Statistics 101 for POCT

What do the numbers mean?

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Objectives

- Interpret statistical analyses as reported by commercial programs
- Identify the statistical analyses relevant to the question being asked
- Critically evaluate data presented in package inserts for mis-used statistics

Statistics

- Definition of Statistics: The science of producing unreliable facts from reliable figures.
  - Evan Esar
- Be able to analyze statistics, which can be used to support or undercut almost any argument.
  - Marilyn vos Savant
- Statistic: a function of a set of observations from a random variable.
  - CLSI Harmonized Database

Method Validation

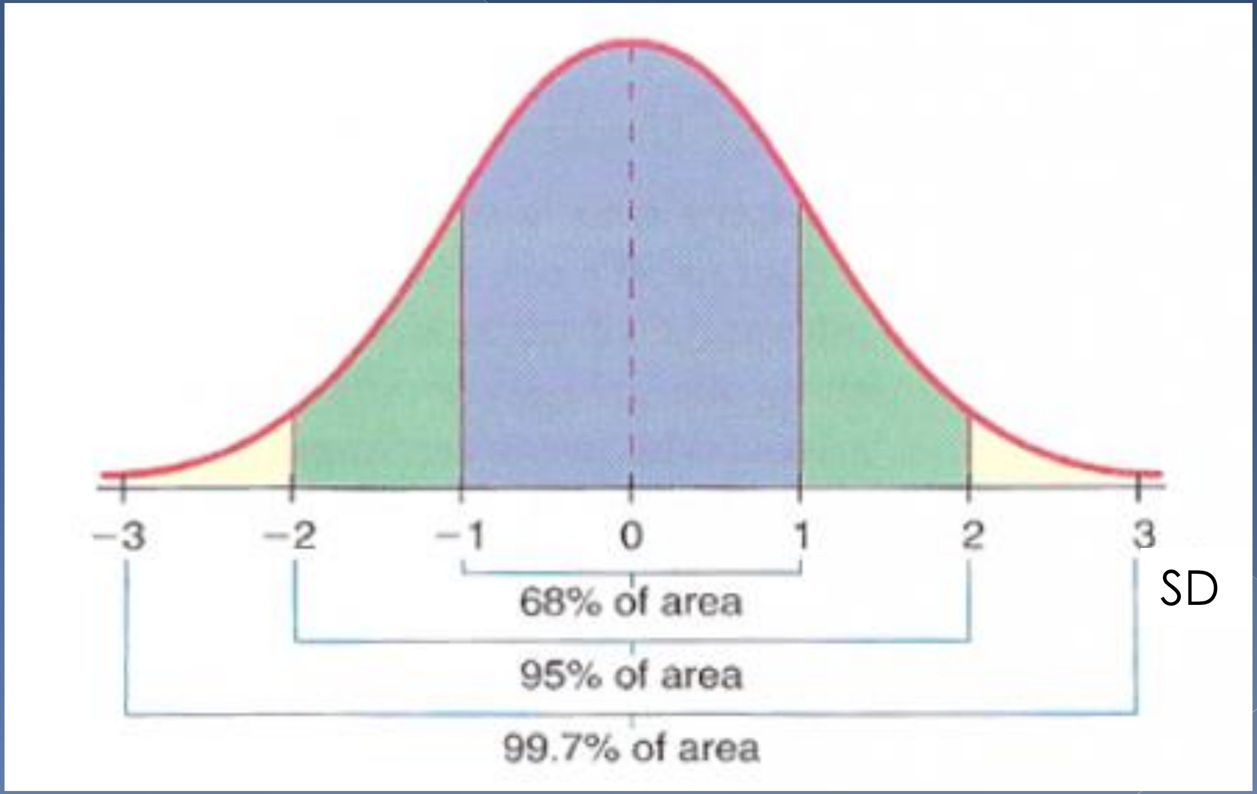
- A new POCT is to be implemented
  - Multiple replicates of controls run
  - Run side by side patient samples with current method
  - Data is:
    - Entered into EP Evaluator OR
    - Entered into Excel spreadsheet and analyzed using AnalysisToolPak or Analyse-It OR
    - Sent to manufacturer
  - Report returned with lots of statistics
    - Report may indicate pass/ fail to unknown specifications
    - Manufacturer rep explains it is all good
- How do I know it is OK?

Resources

- www.qimacros.com
- YouTube videos on performing analyses in Excel
- CLSI EP documents
  - The lab may have copies
- https://www.wikihow.com/Calculate-Precision

