Additional Analytical and Clinical Performance Issues Related to Assays Producing a Single Score

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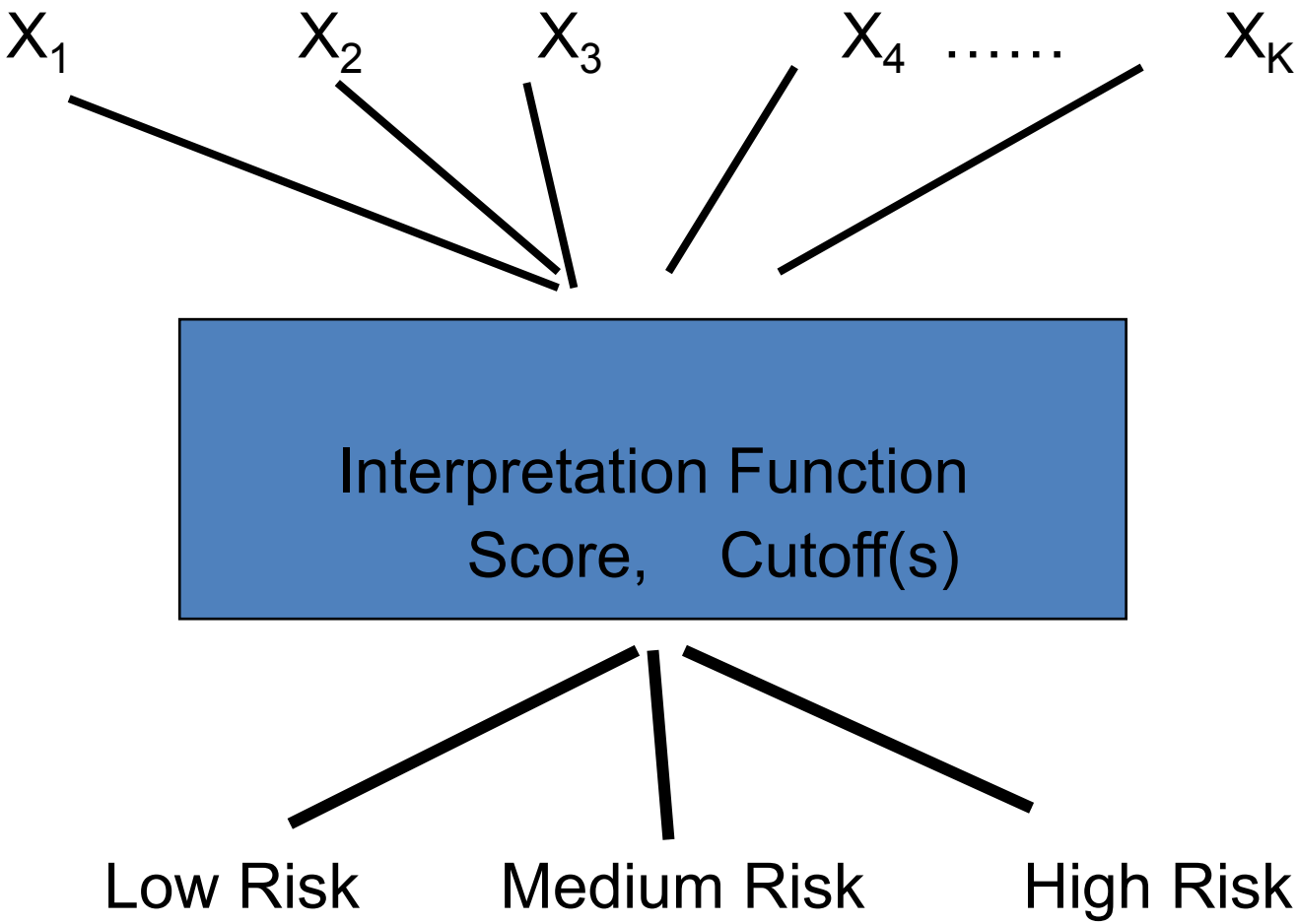
Assay Producing Single Score

A device that:

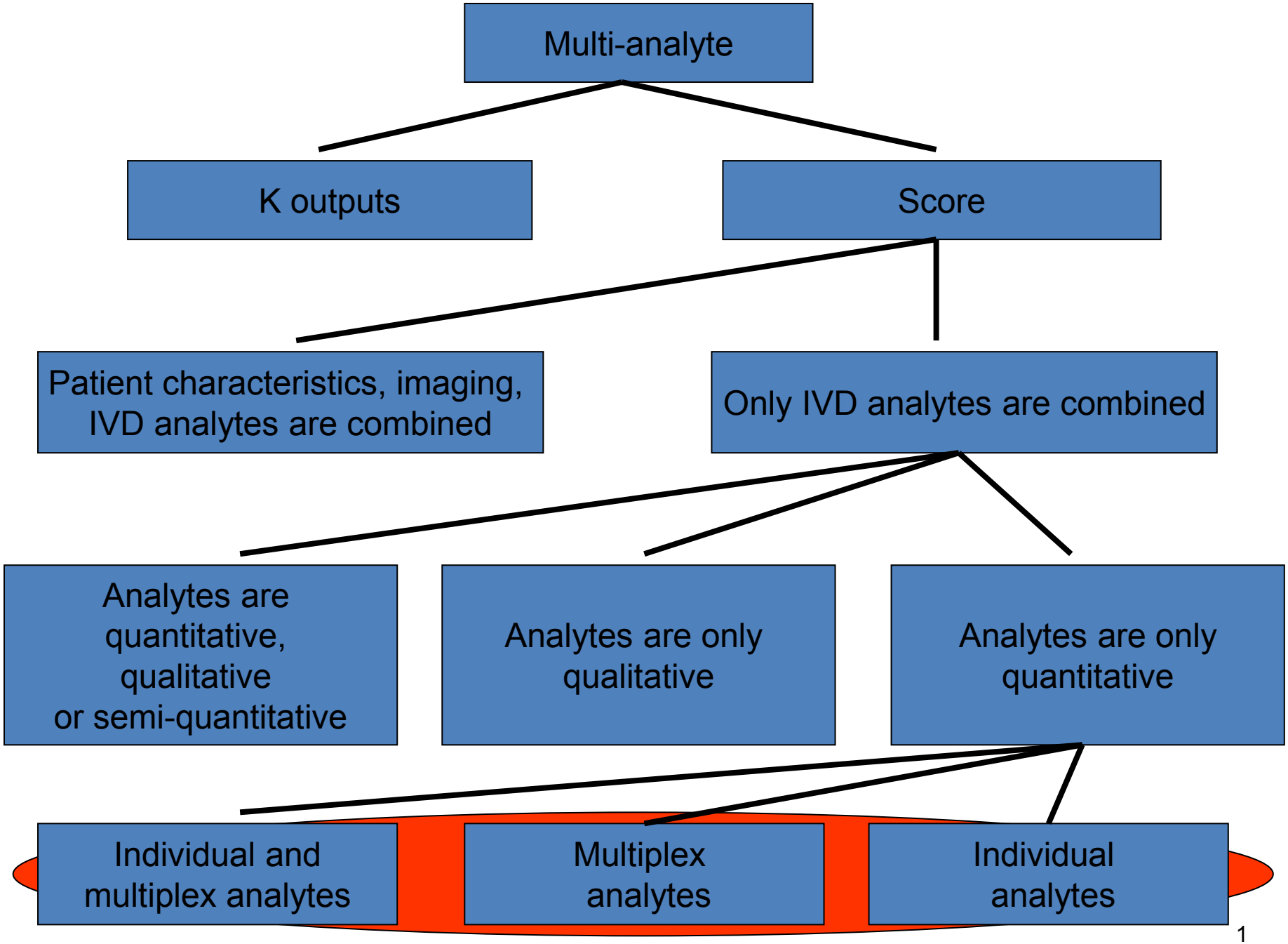
- *Combines the values of multiple variables using an interpretation function to yield a single, patient-specific result* (e.g, a “classification”, “score”, “index”, etc) that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease

