1st EFLM Strategic Conference

Milan, Italy, 24-25 November 2014

Defining analytical performance goals
15 years after the Stockholm Conference

Analytical performance goals

"Model 1B. Simulation studies – investigating the impact of analytical performance of the test on the probability of clinical outcomes"

Performance criteria based on true and false classification and clinical outcomes

Influence of analytical performance on diagnostic outcome using a single clinical component.

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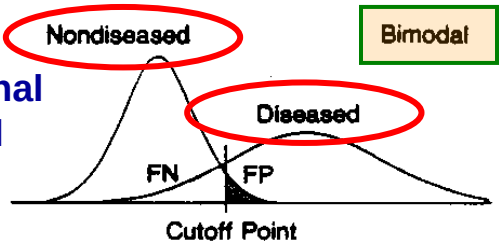
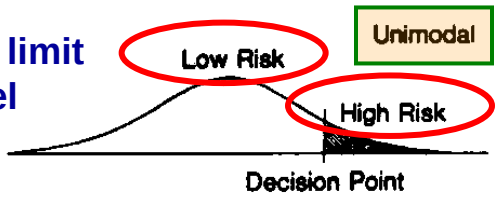
Bi-modal and uni-modal decision models

Traditional model

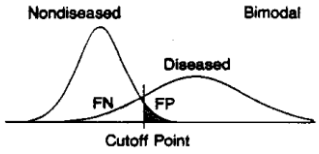


Decision limit model



Hyltoft Petersen P, Hørder M. *Arch Pathol Lab Med* 1988; 112: 435-43

Bi-modal model



Parameters for 2 populations Healthy and Diseased

Theoretical example ln-Gaussian distributions

	Concentrations			Formula	ln concentrations		ln concentrations	
	Healthy	Diseased			Healthy	Diseased	Healthy	Diseased
Mean ($\bar{x}$)	80	110	μ	$\ln(\bar{x})-\frac{1}{2}\sigma^2$	4.372	4.678	4.38	4.70
CV	0.10	0.15	σ	$(\ln(CV^2+1))^{1/2}$	0.100	0.149	0.10	0.15
s	8	16.5						

μ and σ (mean and standard deviation of ln-distribution)

$$\sigma = [\ln(CV^2 + 1)]^{1/2}$$

When CV values are small then σ ~ CV (= CV%/100)

(Example CV = 0.200 then σ = 0.198)

Formula: Fokkema et al. Clin Chem 2006;52:1602-3

	Concentrations			Formula	ln concentrations		ln concentrations	
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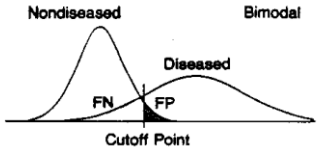
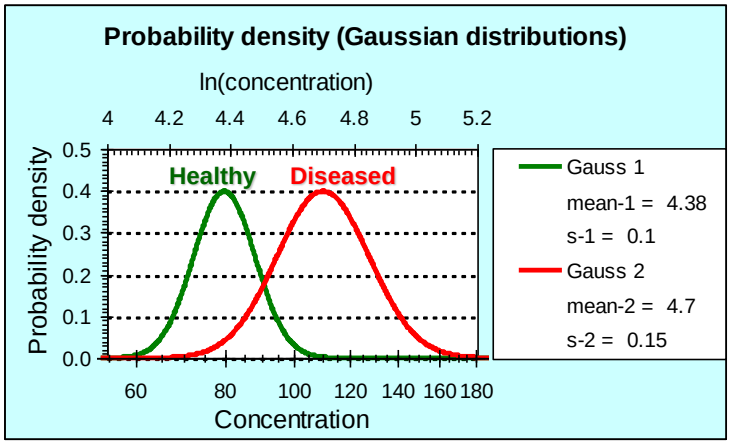
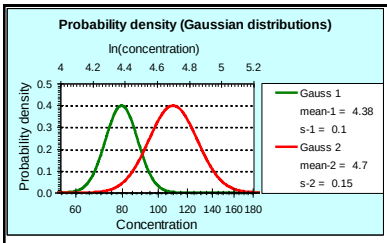
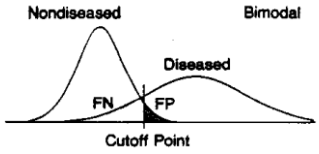