Some Basics

- Quantitative Methods
  - Statistics we use assume a **normal distribution**

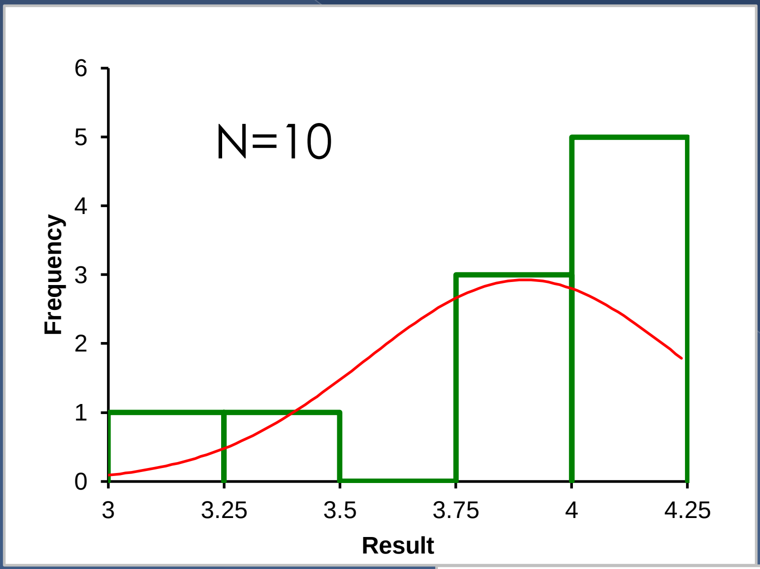


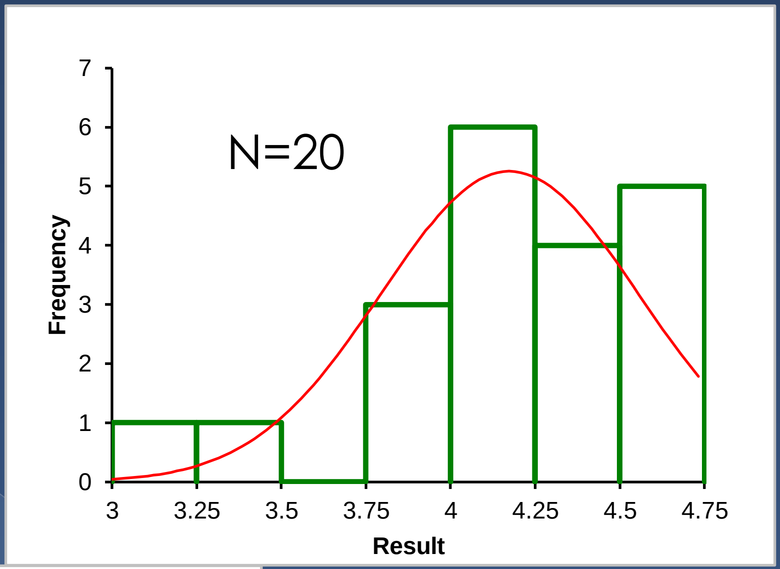
Precision

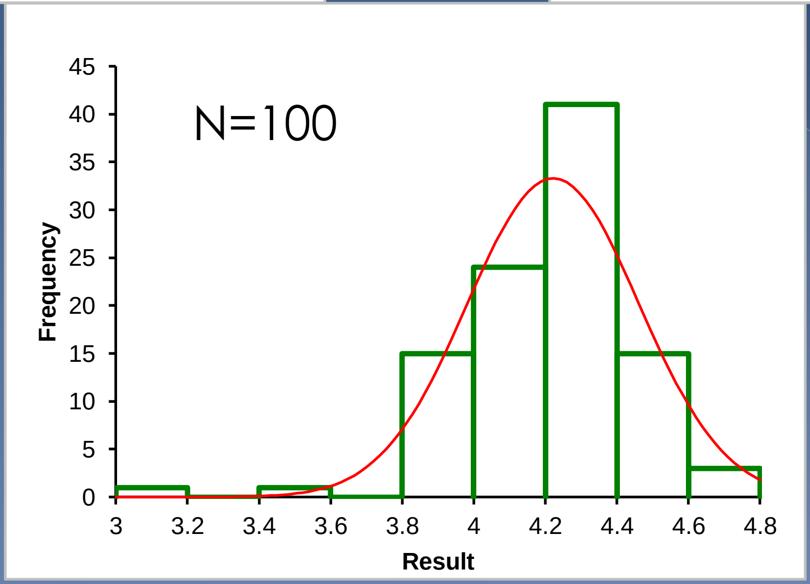
- Measure of the variability of the system
  - How close are multiple replicates?
- Higher number of replicates allows better estimate of precision
- Outliers affect small numbers much more significantly
- Calculations assume a Normal Distribution
  - Frequently untrue assumption, but used anyway.