Draft Guidance for Industry, Clinical laboratories, and FDA Staff “In Vitro Diagnostic Multivariate Index Assays”, published on July 26, 2007
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm079148.htm

Score Paradigm



Analytical Performance: Precision


Multi-analyte
K outputs
Score
Patient characteristics, imaging, IVD analytes are combined
Only IVD analytes are combined
Analytes are quantitative, qualitative or semi-quantitative
Analytes are only qualitative
Analytes are only quantitative
Individual and multiplex analytes
Multiplex analytes
Individual analytes

Precision

Multi-analyte (K analytes)

Precision experiment for Score

Example:
Score = $F(X_1, X_2, X_3, X_4, \ldots, X_{20})$
X – value of analyte (protein)

Score values: 2.0 to 10.0

Precision study:
4 samples with mean Score values:

3.8, 5.7, 6.9, 9.9

cutoff for Score = 5.0

Basic Points

- The usual precision study provides information about precision for some particular combinations of the individual analytes amounts which were present in the samples of the precision studies described above.

- There are many possible combinations of the individual analytes amounts which give the same value of the test score and therefore, the samples with the same score but different combinations of the individual analyte amounts can have different precisions.

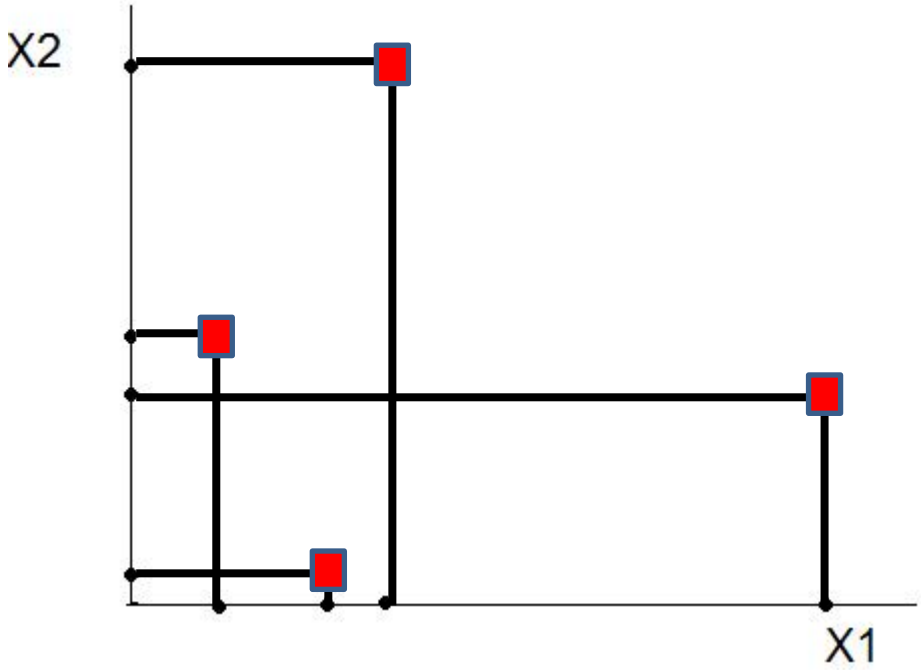
- The additional simulation provides information about precision profile of the test score system for different combinations on individual analytes values.

Details 

For sake of simplicity,
consider two individual analytes X_1 and X_2,
score is $f(X_1, X_2)$.

Within-laboratory precision for each analyte is available:

- Precision of X_1: 4 concentrations, SD, %CV
- Precision of X_2: 4 concentrations, SD, %CV



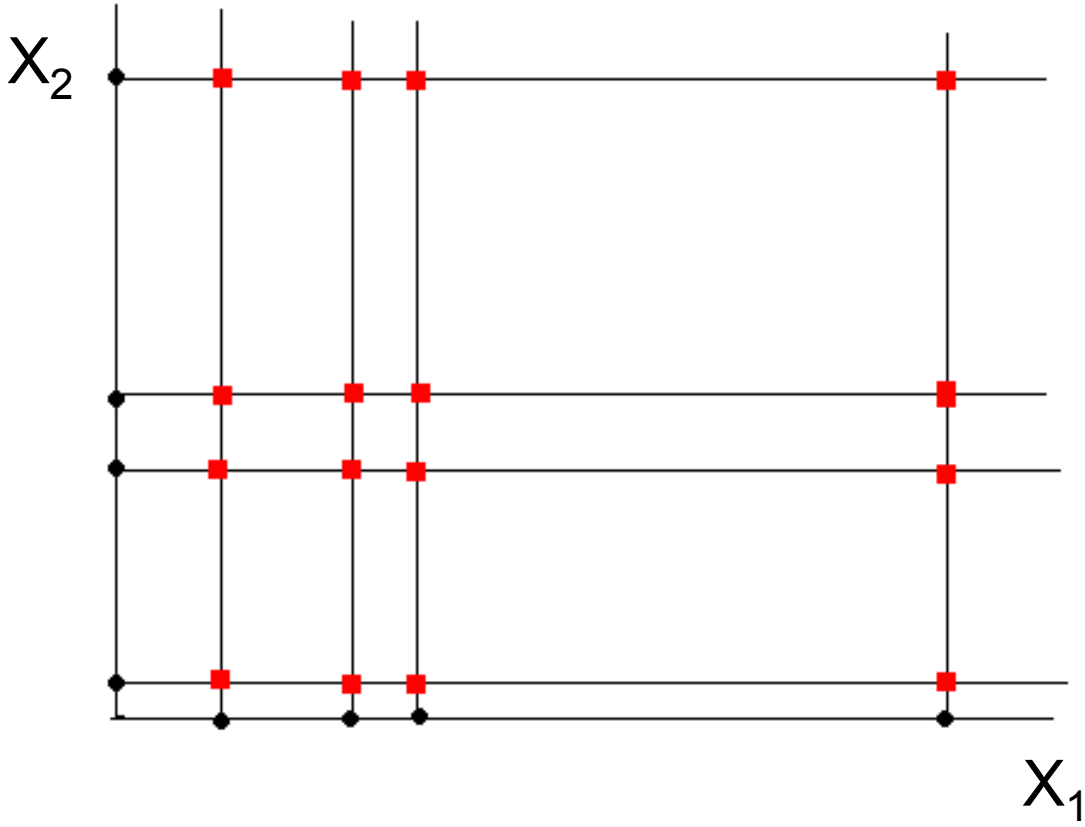
Example: Hypothetical example
Score = f(X_1, X_2)

