HIV Prevention Trials Network

Comparison Testing Demystified:

Applications of Correlation Testing

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National Institute of Allergy and Infectious Diseases

NIMH National Institute of Mental Health

National Institutes of Health

U.S. Department of Health and Human Services

National Institutes of Health

NIDA National Institute on Drug Abuse

ACKNOWLEDGEMENTS

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HIV Prevention Trials Network

Comparison Testing Demystified

Paul Richardson.

- Why do we need to perform comparison testing?

Mark Swartz.

- How do we perform correlation testing?

Anne Sholander.

- Applications of correlation testing as an alternate to commercial EQA.

Objectives

After this presentation you should be able to:

- Define correlation testing
- Explain why correlation is necessary
- Explain when correlation testing is required
- Define the recommended frequency of correlation
- Explain how to develop acceptability criteria for correlation
- Troubleshoot failed correlation
- Explain applications for correlation testing as an alternative to commercial EQA panels

Definition of Correlation

Correlation:

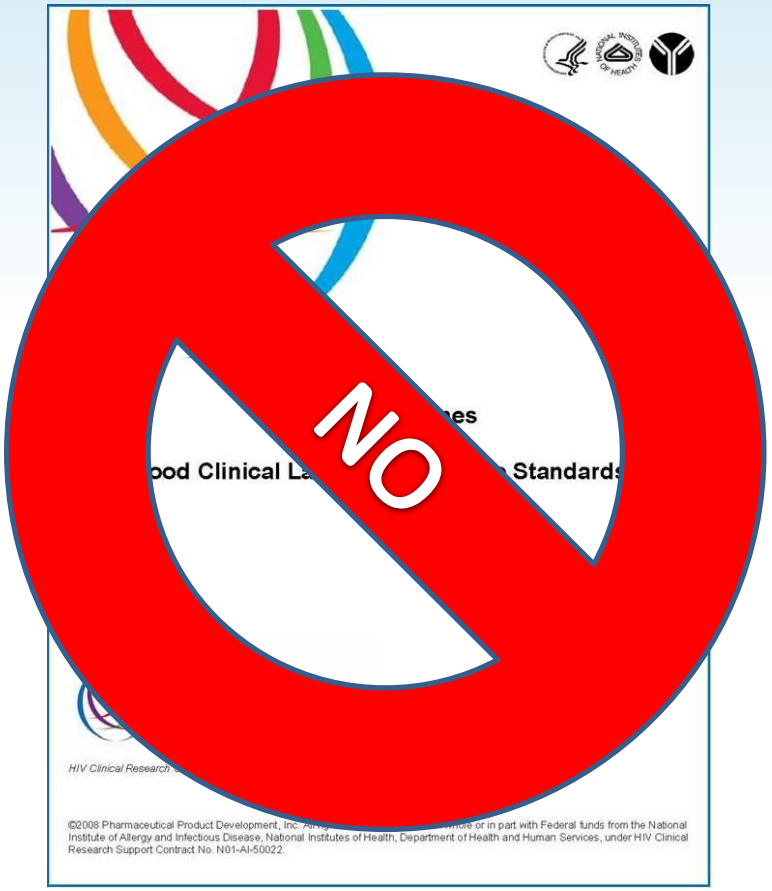
An examination using mathematical or statistical variables of two or more items to establish similarities and dissimilarities.

Comparison Testing

Is it because the guidelines tell us to?

DAIDS Guidelines for Good Clinical Laboratory Practice Standards

Final Version 2.0, 25 July 2011



Is it because the guidelines tell us to?

Parallel testing is discussed but only in terms of new reagent lots.

Do not have time to discuss parallel testing here

Is it because the guidelines tell us to?

But the DAIDS Audit Shell does ask:

Is there a back-up method for each assay ?

Are there periodic comparison checks between the primary and back-up methods?

