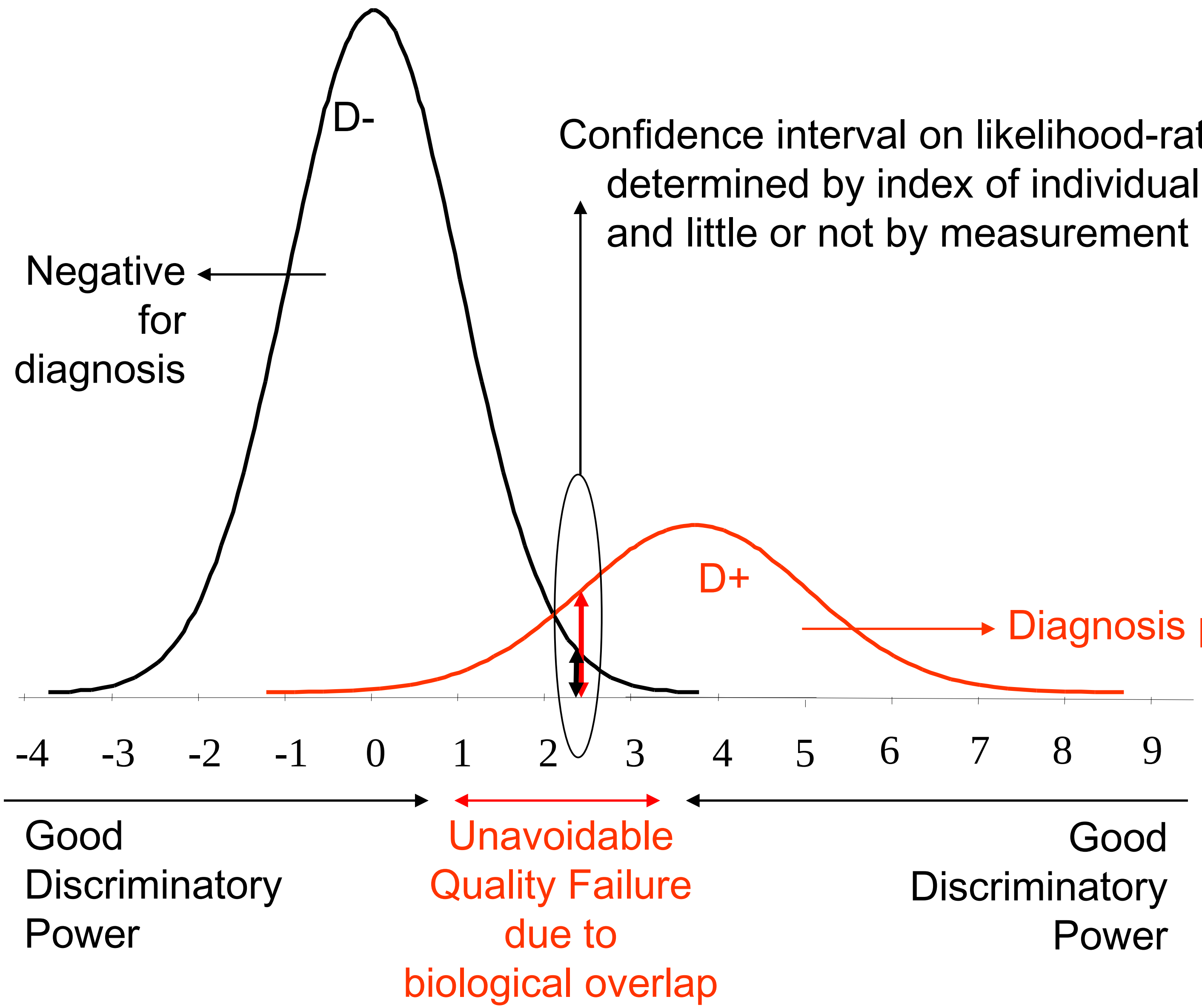
Step 3 : Design appropriate control procedures

Risk analysis

Step 1 : Analysis of uncertainty of measurement

- list sources of unavoidable & of **avoidable error**
- analyze potential magnitude of error
- analyze potential occurrence
  frequency and nature : intermittent or persistent
  random or bias

Are you concerned about the uncertainty of measurement ?