X_1	Mean	**5.0**	**20.0**	**200.0**	**2000.0**
	SD	1.0	2.0	20.0	300.0
	%CV	**20%**	**10%**	**10%**	**15%**
X_2	Mean	**0.5**	**30.0**	**100.0**	**1000.0**
	SD	0.1	1.5	5.0	60.0
	%CV	**20%**	**5%**	**5%**	**6%**

Correlation in results of X_1 and X_2

- If individual measurements of analytes => random measurements errors of analytes X_1 and X_2 are not correlated
- If multiplex assay => X1 and X2 can be correlated (this correlation can be estimated using precision data for 4 scores)

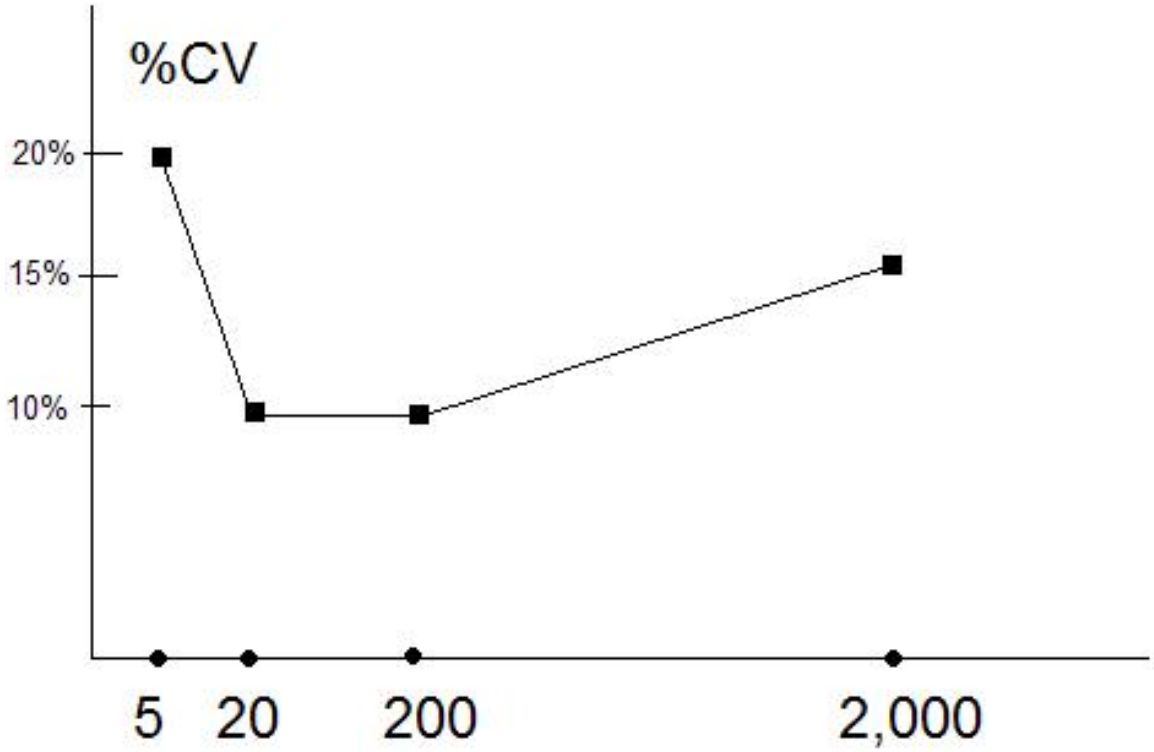
- Score can be calculated at 16 points
- Precision at 16 points can be evaluated using Monte Carlo simulation with normal distributions of random errors for each X_i
- Consider an issue of correlation



We can estimate precision for the Score for the ENTIRE RECTANGLE using PRECISION PROFILES of X_1 and X_2

Within-laboratory precision profile for X_1

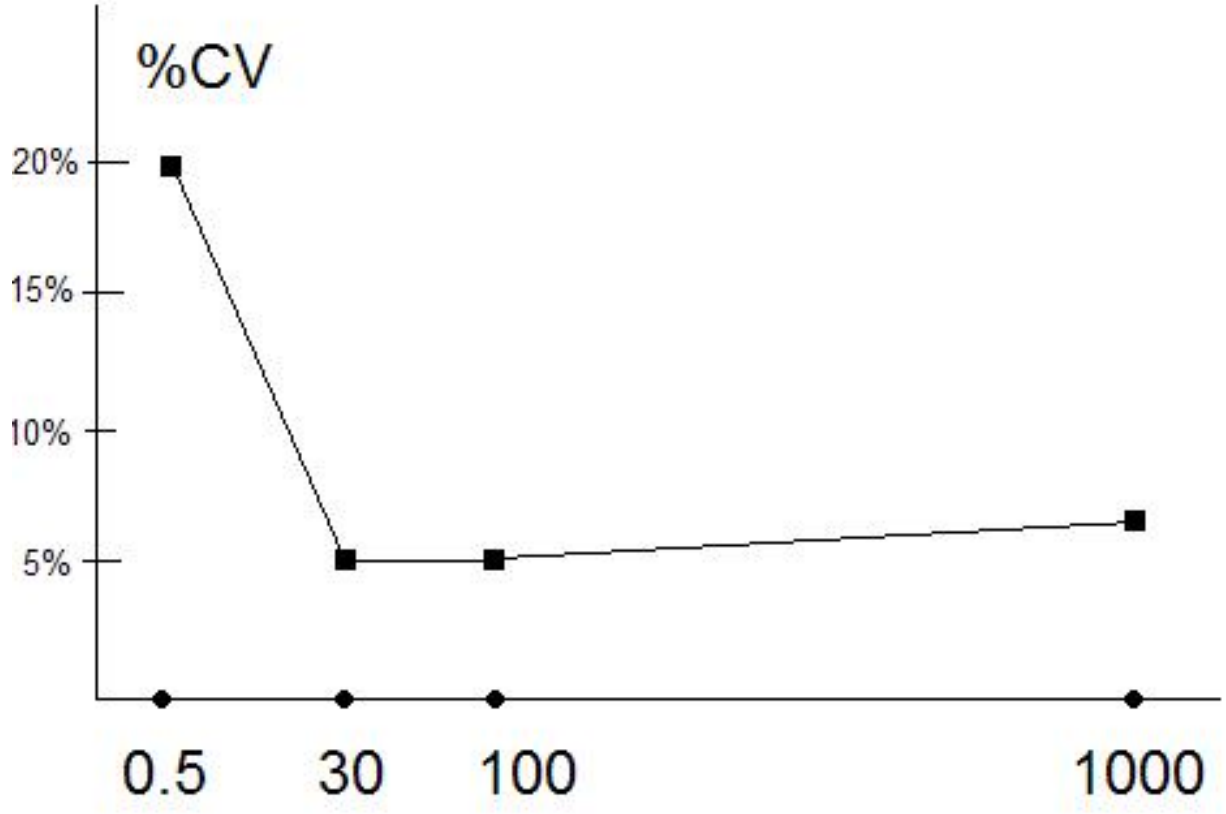
X_1	Mean	5.0	20.0	200.0	2000.0
	SD	1.0	2.0	20.0	300.0
	%CV	20%	10%	10%	15%