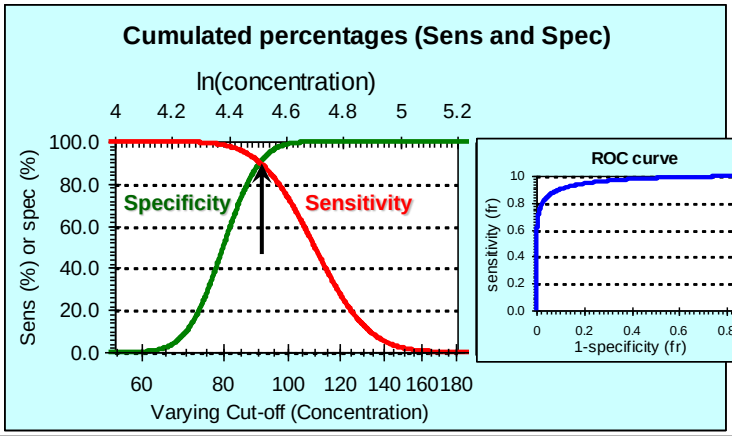
Distributions ln-scale



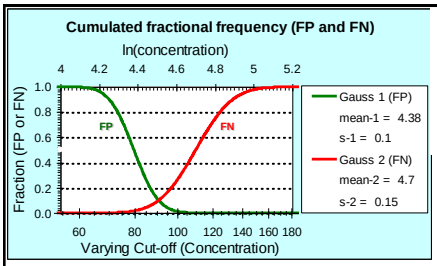




Sensitivity and Specificity for varying cut-off



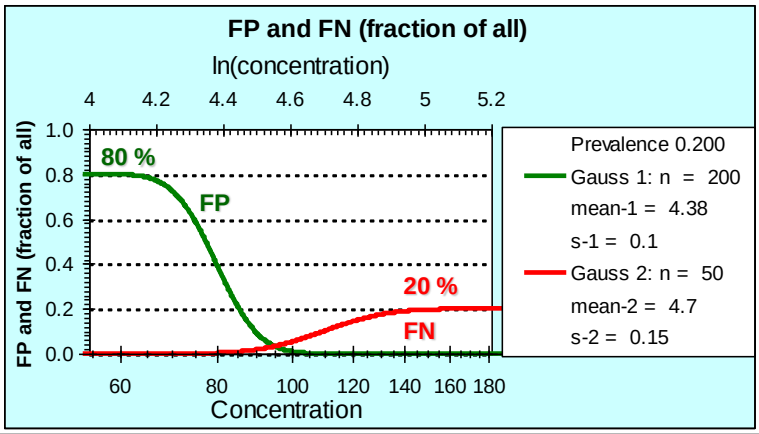
Sensitivity = Specificity at 4.5 ~ 90



False positive (FP) and False negative (FN) in stead of Sensitivity and Specificity

Prevalence = 0.20

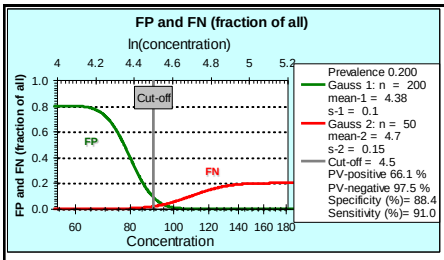
Calculation of fraction of all

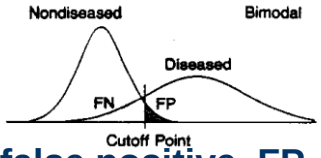


Healthy 200

Diseased 50

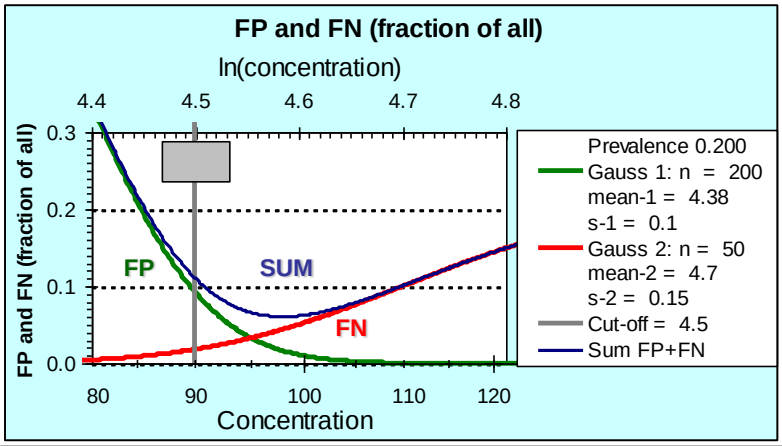
Total 250



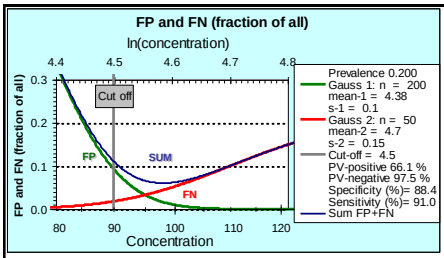


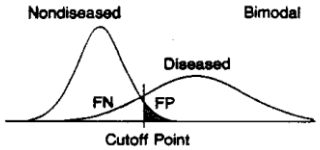
Sum of false positive, FP and false negative FN