Comparison Testing

Comparison Testing

Because it is good practice

Because stuff happens and you may need to use a different lab or method

Comparison Testing

Trafford General Hospital. UK 5th July 1929

Comparison Testing

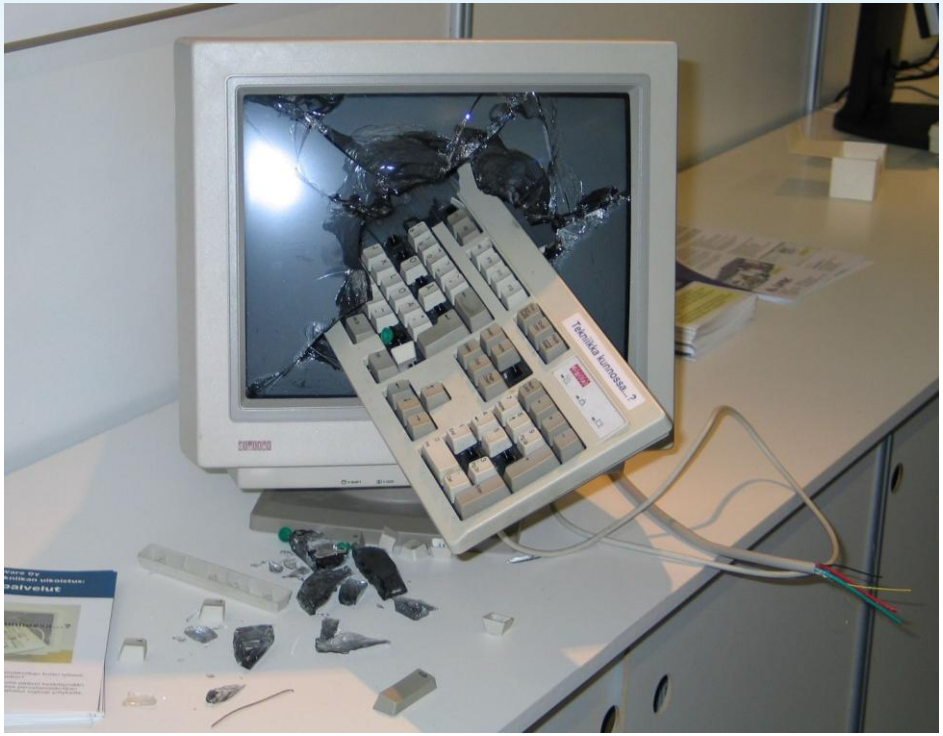
Pathology Lab – Spring Morning 1993

Parallel testing : Back-up comparison

Unexpected staffing problems

Comparison Testing

Broken Lab equipment



Comparison Testing

Delivery problem

Comparison Testing

May fail QA checks such as parallel testing

Old Reagent	New Delivery
152	*19*
73	*21*
487	*794*
298	*112*

Parallel testing : Back-up comparison

Proficiency Testing Problems

Aspartate Aminotransferase U/L

A	31	1.73	UNACC	116
B	110	2.10	UNACC	113
C	279	1.47	ACC	112
D	193	1.55	ACC	114
E	233	1.56	ACC	112

Analyte Score: 60.00%

Bilirubin, Direct mg/dl

Comparison Testing

Need to look for an alternate method

Comparison Testing

Similar instrument within the same laboratory

Comparison Testing

Alternate methodology in an external laboratory

Comparison Testing

Back-up comparison

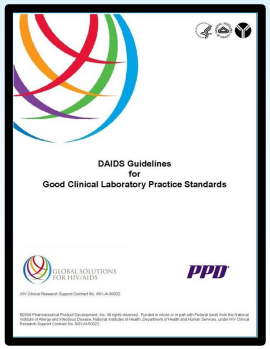
Study-participant specimens tested often to assess comparability of results on a regular basis.

Documentation

Remember GCLP Training:

If it isn't documented, it never happened.