Linear interpolation

Within-laboratory precision profile for X_2

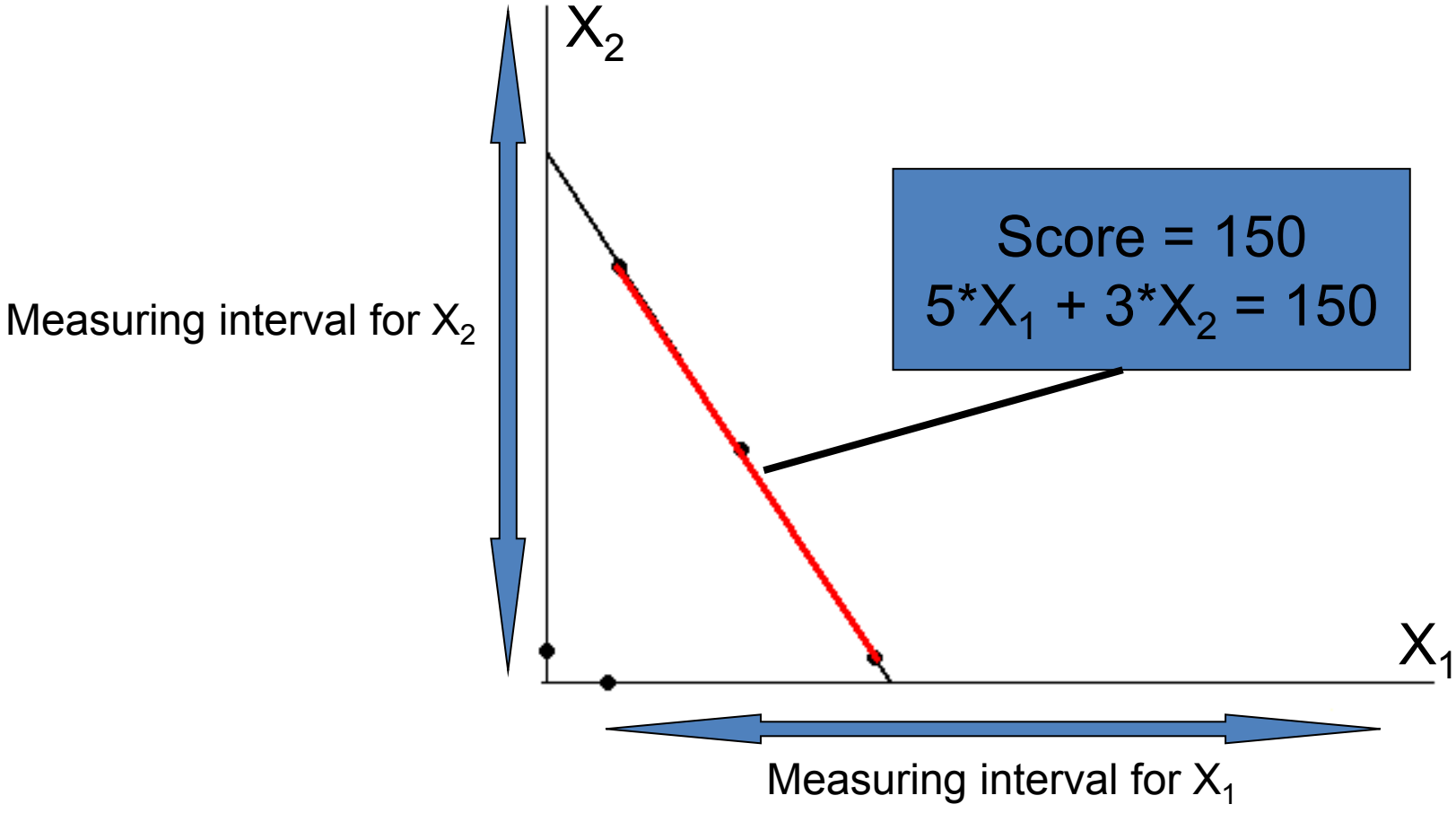
X_2	Mean	0.5	30.0	100.0	1000.0
	SD	0.1	1.5	5.0	60.0
	%CV	20%	5%	5%	6%