Cut-of = 4.5 ~ concn 90



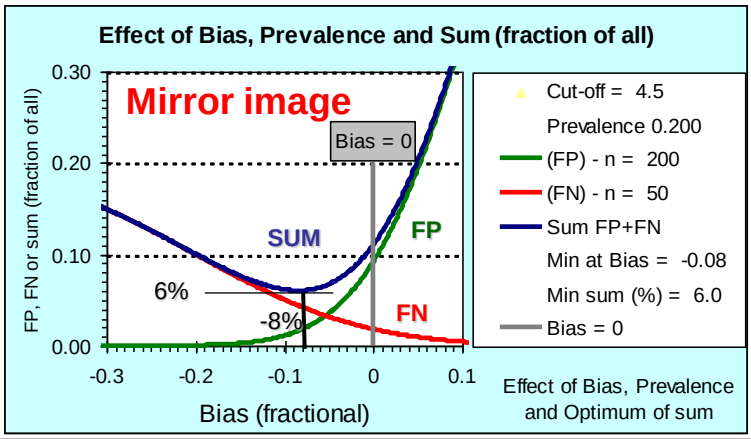
Sens = Spec





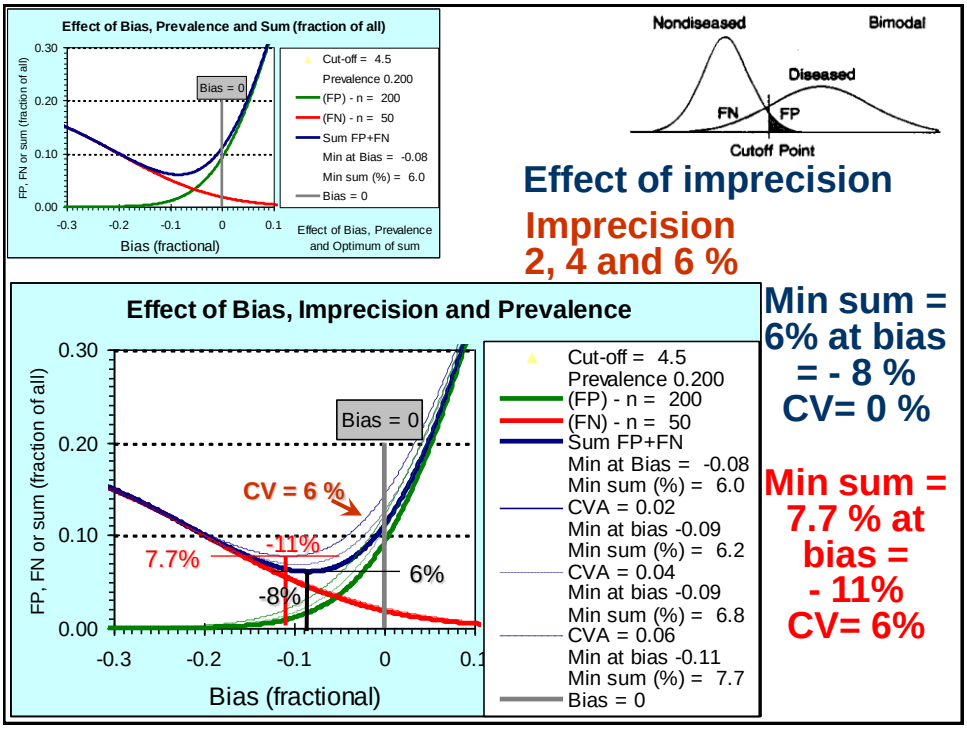
When cut-off is chosen

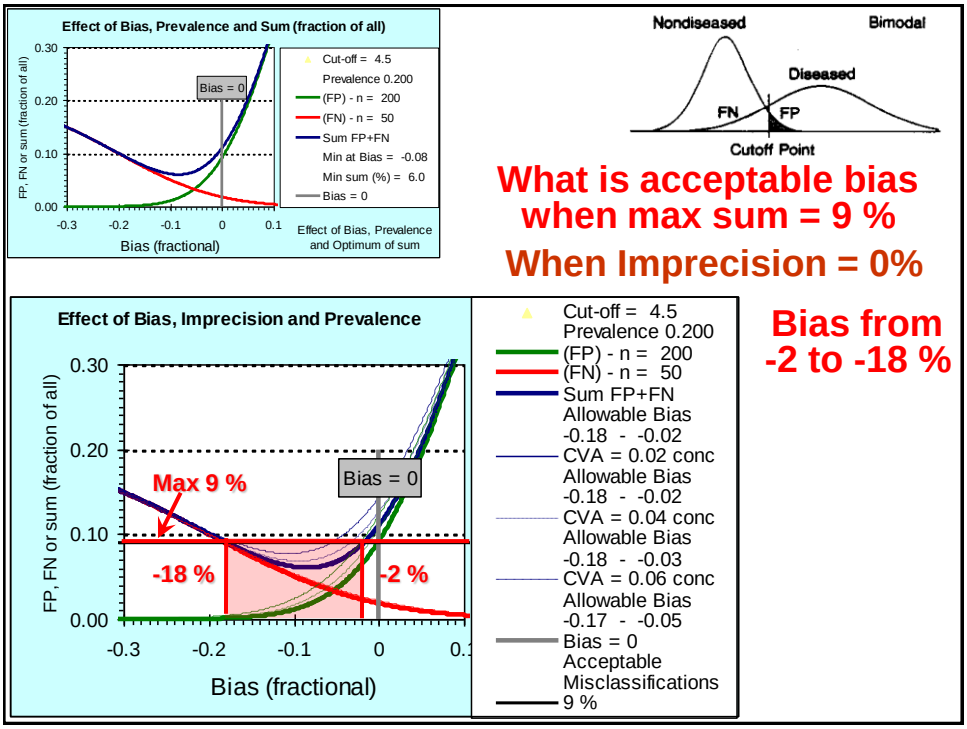
Effect of bias can be calculated



Min sum = 6% at bias = - 8 %

Abscissa is reversed at 4.5 = conc. 90


Effect of Bias, Prevalence and Sum (fraction of all)
Bias = 0
Cut-off = 4.5
Prevalence 0.200
(FP) - n = 200
(FN) - n = 50
Sum FP+FN
Min at Bias = -0.08
Min sum (%) = 6.0
Bias = 0
Effect of Bias, Prevalence and Optimum of sum
FP, FN or sum (fraction of all)
Bias (fractional)
Nondiseased
Bimodal
Diseased
FN
FP
Cutoff Point
Effect of imprecision
Imprecision 2, 4 and 6 %
Effect of Bias, Imprecision and Prevalence
CV = 6 %
-11%
7.7%
6%
-8%
Cut-off = 4.5
Prevalence 0.200
(FP) - n = 200
(FN) - n = 50
Sum FP+FN
Min at Bias = -0.08
Min sum (%) = 6.0
CVA = 0.02
Min at bias -0.09
Min sum (%) = 6.2
CVA = 0.04
Min at bias -0.09
Min sum (%) = 6.8
CVA = 0.06
Min at bias -0.11
Min sum (%) = 7.7
Bias = 0
Min sum = 6% at bias = - 8 % CV= 0 %
Min sum = 7.7 % at bias = - 11% CV= 6%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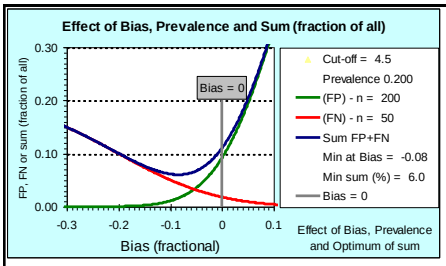
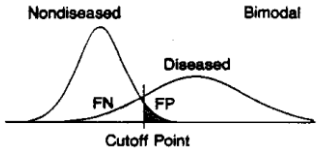
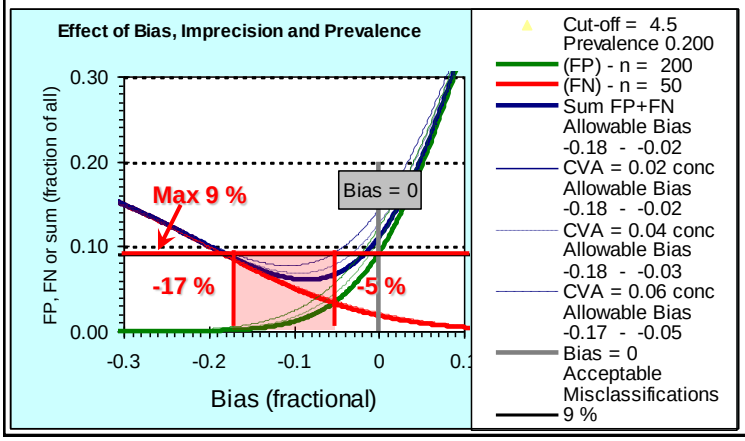
Min sum (%) = 6.0
Bias = 0
Effect of Bias, Prevalence and Optimum of sum
FP, FN or sum (fraction of all)
Bias (fractional)
Nondiseased
Bimodal
Diseased
FN
FP
Cutoff Point
What is acceptable bias when max sum = 9 %
When Imprecision = 0%
Effect of Bias, Imprecision and Prevalence
Max 9 %
-18 %
-2 %
Cut-off = 4.5
Prevalence 0.200
(FP) - n = 200
(FN) - n = 50
Sum FP+FN
Allowable Bias -0.18 - -0.02
CVA = 0.02 conc
Allowable Bias -0.18 - -0.02
CVA = 0.04 conc
Allowable Bias -0.18 - -0.03
CVA = 0.06 conc
Allowable Bias -0.17 - -0.05
Bias = 0
Acceptable Misclassifications 9 %
Bias from -2 to -18 %