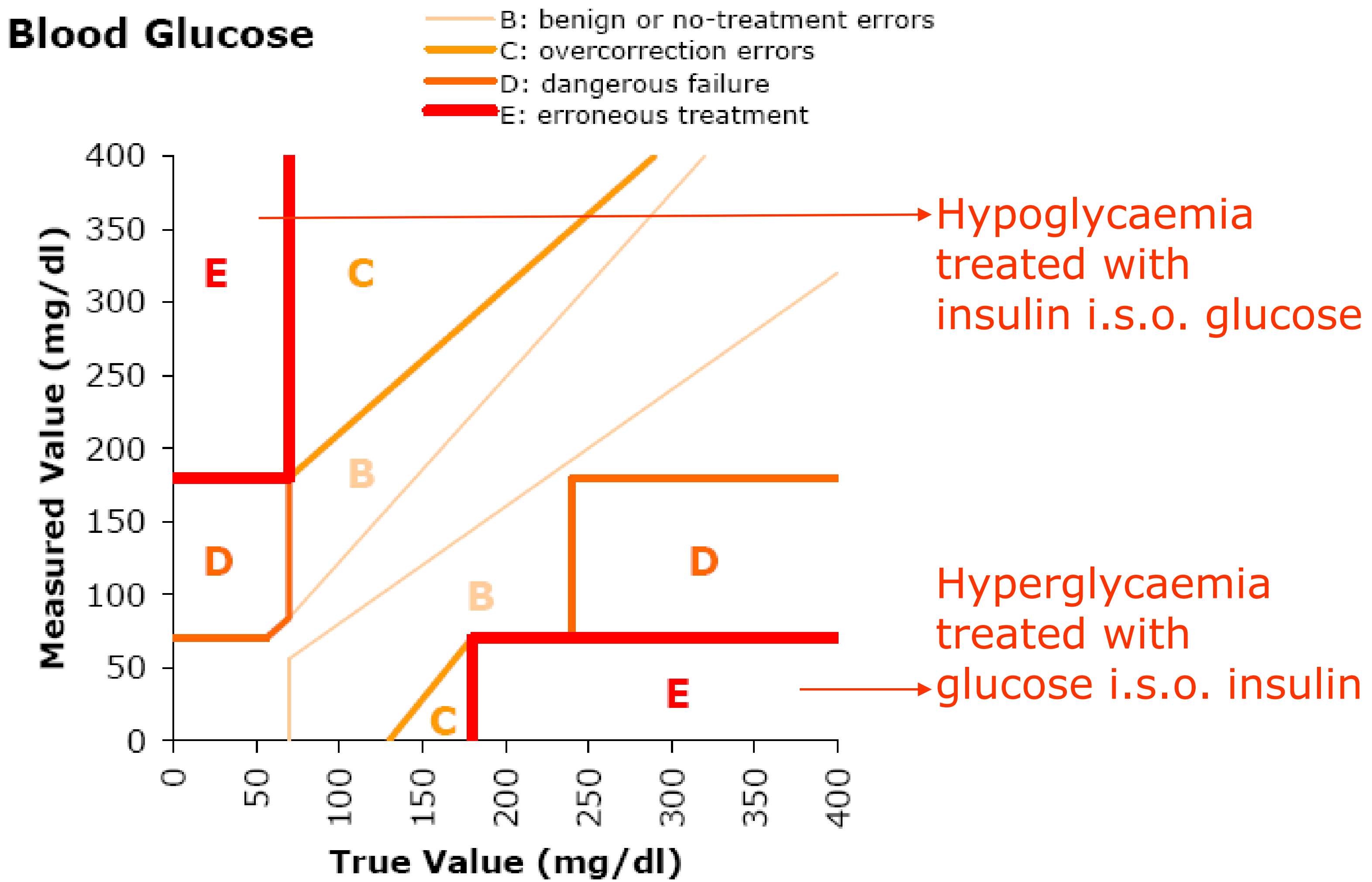
Risk analysis

Step 1 : Analysis of uncertainty of measurement

Step 2 : Analysis of medically important errors

Step 3 : Design appropriate control procedures

Risk analysis



W.L. Clarke, D. Cox, L.A. Gonder-Frederick, W. Carter, S.L. Pohl
Evaluating clinical accuracy of systems for self-monitoring of blood glucose
Diabetes care 10:622-28 (1987)

Detection of medically-significant errors

To negotiate the uncertainty of interpretation
the **clinician** will request additional or follow-up tests to **evaluate**
- the **internal consistency** with previous results
- the **external consistency** with the body of knowledge

In order to come to a decision
the corresponding mental process is geared at
- neglecting inconsistent results
- overvaluing confirmatory evidence

The **clinician** is best positioned for
detection of medically important errors
PROVIDE FOR A DIRECT CHANNEL TO REPORT DOUBTS TO THE LAB

The clinician may have
a blind eye for lab errors
NO CONTROL PROCEDURE HAS
ABSOLUTE SENSITIVITY & SPECIFICITY

Risk analysis

Step 1 : Analysis of uncertainty of measurement

Step 2 : Analysis of medically important errors

Step 3 : Design appropriate control procedures

Risk analysis

Step 3 : Design appropriate control procedures

- from your analysis (step 1-2) list conditions potentially
  - leading to medically important errors
- from your analysis (step 1-2) list nature of the risk : 
  - associated adverse effects
  - frequency and urgency of correction
- list key diagnostic characteristics of these conditions frequency and nature :
  - intermittent or persistent
  - random or bias
- design your control procedure to diagnose the above  with high sensitivity and specificity
  - before error occurs
  - at a frequency in function of the urgency of corrections

Production & Analytical Quality Requirements : Conclusions (1/2)

1. The uncertainty of interpretation refers to uncertainty due to intra-individual variability and biological overlap of conditions to be discriminated

2. The production requirements refer to the logistic and analytical characteristics of the production of test results

3. The corresponding quality requirements refer to the control of the process of production of results in all its facets, from pre-analytical to reporting

Production & Analytical Quality Requirements : Conclusions (2/2)

4. At the time of validation of a new method, we always start with the question : " Has this test proven its clinical utility ? " If so, then the analytical & diagnostic quality has in-the-field been proven to be workable

5. Therefore, the validation exercise should not overly stress analytical or diagnostic requirements, but instead shall focus on LOGISTIC requirements of CARE PROGRAMS served by YOUR LAB

6. The definition of sensible analytical quality targets starts from the clinical scenario & a risk analysis