Linear interpolation

Example: Hypothetical example

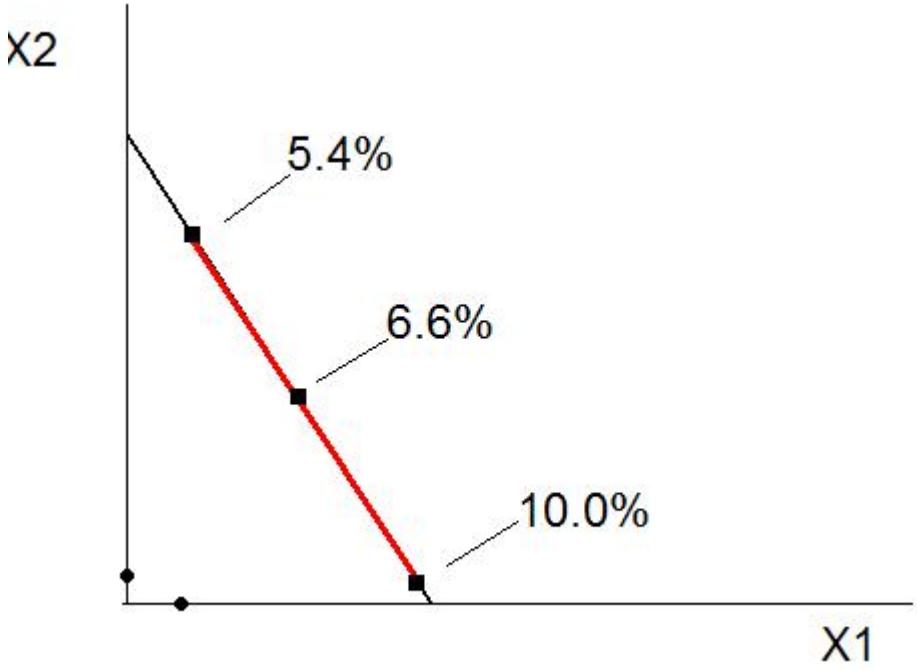
$$\text{Score} = f(X_1, X_2) = 5^* X_1 + 3^* X_2 = 150$$



$4.0 \le X_1 \le 2{,}100$
$0.3 \le X_2 \le 1{,}100$

$20.9 \le \text{Score} \le 13{,}800$

Score	Point	X_1	SD	X_2	SD	SD of Score	%CV of Score
150	(1)	5.0	1.0	41.7	2.1 Precision profile	8.0	**5.4%**
150	(2)	10.0	1.6 Precision profile	33.3	1.7 Precision profile	9.9	**6.6%**
150	(3)	29.7	3.0 Precision profile	0.5	0.1	15.0	**10.0%**



For more details about Monte Carlo simulation of precision, see

Class II Special Controls Guidance Document: Ovarian Adnexal Mass Assessment Score Test System

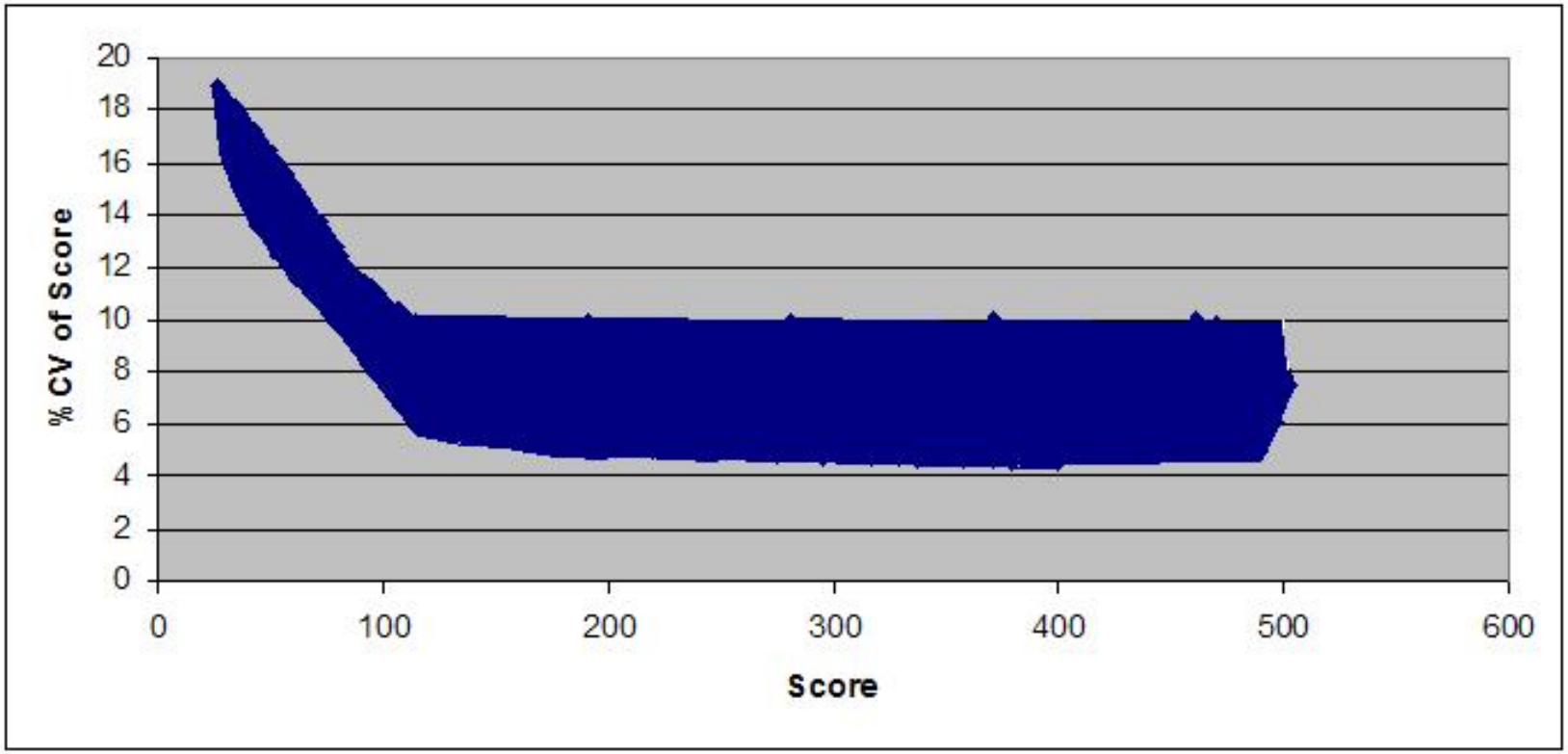
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm237299.htm

