Abbott

Equivocals: What do you mean you don't know!?!

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Based on Research by: AdvaMed Equivocal Working Group

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Haja El Mubarak, Marina Kondratovich, and Kristen Meier.

Why this topic is important to me...

Photograph by Vicki Petrides, permission to share photograph granted by the subjects.

Outline

Definition

Considerations

ALBiD

Comparisons

Example

Summary

Definition from Merriam-Webster...

Merriam-Webster SINCE 1828

equivocal

DICTIONARY | **THESAURUS**

equivocal *adjective*

equiv·o·cal | \ i-ˈkwi-və-kəl 🔊 \

Definition of *equivocal*

1   **a**   : subject to two or more interpretations and usually used to mislead or confuse
     // an *equivocal* statement

     b   : uncertain as an indication or sign
     // *equivocal* evidence

2   **a**   : of uncertain nature or classification
     // *equivocal* shapes

     b   : of uncertain disposition toward a person or thing : UNDECIDED
     // an *equivocal* attitude

     c   : of doubtful advantage, genuineness, or moral rectitude
     // *equivocal* behavior

Synonyms

debatable, disputable, dodgy *[chiefly British]*, doubtable, doubtful, dubious, dubitable, fishy, problematic *(also* problematical*)*, queer, questionable, shady, shaky, suspect, suspicious

Source: https://www.merriam-webster.com/dictionary/equivocal (Accessed May 23, 2019)

Definition from AdvaMed Equivocal Working Group…

Equivocal result

- A <u>valid</u>, non-missing, non-erroneous result that is neither positive nor negative
  - Could be due to biological, pre-analytical, or analytical reasons
  - May or may not require additional testing before reporting

Context

- Qualitative tests with a continuous underlying response, where binary results are preferred but not always possible
- Middle category along a continuum between a positive and a negative test result:

| negative | *equivocal* | positive |

$$C_1 \leq \text{equivocal result} \leq C_2$$
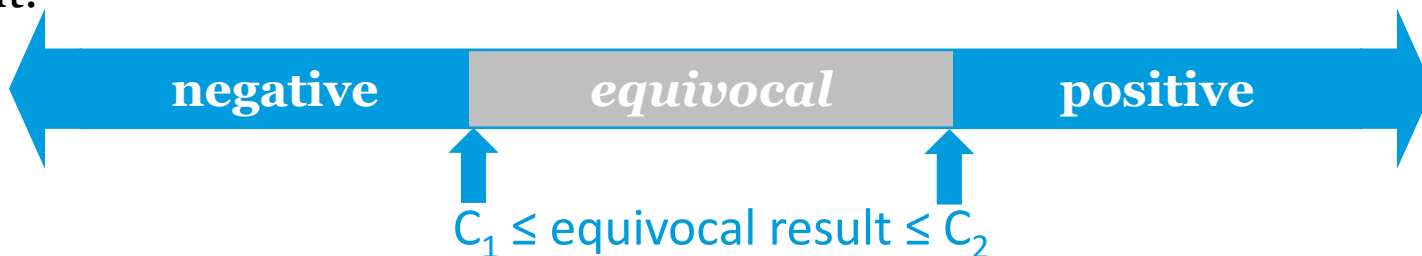
Equivocal zone

- An interval that contains equivocal results

Considerations:
Why should we care about equivocal results?

Impact clinical decisions

Performance near the cutoff may be the distinguishing factor between two methods

Product performance estimates can vary based on...

- Proportion of equivocal results in data set
- How (or whether) equivocal results are used in calculations

Considerations:
What are underlying reasons for equivocal results?