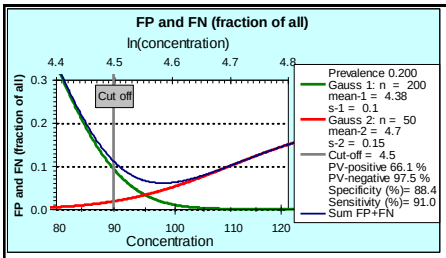
What is acceptable bias when max sum = 9 %

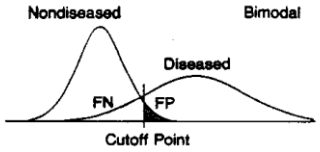
When Imprecision = 6%



Bias from -5 to -17 %

Bias from --2 to -18 % when CV=0



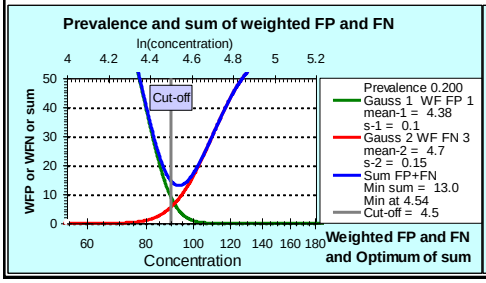


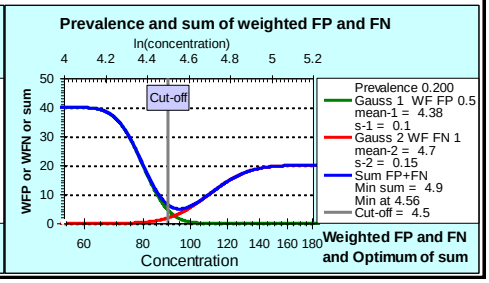
If either FP or FN is considered very different from the other

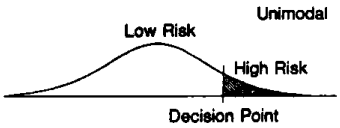
It is possible to give a weighting factor to either FP or FN

Group 1: WF = 1
Group 2: WF = 3

Group 1: WF = 0.5
Group 2: WF = 1







Uni-modal decision model

Influence of Analytical Bias and Imprecision on Guideline-Driven Medical Decision Limits

Example:

HbA1c in diagnosis of diabetes mellitus

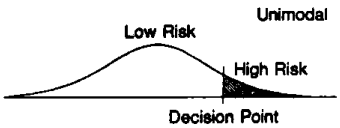
Decision: HbA1c above or below 48 mmol/mol (6.5 % HbA1c)

Sacks et al. *Diabetes Care* 2011;34:c61-c99

Hyltoft Petersen P, Klee GG.

Influence of Analytical Bias and Imprecision on the Number of False Positive Results Using Guideline-Driven Medical Decision Limits.

Clin Chem Acta 2014;430:1-8



HbA1c:

Calculations based on a reference interval

HbA1c reference interval for healthy

According to traditional IFCC criteria

Log-Gaussian distribution (natural logarithm)
ln-mean = 1.727 and ln-standard deviation = 0.053

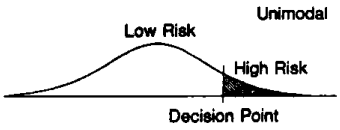
$CV_{WITHIN-SUBJECT}$ = 1.94 % in IFCC units (~ ln = 0.0194)

Recommended cut-off = 48 mmol/mol ~ ln = 3.86

Jørgensen et al. *Scand J Clin Lab Invest* 2002; 62:609-22.