Section VI.B “Repeatability/Reproducibility”
Pages 11-13

Example: Hypothetical example

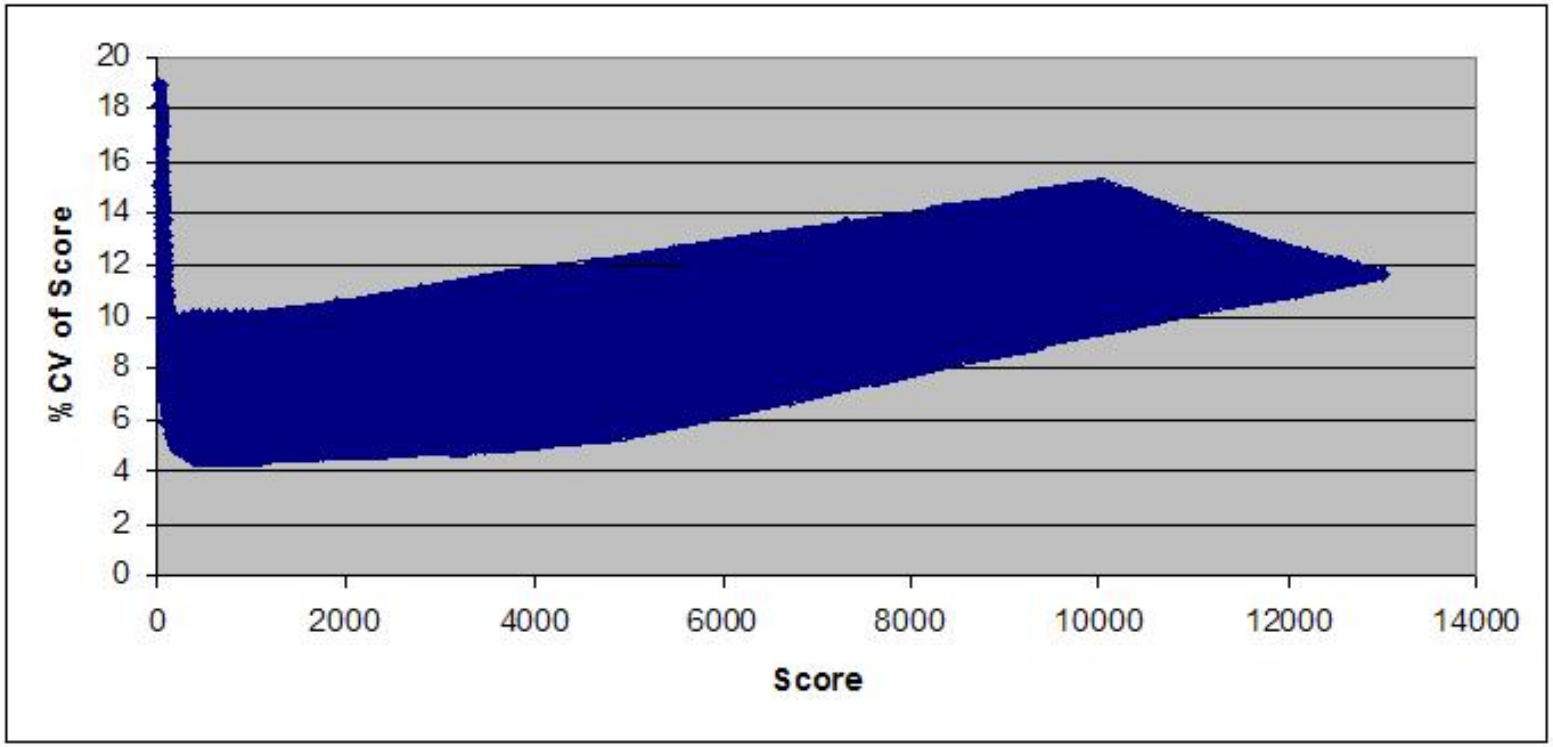
$$\text{Score} = f(X_1, X_2) = 5^* X_1 + 3^* X_2$$

Within-Lab Precision Profile for Score Values 26.6 -500.



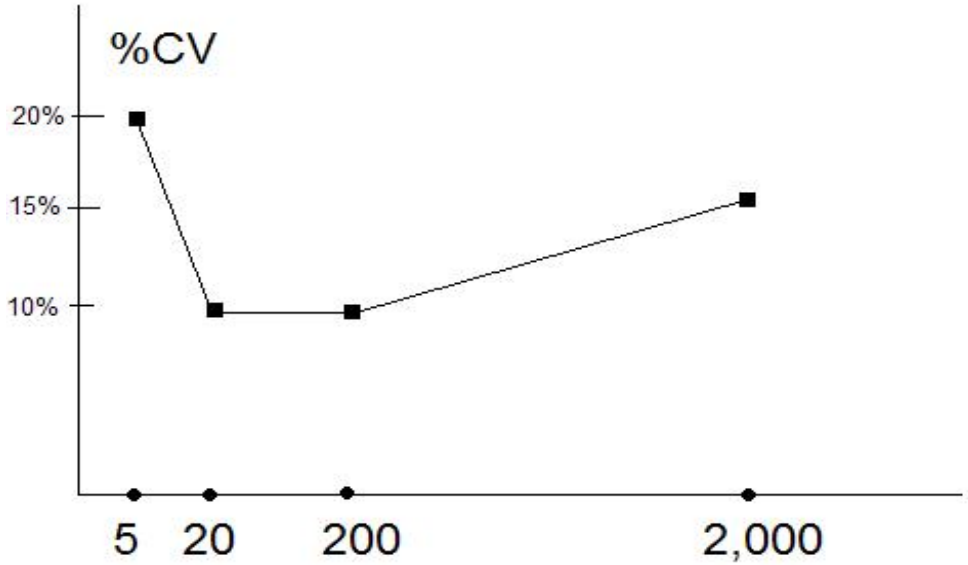
Example: Score=f (X_1, X_2) = 5* X_1 + 3* X_2

Within-Lab Precision Profile for Score Values 26.6 -13,000.



Precision at Clinically Possible Score Values

If we have only one analyte -> precision profile



Clinical study:

•Representative set of subjects from intended use population; each subject has one measurement of the analyte.

•Consider analyte values for all patients in the clinical study (clinically possible analyte values) -> Assumption: one time measurement is close to the mean value of analyte

Precision at Clinically Possible Score Values

For Score:

- ❑ Consider all patients in the clinical study

- ❑ For each patient,
  - o Consider Score and Values of X_1 and X_2;
  - o Using precision profiles of individual analytes, evaluate the precision of the Score with values of X_1 and X_2 for this patient using Monte Carlo simulation;
  - o present this point on the Score precision profile graph.

Precision at Clinically Possible Score Values (cont.)

- Present list of patients for whom precision of their Score was not evaluated because of precision profile for their individual analyte values were not available => You may need precision study for individual analytes at additional concentrations.

- If large number of analytes in the score, precision can be conducted in two stages:

1) Precision of the Score with few samples
2) Clinical study (information about clinically possible combinations of analytes used for calculation of the Score), Monte-Carlo simulation
3) Precision of the Score with new samples based on information from clinical study

Precision Around the Cutoff

- Investigate precision of the Score around the Cutoff for the Score;

Concentrations (X_1, X_2) of individual analytes give a Score close to the Cutoff

$$f(X_1, X_2) = \text{Cutoff}$$

- Define C5 and C95 concentrations around the Cutoff (see CLSI EP12-A2 and EP17-A2)

- For patients in the clinical study with negative Scores, what percent of patients have Scores close to the Cutoff; for patients in the clinical study with positive Scores, what percent of patients have Scores close to the Cutoff.