Biological

- Seroconversion

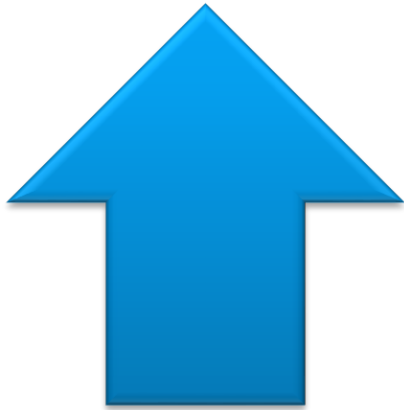- Overlapping patient populations

Pre-analytical

- Short draw

- Mis-handled sample (improper storage, centrifugation, *etc.*)

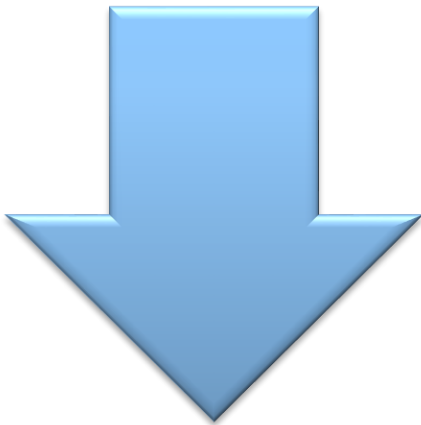**Analytical**

- Imprecision

- Bias

Considerations:
What are the benefits and risks of equivocal results?

Benefits

- Minimizes mis-diagnosis / mis-classification
- Optimizes correct course of treatment

Risks

- Delayed diagnosis and treatment
- Return to clinic
- Additional testing

Considerations:
How might equivocals be resolved to binary outcome?

When a candidate test has equivocal results, additional steps may be taken to resolve the equivocals, thus leading to a binary decision.

Approach Leading to a Binary Decision (ALBiD)

Retest same sample using same test	• Helpful when test has high variability near cutoff
Test same sample using different test	• Helpful when equivocal due to biological or analytical reasons such as potential interference with initial test
Collect new sample and test using same or different method	• Helpful when equivocal due to pre-analytical issue such as sample mis-handling or a biological reason such as seroconversion

Comparisons and Contingency Tables

Comparisons

- Candidate method vs. Target condition (TC)
- Candidate method vs. Comparator method

Contingency Tables

- 2 × 2: No equivocals
- 3 × 2: Equivocals in candidate
- 2 × 3: Equivocals in TC or comparator
- 3 × 3: Equivocals in candidate and in TC or comparator

2 × 2: Candidate vs. Target Condition

		Target Condition			
		Present		**Absent**	**Total**
Candidate	**Positive**	A_1		C_1	N_1
	Negative	A_3		C_3	N_3
	Total	N_A		N_C	N

Accuracy
- Clinical sensitivity = A_1/N_A
- Clinical specificity = C_3/N_C

Prediction
- Positive predictive value (PPV) = A_1/N_1
- Negative predictive value (NPV) = C_3/N_3
- Prevalence = N_A/N

Informativeness
- Likelihood ratio, positive (LR+) = $(A_1/N_A)/(C_1/N_C)$
- Likelihood ratio, negative (LR-) = $(A_3/N_A)/(C_3/N_C)$
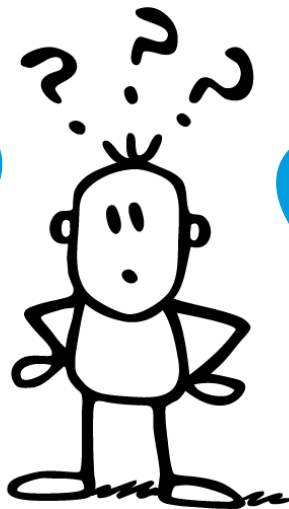
3 × 2: Candidate vs. Target Condition
How should we characterize performance?

	Target Condition			Total
	Present		**Absent**	**Total**
Positive	A_1		C_1	N_1
Equivocal	A_2		C_2	N_2
Negative	A_3		C_3	N_3
Total	N_A		N_C	N

(Row group labeled "Candidate")

Clinical sensitivity?

LR +?

Clinical specificity?

LR -?

PPV?

NPV?