Documentation



Guidelines state labs should retain:

- Instrument printouts
- QC records *-comparison is a QC record*
- Pack inserts
- Certificates of Analysis

Documentation

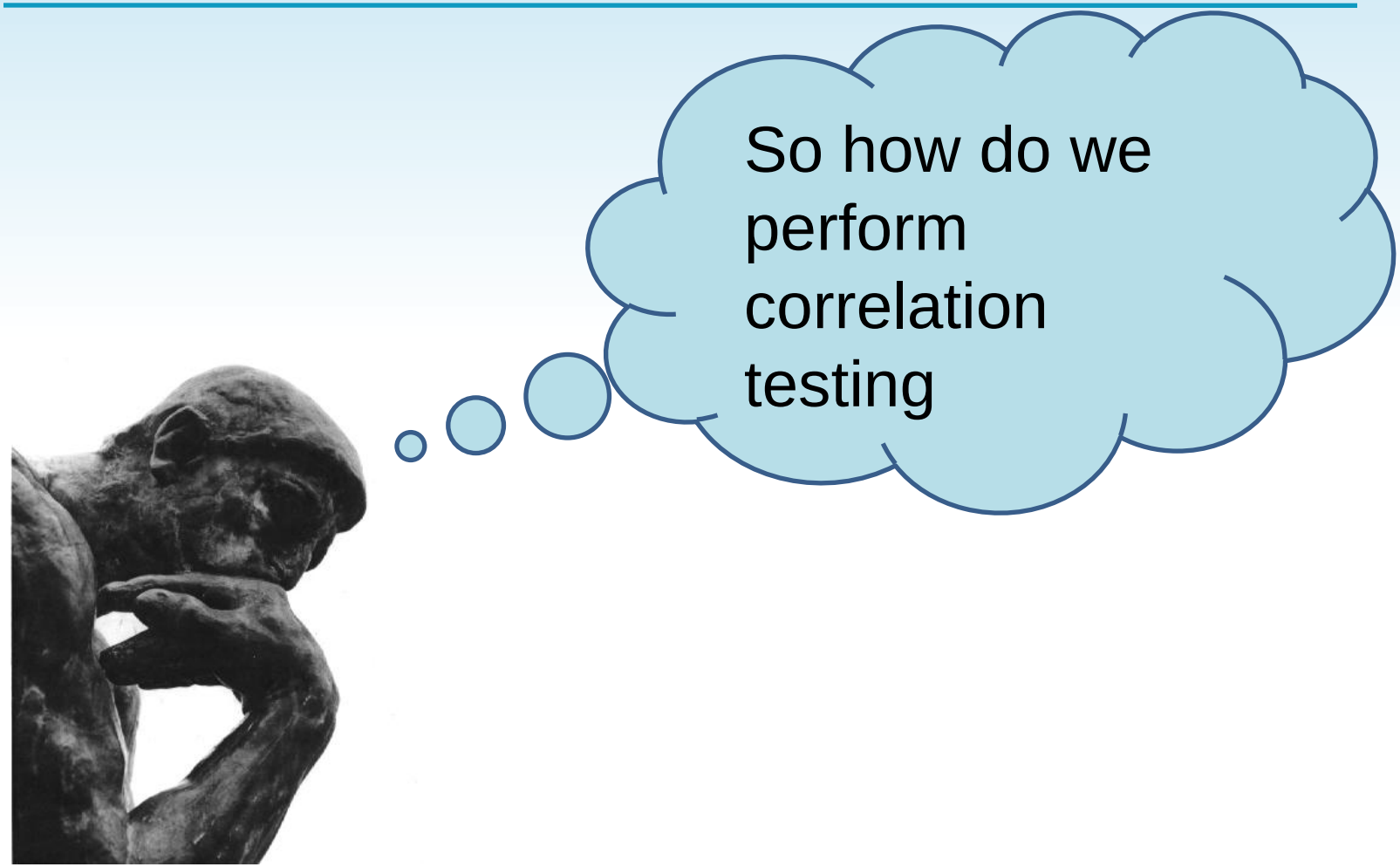
Ensure that the details of your comparison testing are well described in your Quality Manual and site SOPs

Documentation

SOP Should Include:

- What to use for comparison testing
- When to perform
- Acceptability criteria
- How to document acceptability and failures
- What to do if comparison passes
- What to do if comparison fails
- Supervisory review process

Comparison Testing



Comparison Testing Demystified:

Applications of Correlation Testing

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Following the Presentation the PowerPoint Slides will be available on the SMILE Website

www.psmile.org

Acknowledgements

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DAIDS -Daniella Livnat and Mike Ussery

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IMPAACT Network

HPTN - Paul Richardson

Johns Hopkins University - SMILE

Dr. Robert Miller - Principal Investigator
Barbara Parsons - Operation Manager
Kurt Michael - Project Manager
Jo Shim, Mandana Godard & SMILE Staff

National Institute of Allergy and Infectious Diseases

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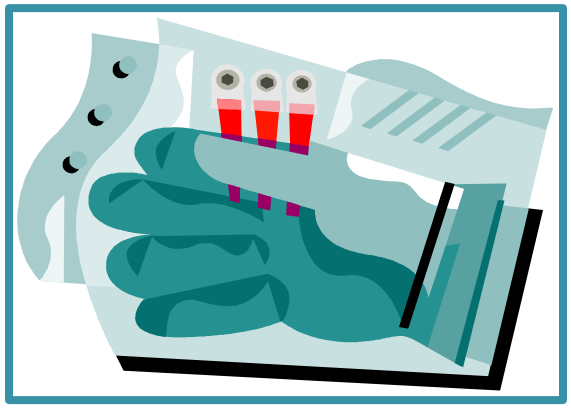
What are we correlating?

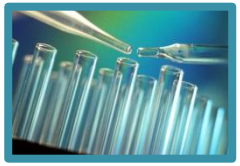
- Primary Instrument
  - Successful EQA performance history
- Backup instrument
  - Same room?
  - Same facility?
  - Clinic?
  - Different lab?

- Same make and manufacturer?
  - Specificity for the analyte
- Same reference ranges?

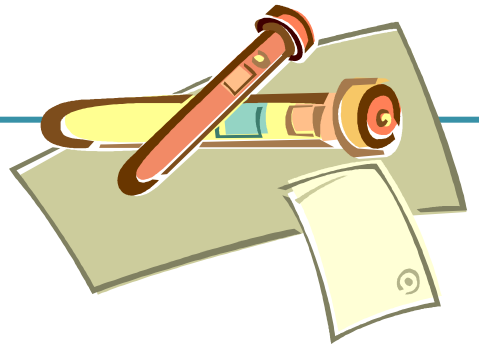
Samples

- Fresh patient samples are ideal
- Stored patient samples are next to ideal
  - How is sample integrity affected by storage?
- Pooled samples
  - Ag/Ab reactions might cause protein precipitation





Samples



- Ideally QC, EQA, linearity, and other standards should not be used
  - Matrix, especially between different instrument makes or models, may mask “true difference” of results
  - Designed for one platform (calibrators/QC)

Samples

- However, it may be necessary to use QC, EQA, linearity, and other standards
  - Lack of patient samples
  - An attempt should be made to span analytical measurement range
  - Volatility of the analyte correlated (storage and transport)
  - Manufacturer designed materials specifically for validation/correlation

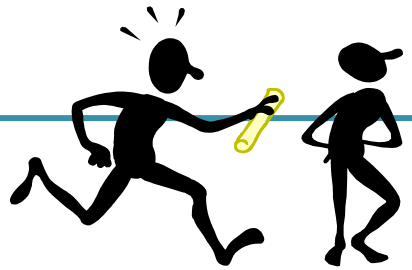
How many? How often?