Precision

Precision – N affects result







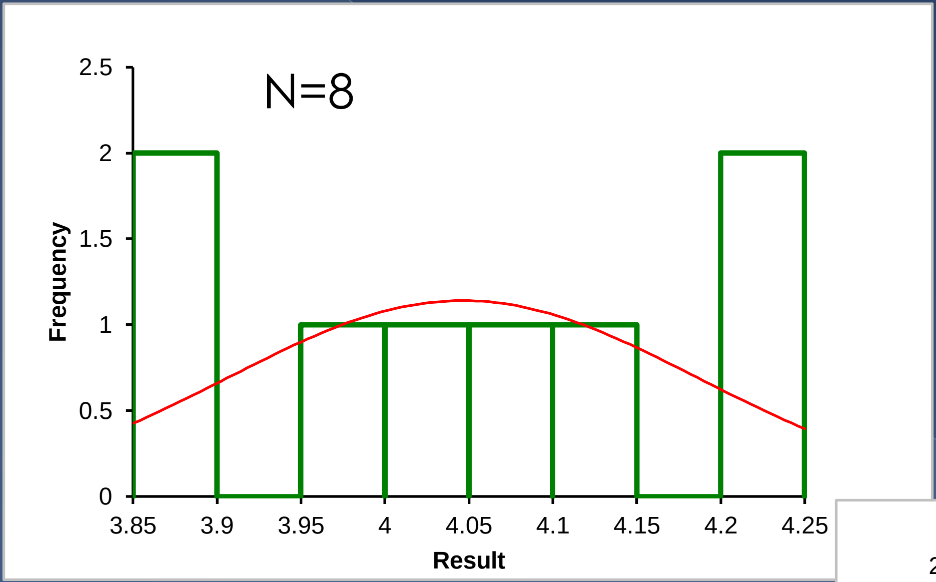
Precision Statistics

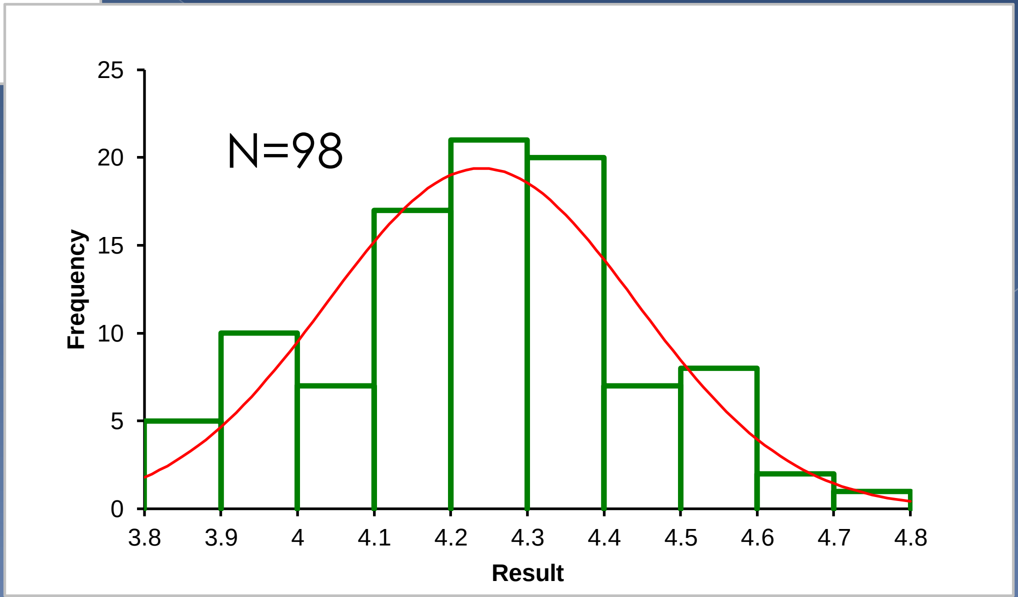
- Mean – central tendency of the data
  - Peak of the bell curve (Average used in practice)
- Median
  - Value where 50% of samples are lower & 50% higher
- Standard deviation (SD) – measure of variability
  - Width of the bell curve
  - Relates to difference between individual results and the mean
- Standard error (SE) – measure of SD of the mean
  - Calculated from variance (SD^2) & N
- 95% Confidence interval
  - Estimate of "truth" from data collected
  - 95% probability that the "true" value is within the interval defined

Statistics Calculated

Statistic	N=10	N=20	N=100
Mean	3.90	4.17	4.22
95% CI mean	3.65 – 4.14	4.00 – 4.35	4.14 – 4.27
SE	0.11	0.08	0.02
SD	0.34	0.38	0.24
CV = $(\frac{Mean}{SD}) * 100$	8.7%	9.1%	5.7%
Median	3.99	4.21	4.25
95% CI median	3.45 – 4.20	4.01 – 4.44	4.19 – 4.29

Outlier Removal





Outliers

Statistic	N=10	N=8	N=100	N=98
Mean	3.90	4.04	4.22	4.24
95% CI mean	3.65 – 4.14	3.92 – 4.16	4.14 – 4.27	4.20 – 4.28
SE	0.11	0.05	0.02	0.02
SD	0.34	0.14	0.24	0.20
CV = $(\frac{Mean}{SD}) * 100$	8.7%	3.5%	5.7%	4.8%
Median	3.99	4.05	4.25	4.25
95% CI median	3.45 – 4.20	3.86 – 4.23	4.19 – 4.29	4.20 – 4.30

Precision - Caveats

- Statistics often look better at higher mean values
  - If mean is 0.1 an SD of 0.05 is 50% CV
  - If mean is 100 an SD of 5.0 is 5% CV
- Evaluate values reported in inserts
  - Should be near clinical decision points
  - Required for newer products
  - For older products expect to see more variability in end-user results