3 × 2: Candidate vs. Target Condition
Prevalence, Risk and Likelihood Ratios

		Target Condition			
		Present		Absent	Total
Candidate	**Positive**	A_1		C_1	N_1
	Equivocal	A_2		C_2	N_2
	Negative	A_3		C_3	N_3
	Total	N_A		N_C	N

Pre-test probability (Prevalence)
- TC Prevalence = N_A/N

Post-test probability (Risk)
- TC Risk when test positive = A_1/N_1
- TC Risk when test equivocal = A_2/N_2
- TC Risk when test negative = A_3/N_3

Informativeness (Likelihood ratios)
- Likelihood ratio, positive (LR+) = $(A_1/N_A)/(C_1/N_C)$
- Likelihood ratio, equivocal (LR eq) = $(A_2/N_A)/(C_2/N_C)$
- Likelihood ratio, negative (LR-) = $(A_3/N_A)/(C_3/N_C)$

Approach Leading to a Binary Decision (ALBiD)

ALBiD

- When a candidate test has equivocal results, additional steps may be taken to resolve the equivocals, thus leading to a binary decision.
- During product design verification and validation, additional steps are not always practical.
  So...what to do?

ALBiD sensitivity / specificity – the performance of the binary decision based on the test with equivocals

- If lowest ALBiD sensitivity/specificity are acceptable, then test with equivocals is acceptable regardless of resolution
- If highest ALBiD sensitivity/specificity are not acceptable, then test with equivocals is not acceptable regardless of resolution

3 × 2: Candidate vs. Target Condition
ALBiD sensitivity and specificity

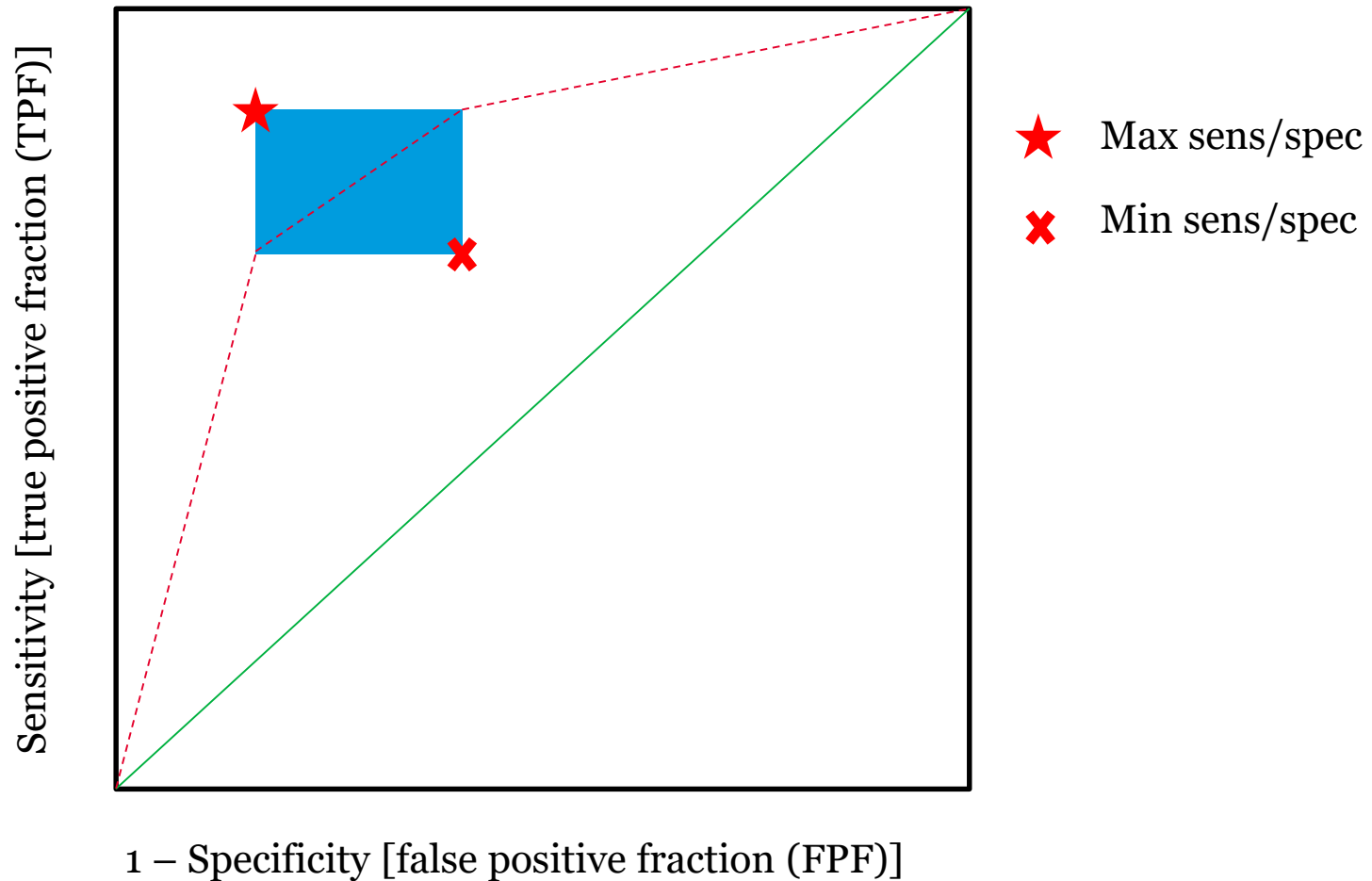|		Target Condition			
		Present		**Absent**	**Total**
Candidate	**Positive**	A_1		C_1	N_1
	Equivocal	A_2		C_2	N_2
	Negative	A_3		C_3	N_3
	Total	N_A		N_C	N