- No requirements. However, considerations must be made…
  - Type I vs Type II error
    - Type I – detecting an insignificant error
    - Type II – not detecting a significant error
  - An attempt should be made to cover measurement range
  - Ability to acquire proper specimens
  - Availability of reagents
  - Time spent procuring, storing, transporting, measuring samples and evaluating results

Special Instances

- Failure of periodic monitoring of comparison testing
- EQA Failure
- Internal Quality Control result failure
- Reagent or calibrator lot change
- Major instrument maintenance
- Clinician inquiry regarding the accuracy of results

Getting ready…



- Preparing instrumentation
  - All maintenance up to date?
  - Quality Controls within range? Any bias?
- Store samples for the same amount of time, Run on both instruments at the same time

How not to Evaluate Your Data……

	Instr. 1	Instr. 2	Δ
Sample 1	6000.0	60	5940.0
Sample 2	7000.0	70	6930.0
Sample 3	8000.0	80	7920.0
Sample 4	9000.0	90	8910.0
Sample 5	10000.0	100	9900.0

Correlation Coefficient (r) = 1.00

Glucose

	Instr. 1			Instr. 2		
	Replicate 1	Replicate 2	Mean	Replicate 1	Replicate 2	Mean
Sample 1	92	93	92.5	91	87	89
Sample 2	58	59	58.5	58	57	57.5
Sample 3	136	137	136.5	130	127	128.7
Sample 4	302	303	302.5	278	275	276.5
Sample 5	215	214	214.5	209	205	207

Glucose

	Instr. 1			Instr. 2		
	Replicate 1	Replicate 2	Mean	Replicate 1	Replicate 2	Mean
Sample 1	92	93	92.5	91	87	89

Grand Mean = (92.5 + 89)/2 = 90.75

Difference (Δ)= 92.5 - 89= 3.5

% Difference = 3.5/90.75 x 100 = 3.85%

Guidelines for Grading Criteria

- Recommendations based on clinical studies
- Recommendations from clinicians at your institution
- Recommendations based on biological variability
- Minimum requirements set by accreditation agency
- EQA criteria
- Capability of the instrument based on internal imprecision data

Cumulative Statistics

06 MAY 2012

The Johns Hopkins Medical Laborato
The Department of Pathology
QUALITY CONTROL SUMMARY STATISTICS - WEEKL
MAIN CHEMISTRY LAB WEEK ENDING 05-M

COMP / QC TYPE - LOT / PROC	CURRENT WEEK VALUES 'N'	MEAN	- DELTA	SD	- DELTA	CV	T-TEST	F-TEST	CUMULATIVE 'N'	MEAN	SD	CV	REFERENCE MEAN	SD	CV
PHOSPHATE															
BIORAD UNASSAYED CHEM 2-LOT 16632															
HITACHI MODULAR P3, S	2	7.60	0.18	0.000	-0.140	0.0	0.896	0.000	412	7.50	0.157	2.1	7.62	0.25	3.28
GLUCOSE															
BIORAD UNASSAYED CHEM 1-LOT 16631 EXP DATE: : 8/31/13															
HITACHI MODULAR D1,SN	6	86.50	1.33	0.840	-1.220	1.0	2.560	0.223	418	84.67	1.770	2.1	86.20	2.53	2.94
HITACHI MODULAR D2,SN	2	84.00	-2.67	0.000	-1.460	0.0	0.660	0.000	445	85.00	2.140	2.5	86.20	2.53	2.94
ROCHE C701-71,SN1025-	35	84.60	-2.40	1.440	1.440	1.7	1.650	0.000	36	84.67	1.470	1.7	86.20	2.53	2.94
ROCHE C701-72,SN1139-	30	86.13	-0.87	1.500	1.500	1.7	0.570	0.000	31	86.16	1.490	1.7	86.20	2.53	2.94
ROCHE C701-73,SN1139-	33	85.48	0.48	1.180	1.180	1.4	0.410	0.000	34	85.47	1.160	1.4	86.20	2.53	2.94
ROCHE C701-74,SN1139-	35	85.60	-0.40	0.650	0.650	0.8	0.610	0.000	36	85.61	0.640	0.7	86.20	2.53	2.94
HITACHI MODULAR P1,SN	7	85.29	0.61	1.800	0.570	2.1	1.480	0.903	409	86.34	1.900	2.2	86.20	2.53	2.94
HITACHI MODULAR P3, S	2	85.00	-1.29	1.410	0.100	1.7	1.530	0.922	451	86.59	1.480	1.7	86.20	2.53	2.94
BIORAD UNASSAYED CHEM 2-LOT 16632 EXP DATE: : 8/31/13															
HITACHI MODULAR D1,SN	6	285.00	2.80	1.790	-3.230	0.6	1.880	0.131	419	281.26	4.930	1.8	284.00	6.39	2.25
HITACHI MODULAR D2,SN	2	280.50	-8.25	2.120	-2.310	0.8	0.510	0.119	442	282.71	6.150	2.2	284.00	6.39	2.25
ROCHE C701-71,SN1025-	35	281.257	-5.743	4.5300	4.5300	1.6	1.2500	0.0000	36	281.417	4.5700	1.6	286.842	6.390	2.228
ROCHE C701-72,SN1139-	31	284.290	-4.710	5.0100	5.0100	1.8	0.9200	0.0000	32	284.438	5.0000	1.8	286.842	6.390	2.228
ROCHE C701-73,SN1139-	34	283.765	5.765	4.3300	4.3300	1.5	1.3100	0.0000	35	283.600	4.3800	1.5	286.842	6.390	2.228
ROCHE C701-74,SN1139-	33	282.939	-1.061	2.8200	2.8200	1.0	0.3700	0.0000	34	282.971	2.7800	1.0	286.842	6.390	2.228
HITACHI MODULAR P1,SN	7	282.6	2.4	3.46	0.14	1.2	0.15	0.62	405	282.8	4.36	1.5	284.0	6.4	2.3
HITACHI MODULAR P3, S	2	283.5	0.8	2.12	-2.15	0.7	0.39	0.29	452	284.6	3.96	1.4	284.0	6.4	2.3