Summary

1) Precision profile for the Score based on precision profiles of individual analytes and Monte Carlo simulation of error propagation provides additional valuable information.

2) Investigate precision of the Score for clinically possible score values.

3) Percent of subjects in the clinical study with Score values close to the cutoff provides information about clinical impact of Score random measurement error.

Clinical Performance: Likelihood Ratios

Example: T_1 – pre-surgical assessment (pos, neg)
T_2 – qualitative test (pos, neg)

Can T_2 (New test) be used instead of T_1?

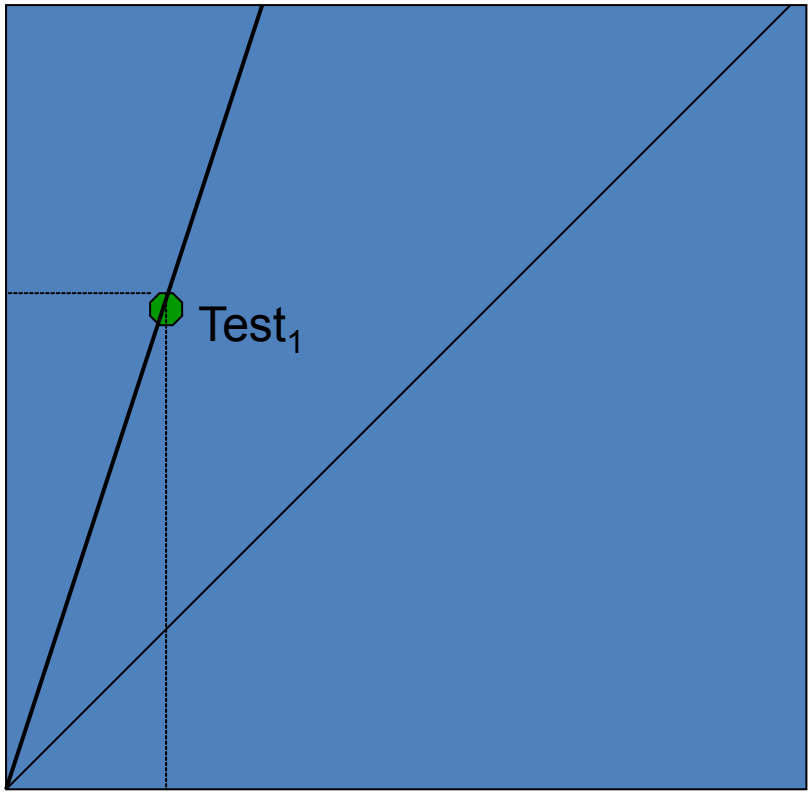
	T_1 test alone	**T_2 test alone**
sensitivity	**74.8% (113/151)**	**84.8% (128/151)**
specificity	**79.2% (281/355)**	**49.9% (177/355)**

How to compare these two tests?

Two tests should be compared using the likelihood ratios (not sensitivity, specificity).

For more details,
Biggerstaff, B.J. (2000). Comparing diagnostic tests: a simple graphic using likelihood ratios. *Statistics in Medicine* 19: 649-663.
Kondratovich, M.(2008) Comparing Two Medical Tests When Results of Reference Standard Are Unavailable for Those Negative via Both Tests, *Journal of Biopharmaceutical Statistics,* 18: 1; 145-166.

Same prevalence
$Test_1$: (Se_1, Sp_1, π) and $Test_2$: (Se_2, Sp_2, π)



$$\frac{R_1}{1-R_1} = PLR \times \frac{\pi}{1-\pi}$$

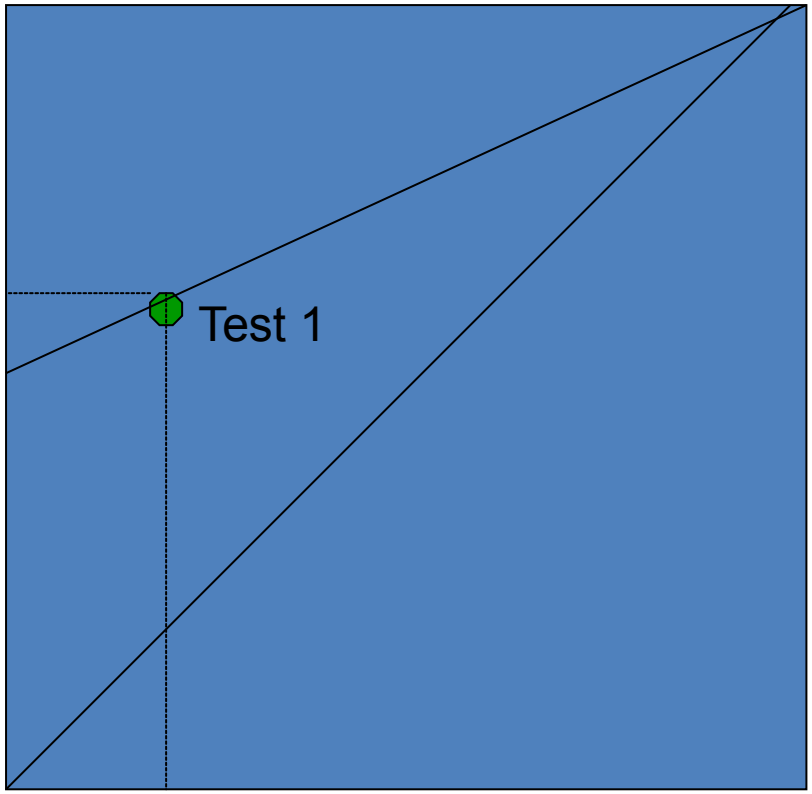
$PLR_1 = PLR_2 \Leftrightarrow PPV_1 = PPV_2$

PLR=Se/(1-Sp)

PLR is a tangent of the line (0,0) –(Se_1, Sp_1)

The larger PLR, the higher PPV.