Minimum

- ALBiD sensitivity, min $= A_1/N_A$
- ALBiD specificity, min $= C_3/N_C$

Maximum

- ALBiD sensitivity, max $= (A_1 + A_2)/N_A$
- ALBiD specificity, max $= (C_2 + C_3)/N_C$

3 × 2: Candidate vs. Target Condition
ALBiD Sensitivity/Specificity – ROC Plane

★ Max sens/spec

✖ Min sens/spec

3 × 2: Candidate vs. Target Condition Example

	Target Condition			
	Present		**Absent**	**Total**
Positive	242		6	248
Equivocal	5		23	28
Negative	3		1000	1003
Total	250		1029	1279

(Candidate — row label for Positive/Equivocal/Negative/Total)

Prevalence (Pre-test probability)	19.5% (250/1279)

	Positive	**Equivocal**	**Negative**
Risk (Post-test probability)	97.6% (242/248)	17.9% (5/28)	0.3% (3/1003)
Likelihood Ratio	166.01	0.89	0.01

3 × 2: Candidate vs. Target Condition Example, continued

		Target Condition			
		Present		**Absent**	**Total**
Candidate	**Positive**	242		6	248
	Equivocal	5		23	28
	Negative	3		1000	1003
	Total	250		1029	1279

	ALBiD Sensitivity	**ALBiD Specificity**
Minimum	96.8% (242/250)	97.2% (1000/1029)
Maximum	98.8% (247/250)	99.4% (1023/1029)
Percent Equivocals	2.2% (28/1279)	

Summary

- An equivocal result is a valid, non-missing, non-erroneous result that is neither positive nor negative

- Consider whether the benefits of having an equivocal zone outweigh the risks by understanding the product intended use, underlying reasons for equivocals and the consequences of reporting (or not reporting) equivocal results

- For 3 × 2 cases versus a TC, calculate...
  - Prevalence (pre-test probability)
  - Risk (post-test probability)
  - Likelihood ratios

- Consider providing an ALBiD for equivocal results, and when doing so calculate...
  - Minimum and maximum ALBiD sensitivity and specificity with percentage of equivocals

References

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