Carlsen et al. Clin Chem Lab Med 2011;49:1501-7

Sacks et al. *Diabetes Care* 2011;34:c61-c99



HbA1c:

Distribution of healthy set-points

Proposal for harmonization of terms

Ana-Maria Simundic et al. Clinical Chemistry 2015, in press:

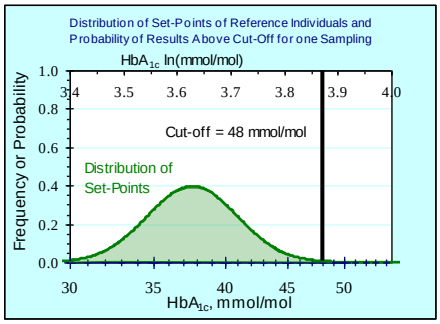
Within-subject biological variation: CV_I

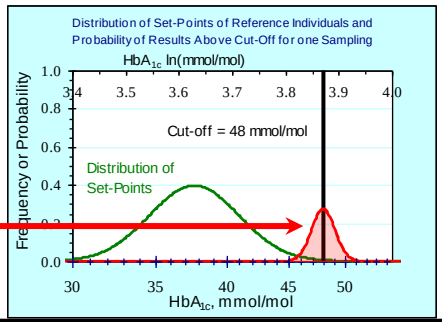
Between-subject biological variation: CV_G

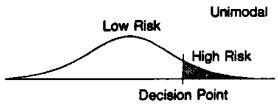
Analytical variation: CV_A

$CV_{WITHIN\text{-}SUBJECT}$ = 1.94 %

Distribution of values from a person with set-point = cut-off



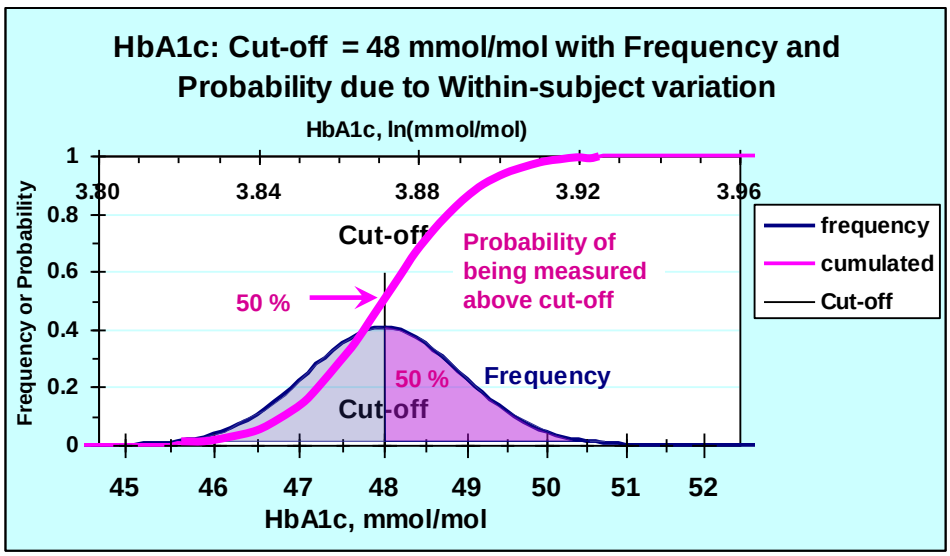


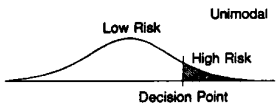


HbA1c:

Distribution for a person with set-point = cut-off

Frequency **Cumulated frequency (probability)**

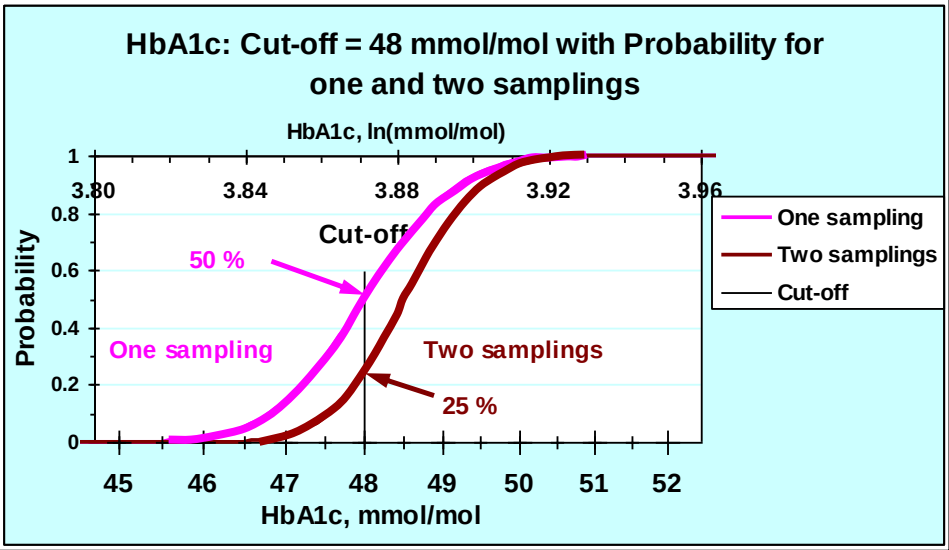


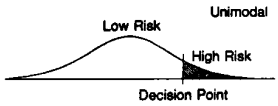


HbA1c:

Distribution for a person with set-point = cut-off

Effect of one and two samplings

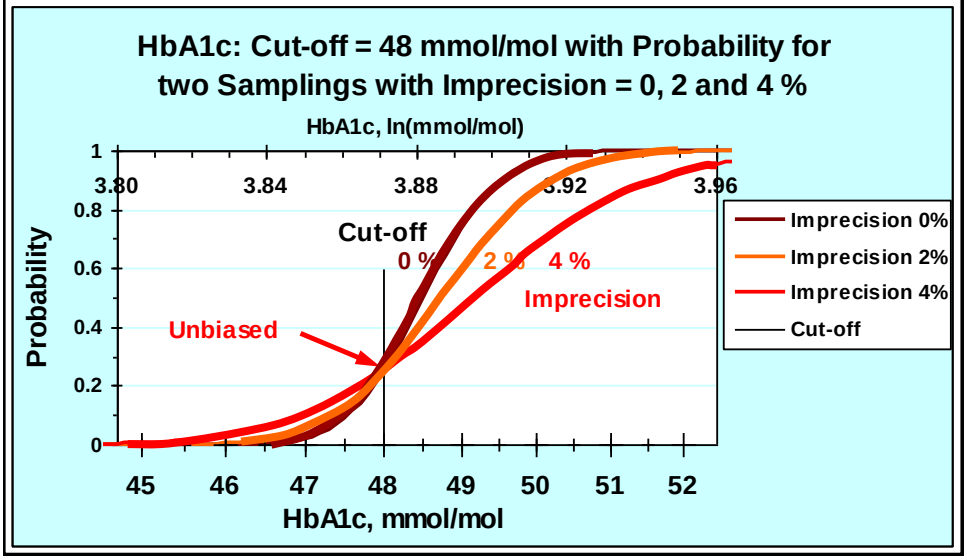


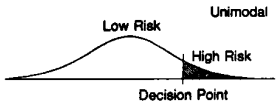


HbA1c:

Distribution for two samplings

Effect of imprecision: 2 % and 4 %



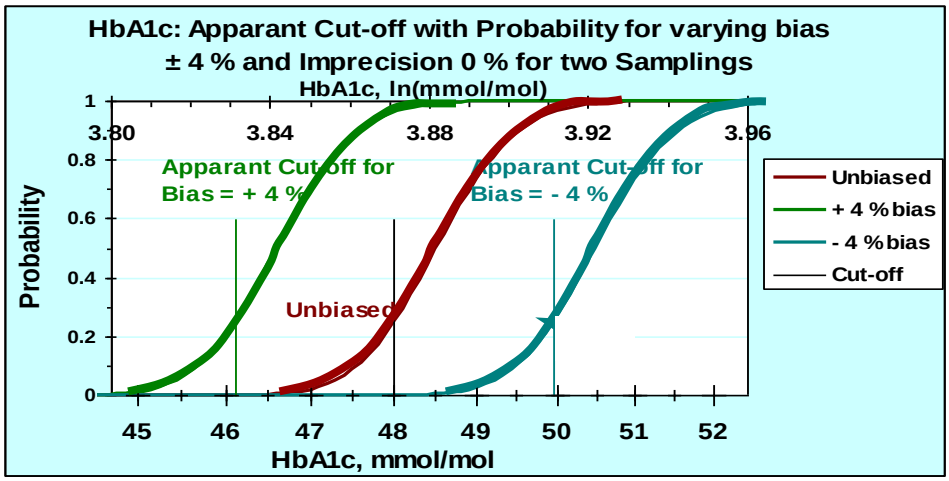


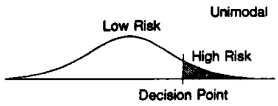
HbA1c:

Distribution for two samplings

Effect of Bias

The effect of positive bias is like moving the cut-off to the left





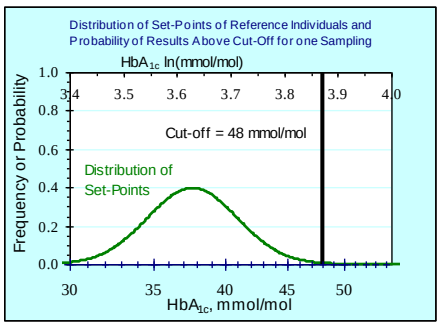
HbA1c:

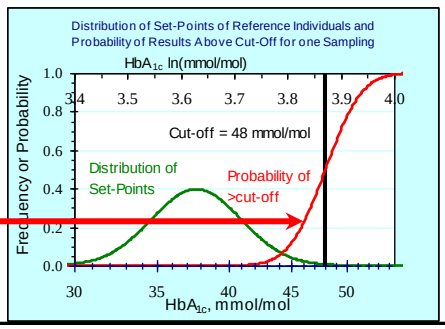
Distribution of healthy set-points

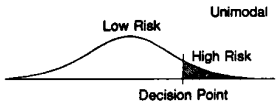
One sampling

$CV_{WITHIN-SUBJECT}$ = 1.94 %

Probability for a person with set-point = cut-off to be measured above cut-off



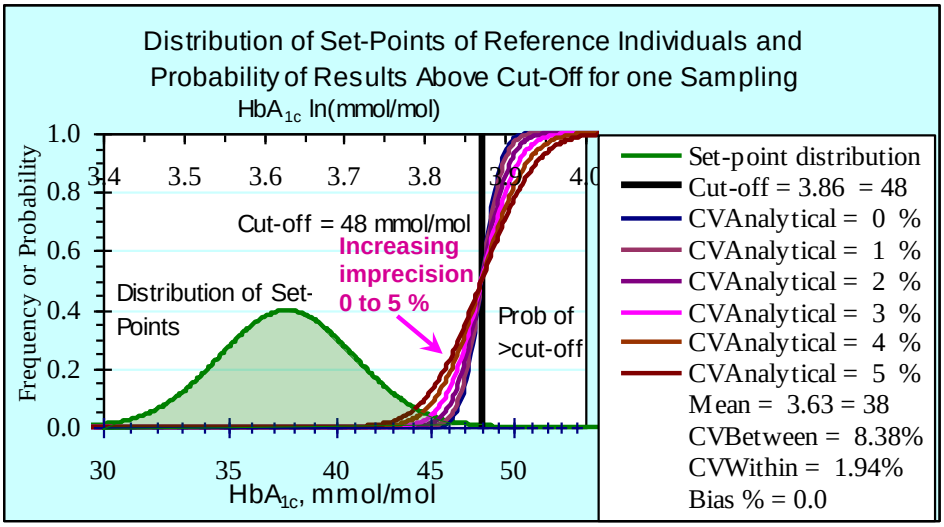


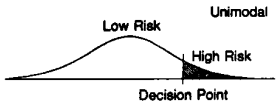


HbA1c:

Distribution of set-points

Cumulated frequency (probability functions)
One sampling

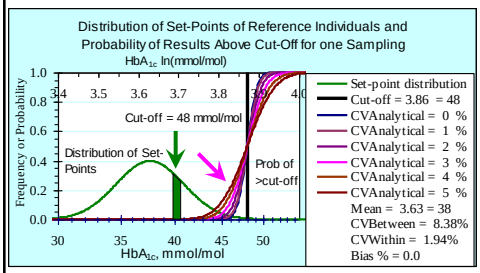


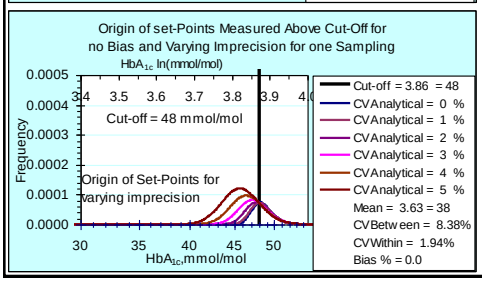


HbA1c:

Distribution of set-points

Cumulated frequency (probability functions)
One sampling



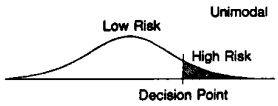


Now we take a sample within a small interval of healthy set-points

and multiply with the probability of these set-points exceed the cut-off

to get the FP for healthy with this set-point

and by repeating the process for all intervals we get the distribution of origins of set-points of FP



HbA1c:

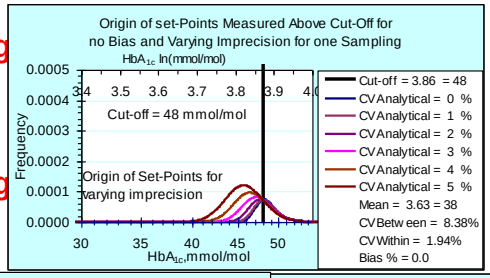
Varying imprecision and bias

One and two samplings

Origin of set-points for healthy individuals measured above 48 mmol/mol (*healthy diagnosed as diabetics*)

One Sampling

Bias = 0 %

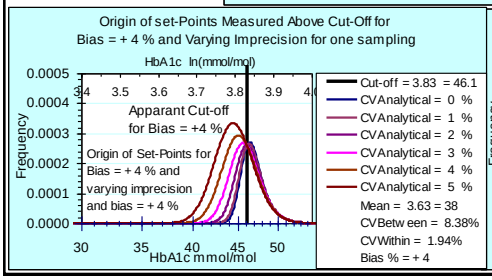


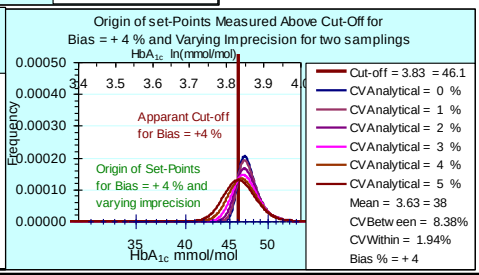
One Sampling

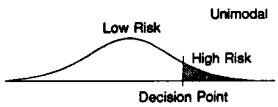
Bias = + 4 %

Two Samplings

Bias = + 4 %

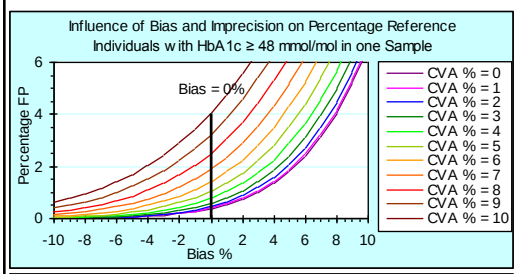




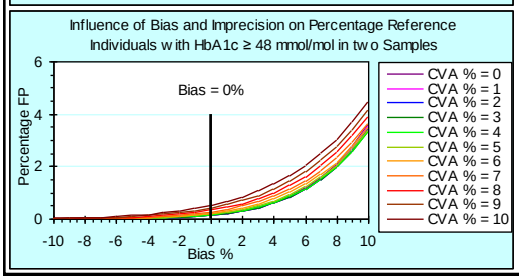


HbA1c:

Percentage of healthy individuals measured > 48 mmol/mol false positive diabetics as function of bias % for varying percentages of imprecision

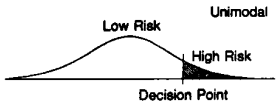


For one sampling



For two samplings

The effect of two samplings ≥ 48 mmol/mol is a considerable reduction of false positive due to imprecision and a moderate reduction of the bias effect

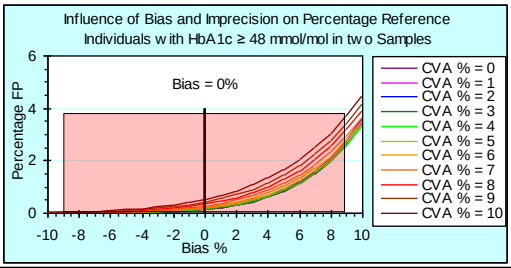


HbA1c:

What are the recommended quality specifications from Sacks et al. *Clin Chem* 2011;57:793-8

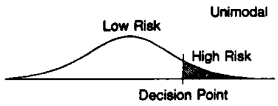
Desirable specifications for HbA1c measurement are an intralaboratory CV < 2% and an interlaboratory CV < 3.5 %

The CV 3.5 % DCCT units corresponds to 5.2 % at 48 mmol/mol in IFCC units, and reduced by the 2 %, the final allowable bias is from ± 9 % at a 95 % interval and false positives could be from 0 to 2.8 %



$$CV(IFCC) = \frac{CV(DCCT) \times \bar{X}(DCCT) \times 10.93}{\bar{X}(DCCT) \times 10.93 - 23.52}$$