Accuracy

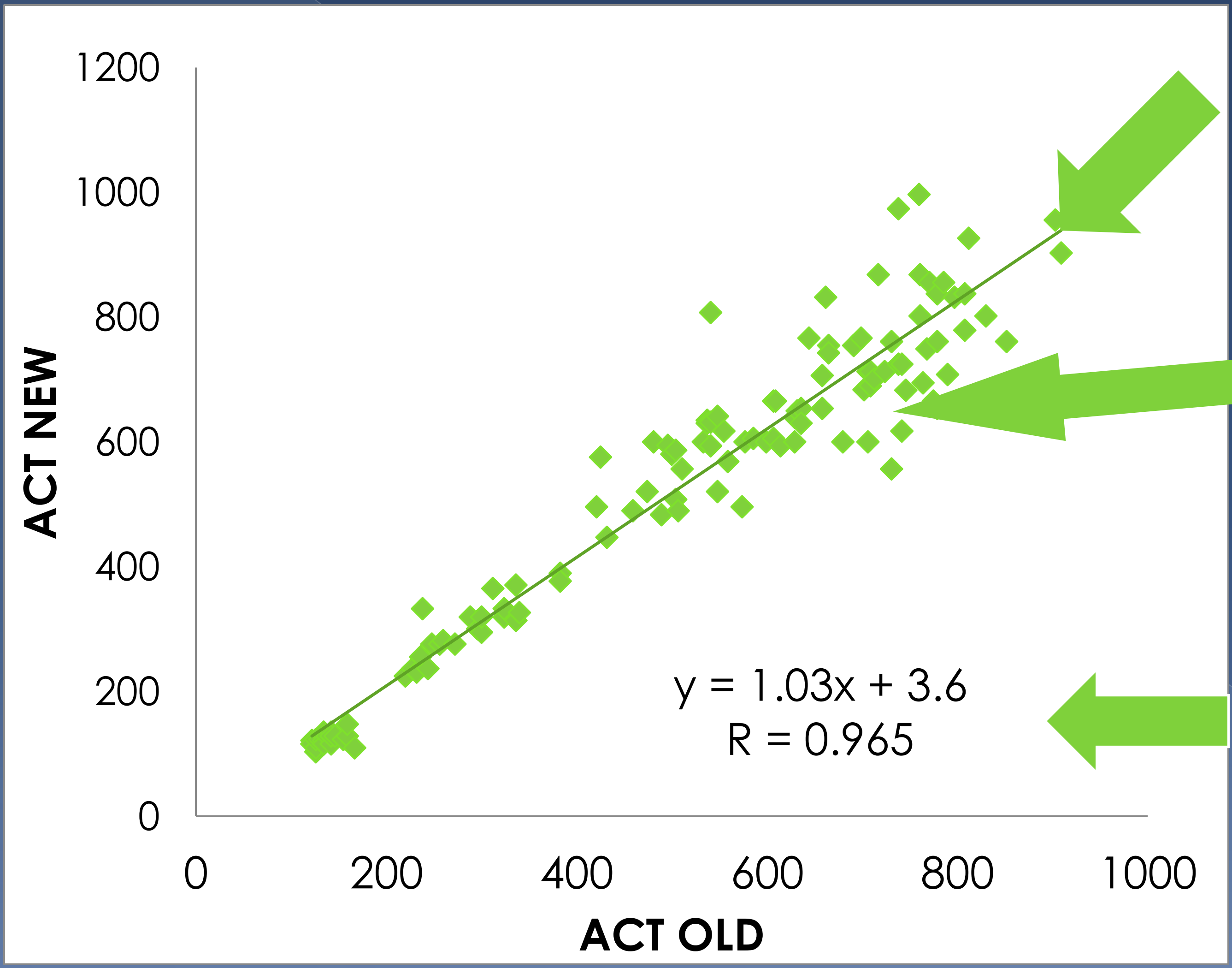
- Comparison to “truth”
  - Truth usually defined as current system
  - Truth a myth for many analytes
    - Notably coagulation, troponin I, other non-standardized analytes
- How close does POCT come to lab result
  - Correlation using patient samples

Accuracy

Correlation Graph

- Data points
  - Each split sample generates one point
  - Horizontal (X) axis is Lab (current system)
  - Vertical (Y) axis is point of care (new) device
- Regression line
  - Mathematical prediction of relationship between two devices