Same prevalence
Test 1: (Se_1, Sp_1, π) and Test 2: (Se_2, Sp_2, π)



$$\frac{R_0}{1-R_0} = NLR \times \frac{\pi}{1-\pi}$$

$NLR_1 = NLR_2 \Leftrightarrow NPV_1 = NPV_2$

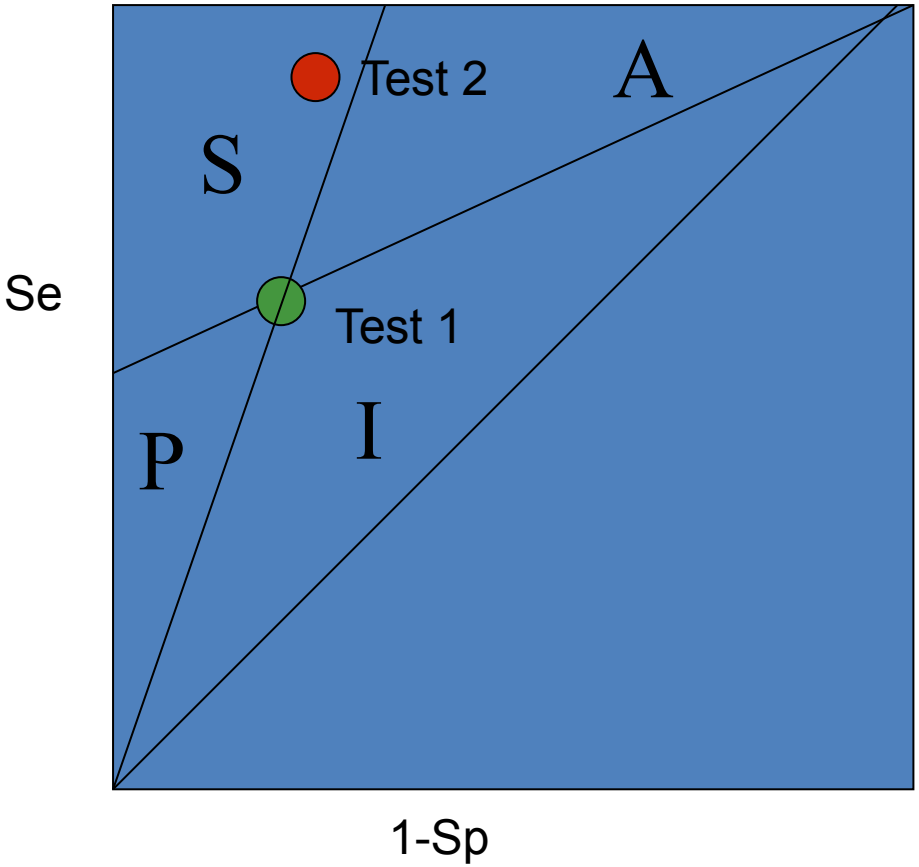
NLR=(1-Se)/Sp

NLR is a tangent of the line (1,1) –(Se_1, Sp_1)

⇔

The smaller NLR, the lower 1-NPV (higher NPV).

Regions:



S – superior overall ($PPV_2 > PPV_1$ and $NPV_2 > NPV_1$)

I – inferior overall ($PPV_2 < PPV_1$ and $NPV_2 < NPV_1$)

A – superior for confirming absence of disease ($PPV_2 < PPV_1$ and $NPV_2 > NPV_1$)

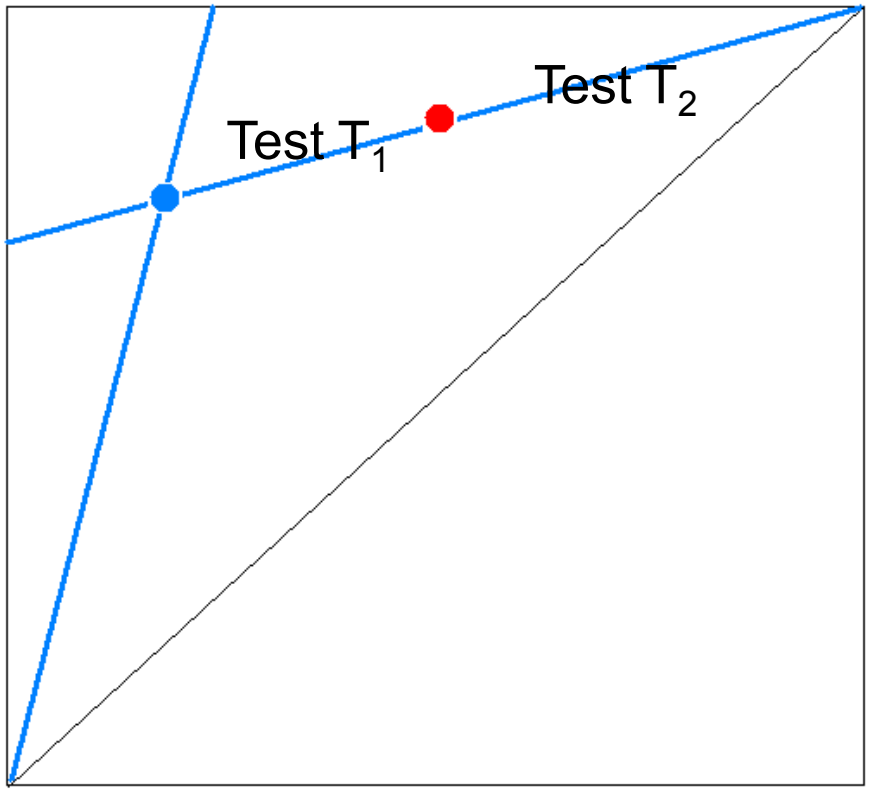
P – superior for confirming presence of disease ($PPV_2 > PPV_1$ and $NPV_2 < NPV_1$)

Example: T_1 – pre-surgical assessment (pos, neg)
T_2 – qualitative test (pos, neg)

Can T_2 be used instead of T_1?

	T_1 test alone	T_2 (New) test alone
sensitivity	74.8% (113/151)	84.8% (128/151)
specificity	79.2% (281/355)	49.9% (177/355)
PLR = se/(1-sp)	**3.59** **95% CI: 2.887 to 4.50**	**1.69** **95% CI: 1.49 to 1.92**
NLR = (1-se)/sp	**0.32** 95% CI: 0.24 to 0.42	**0.31** 95% CI: 0.21 to 0.45
Prevalence = 29.8%		
PPV	**60.4% (113/187)**	**41.8% (128/306)**
1-NPV	11.9% (38/319)	11.5% (23/200)

Relationship between test T_1 and test T_2



Can T_2 be used instead of T_1? **NO!!!**

Clinical Performance:

Relevance of Analytes Included In Score

a) Individual measurement of each analyte
b) Multiplex assay

a) Individual measurement of each analyte

- You should justify inclusion of each individual analyte in the use of the Score test.

- One option is to demonstrate that the individual analytes included in the calculation of the score are informative for target condition using the data from the clinical study. For this, perform ROC analyses for each individual analyte.

- If the data of the clinical study did not demonstrate that some individual analytes are informative for the target condition, you should justify why these analytes were included in the calculation of the Score test.

b) Score value is based on multiplex assay Only Score is clinically evaluated

Range of Score values

- Provide information about range of the numerical score values of the test score system based on the measuring range of the individual analytes.

- If, in addition to providing the qualitative test Score results based on the cutoff(s), you plan to report the numerical values of the Score, the data should demonstrate that the higher numerical values of the Score are related to the progressively higher or progressively lower probabilities of target condition.

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