Personal information from
Thomas Røraas and Sverre Sandberg,
NOKLUS, Bergen, Norway



Cholesterol:

There is no reference interval for Cholesterol due to the strict decision limit of 6.2 mmol/L

But a range for the total population can be estimated

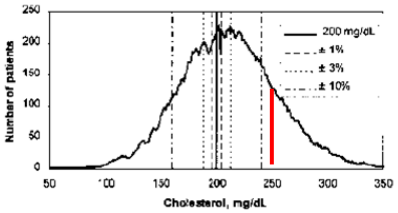
95 % limits 150-275 mg/dL = 3.89-7.12 mmol/L

Log-Gaussian distribution (natural logarithm)

CV_{TOTAL} =15.2 % ~ ln = 0.152

$CV_{WITHIN\text{-}SUBJECT}$ = 6.0 % ~ ln = 0.060

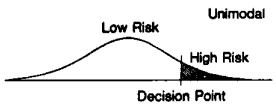
$CV_{BETWEEN\text{-}SUBJECT}$ = 13.9 % ~ ln = 0.139



Recommended cut-off = 6.2 mmol/L ~ ln = 1.825

Klee et al. *Scand J Clin Lab Invest* 1999;59:509

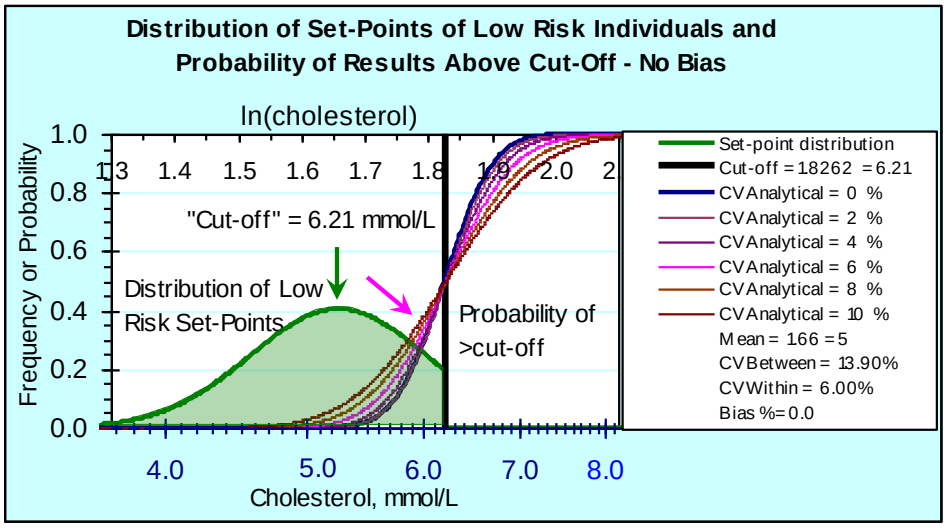
Ricos et al. *Scand J Clin Lab Invest* 1999;59:491

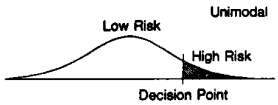


Cholesterol:

Distribution for persons with set-points below 6.2 mmol/L
No one above 6.2, due to the definition

One sampling **Cumulated frequency (probability functions)**

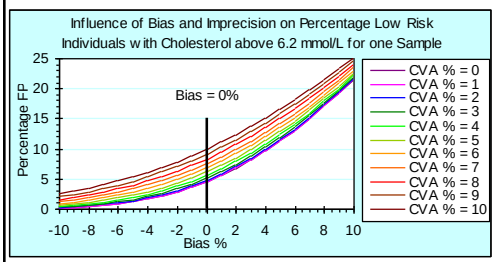




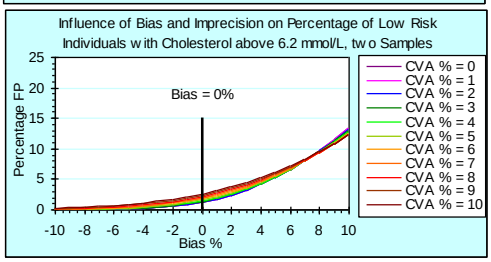
Cholesterol:

Percentage of false positive

As function of bias % for varying percentages of imprecision

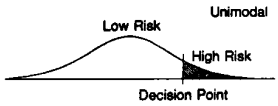


For one sampling



For two samplings

The effect of two samplings ≥ 6.2 mmol/L removes the effect of imprecision and a moderate reduction of the bias effect



Cholesterol:

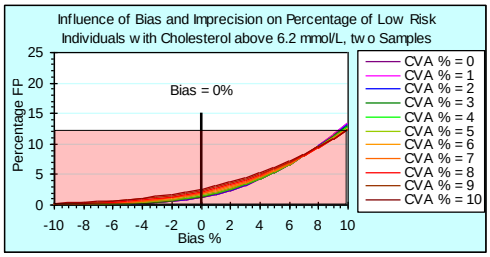
Effect of imprecision is negligible for all CV %

Effect of bias:

Approximate doubling of false positive for ΔBias = +2 % e.g. from 1.21 to 2.36 % for bias from 0 to +2 %

What are the requirements from CLIA 88

± 10 % which means from 0 to 12 % false positive



For two samplings

The effect of two samplings ≥ 6.2 mmol/L removes the effect of imprecision and a moderate reduction of the bias effect

Conclusions:

Analytical performance goals

"Model 1 B. Simulation studies – investigating the impact of analytical performance of the test on the probability of clinical outcomes"

is a reliable method for estimation of analytical quality requirements for diagnostic

The effect of two samplings for diagnosis reduces the effect of imprecision considerably and decreases the effect of bias moderately

EFLM must be involved in estimation of analytical quality requirements for Clinical Guidelines with

"Guideline-Driven Medical Decision Limits"