Results - Correlation Graph



Regression line

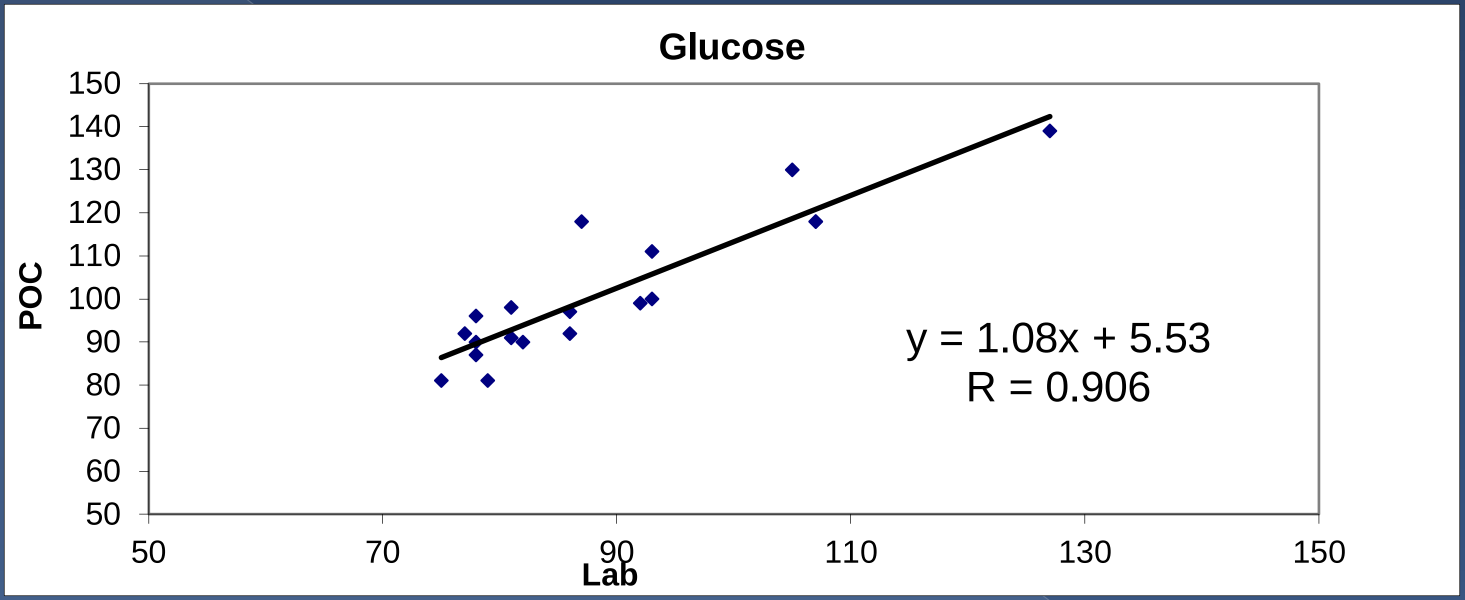
Data points

Regression equation

Correlation Graph

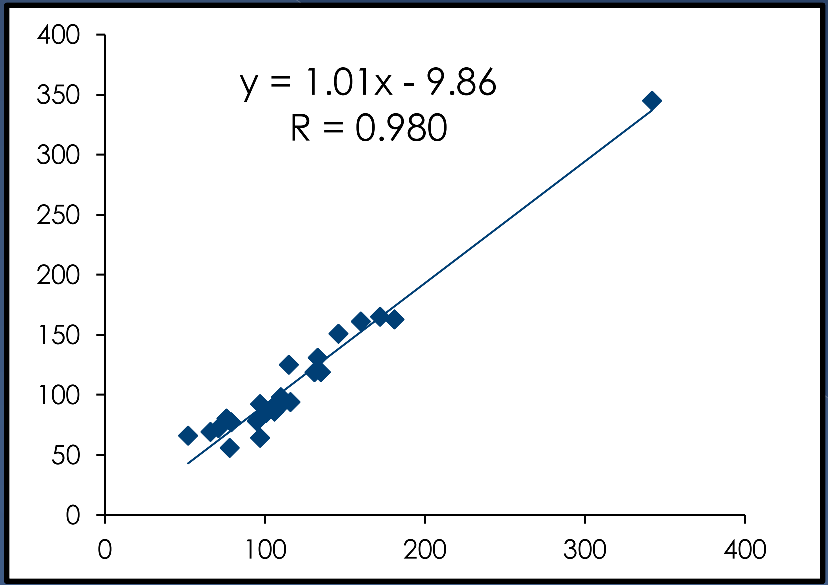
- Regression equation
  - 3 parts: $Y = mX + b$ $(y = 1.03x + 3.6)$
    - Y = POC (new) result; X = lab (current) result
    - m = slope - perfect correlation m = 1.0
    - b = intercept - perfect correlation b = 0.0
  - r value - correlation coefficient
    - NOT r^2
    - Describes how much of the change in Y value is due to the change in the X value
    - r = 0.91 mean 91% correlation

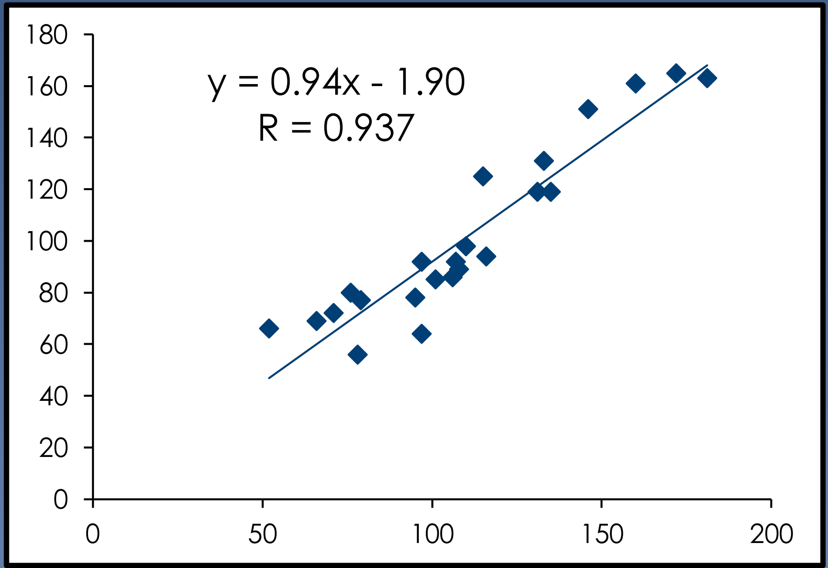
Correlation - Is this good?



- Cannot judge
  - All values close to normal range
  - Nothing above 150
- Evaluate the axes when looking at correlation graphs

Correlation – What to look for





- Assay range to 500, so spread seems OK
  - Isolated value drives correlation
- Original data set showed out of range values
  - These **must** be excluded before regression run
- Revised data has same issues as prior glucose results

Accuracy - Caveats

- Data need to span the clinically important range
  - Single extreme values should be omitted
  - Out of range values must be omitted

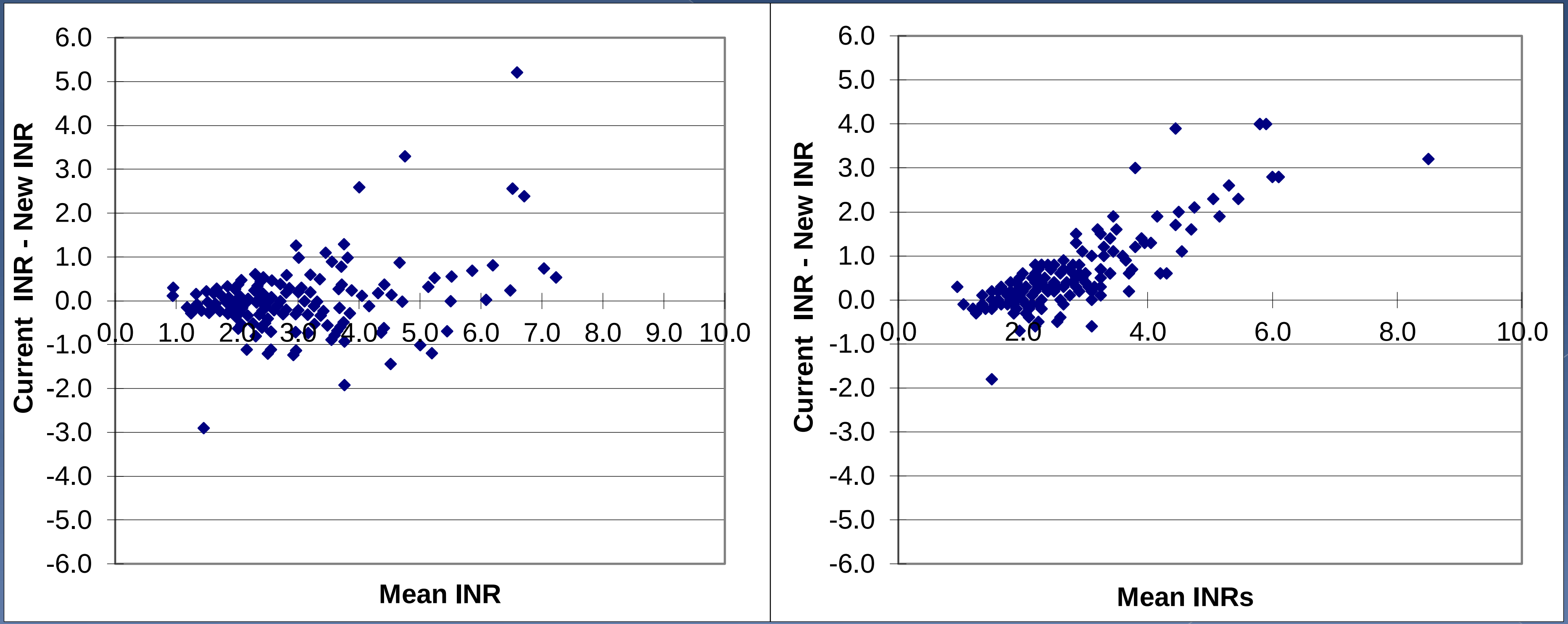
Correlate does <u>NOT</u> mean Match

Bias evaluation

- Difference plot
  - Bland Altman analysis
  - Plot either reference result or average of two methods as X
    - Reference result used when considered "truth"
      - *e.g.*, POC electrolytes versus lab
    - Average used when "truth" is uncertain
      - *e.g.*, ACT comparisons
  - Plot difference between two results as Y

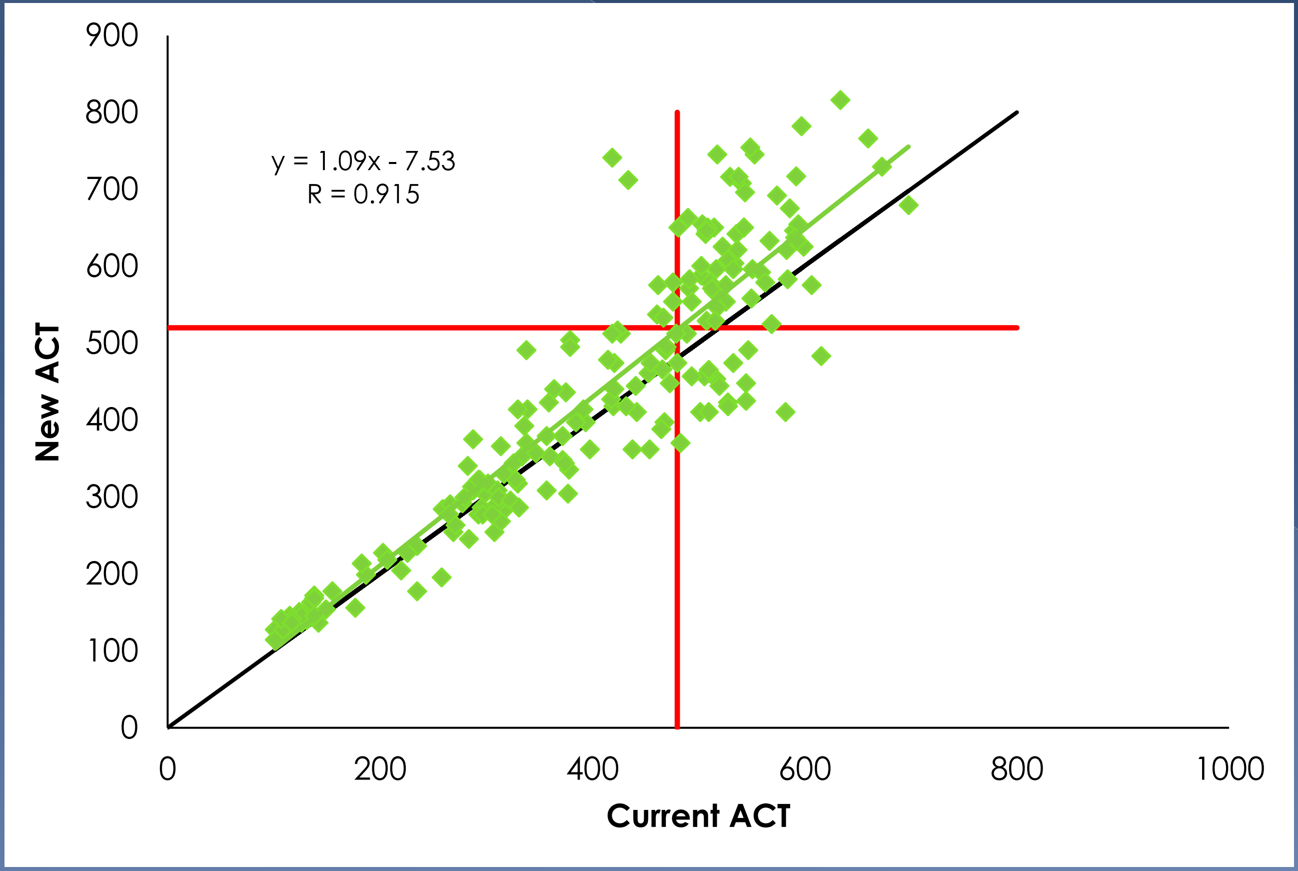
Bland-Altman Plot

- Look for bias
  - Constant or variable?
  - Clinically significant?



Look for clinical differences

- Change of clinical decision limit can maintain current practice standards



Target Time change from 480 to 520 seconds

Evaluate clinical differences

	LAB			
POC A	**>0.1**	**<0.1**		
>0.1	28	1	**PPV**	**97%**
<0.1	2	9	**NPV**	**82%**
	Sensitivity	**Specificity**	**Concordance**	
	93%	**90%**	**93%**	

	LAB			
POC B	**>0.1**	**<0.1**		
>0.1	18	0	**PPV**	**100%**
<0.1	12	10	**NPV**	**45%**
	Sensitivity	**Specificity**	**Concordance**	
	60%	**100%**	**70%**	

Sensitivity & Specificity

- Sensitivity
  - ability of an assay to identify patients with a specific condition (*true positives*)
- Specificity
  - ability of an assay to identify patients without a specific condition (*true negatives*)
- Positive predictive value
  - likelihood that a patient with a positive result (or above the cut-off) truly has the condition
- Negative predictive value
  - likelihood that a patient with a negative result (or below the cut-off) is truly normal

2 x 2 Table

		"True" Result		
		Positive	**Negative**	
New System Result	**Positive**	True positive (TP)	False positive (FP)	Positive predictive value (PPV)
	Negative	False negative (FN)	True negative (TN)	Negative predictive value (NPV)
		Sensitivity	Specificity	Concordance

$$Sensitivity = \frac{TP}{TP + FN}$$

$$Specificity = \frac{TN}{TN + FP}$$

$$PPV = \frac{TP}{TP + FP}$$

$$NPV = \frac{TN}{TN + FN}$$

$$Concordance = \frac{TP + TN}{Total\ Sample\ Number}$$

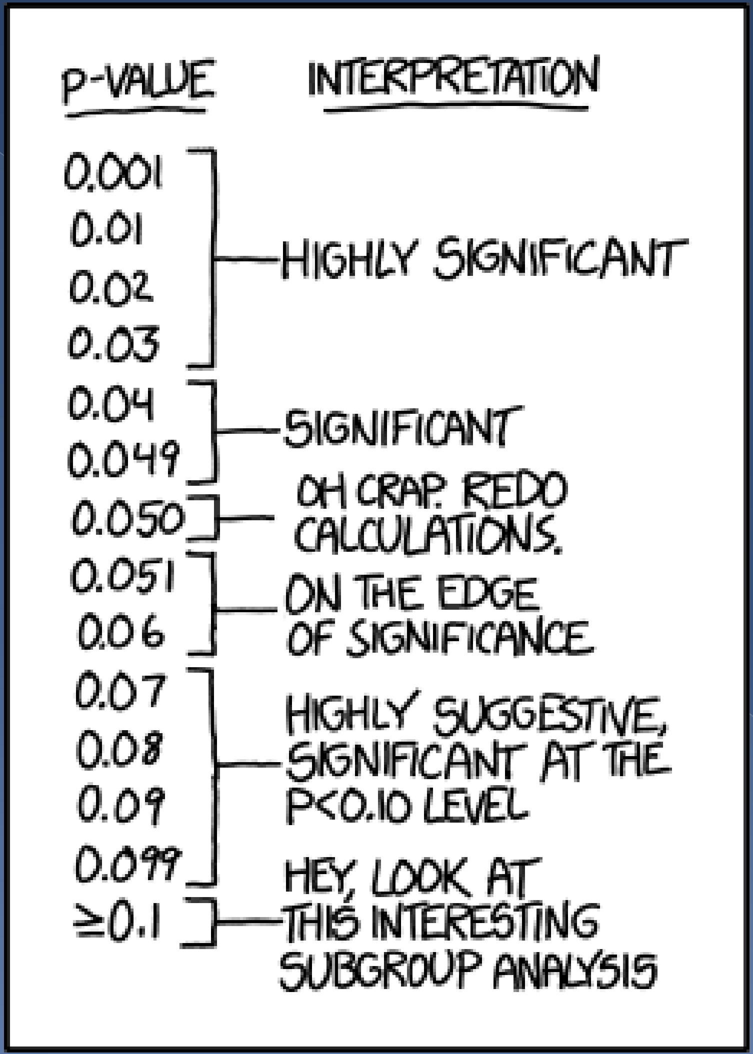
Caveat Emptor

- Qualitative tests always include sensitivity and specificity claims
  - Older products have limited clinical data
    - Only spiked samples evaluated
    - Only frozen clinical samples evaluated
    - Too few samples evaluated
  - Newer products will include confidence intervals
    - Do not want test where CI spans 50% (coin toss)

Probability (p-value)

- Paired t-test
  - Compare the difference between paired samples
  - Null hypothesis is tested
    - mean difference is zero
  - Means of populations compared
  - Assume normal distribution; equal variance
- ANOVA (Analysis of Variance)
  - Compare means of groups of measurement
  - Null hypothesis is tested
    - means of the measured variables are the same
  - Variances of populations compared
  - Assume normal distribution; equal variance

p-value



- xkcd.com 1/26/2015

p-value

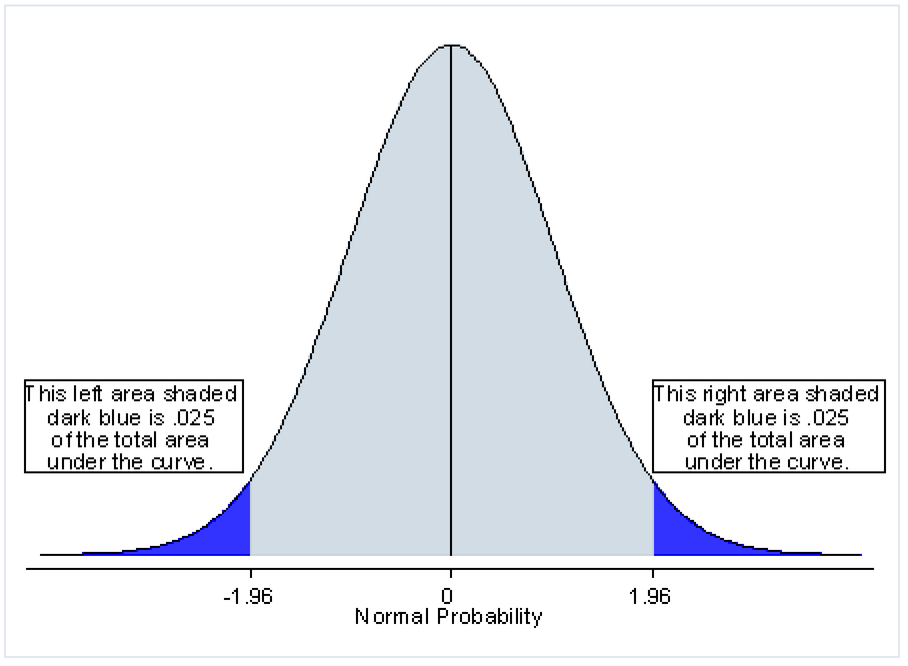
- Statistical significance can be defined at multiple levels
- For diagnostics, generally defined as

  $p \leq 0.05$

  - 95% confidence
  - ~ $\pm$ 2 SD from mean

Interpreting p

- If viewing results of analysis:
  - $p \leq 0.05$ — two samples are different
  - $0.05 < p < 0.1$ — ? trend towards difference
  - $p > 0.1$ — two samples are the same



What else?

- There are as many ways to crunch data as there are people to do it.
- Keep in mind what you are looking for
  - Clinical utility
    - statistical difference may not matter
- Understand what you want BEFORE you collect the data
  - Define studies by the information you want

Remember

- There are three kinds of lies:
  lies, damned lies and statistics.
  - Benjamin Disraeli

- Torture numbers, and they'll confess to anything.
  - Gregg Easterbrook

QUESTIONS?

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