CLIA Total Allowable Error = 10%

Glucose

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Grand Mean = (92.5 + 89)/2 = 90.75

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Critical Difference

06 MAY 2012

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Evaluation

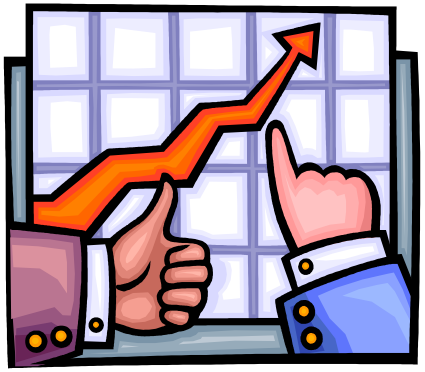
$$\frac{\text{\% Difference (3.85\%)}}{\text{Cumulative CV (2.5\%)}} = 1.54$$

This ratio measures the % Difference as a multiple of the Cumulative CV of the worst performing instrument.

Documentation

Analyte	Instr. 1 Mean	Instr. 2 Mean	Grand Mean	Δ	%Δ	Cume CV	%Diff/CV ratio	Accept. % Diff/CV Ratio	Pass/ Fail
Glucose	92.5	89	90.75	3.5	3.9	2.5	1.5	≤3	PASS
Glucose	58.5	57.5	58	1	1.7	2.5	0.7	≤3	PASS
Glucose	136.5	128.7	132.6	7.8	5.9	2.5	2.4	≤3	PASS
Glucose	302.5	276.5	289.5	26	9.0	2.2	3.6	≤3	FAIL
Glucose	214.5	207	210.75	7.5	3.6	2.2	1.4	≤3	PASS

Troubleshooting



- Different methodologies
- Difference in calibration
- Difference in imprecision
- Difference in reagent lot or shipment (storage)

Troubleshooting cont.

- Difference in lot of calibrators or assignment of values
- Difference in age of calibrators (date opened)
- Difference in reagent life on instrument
- Difference in instrument parameters (dilution ratios, incubation times, etc.)


MUST
CLINICAL & RESEARCH

Correlation as an Alternative to Commercial EQA Panels

How can correlation testing be used to EQA multiple methods, locations, clinics?

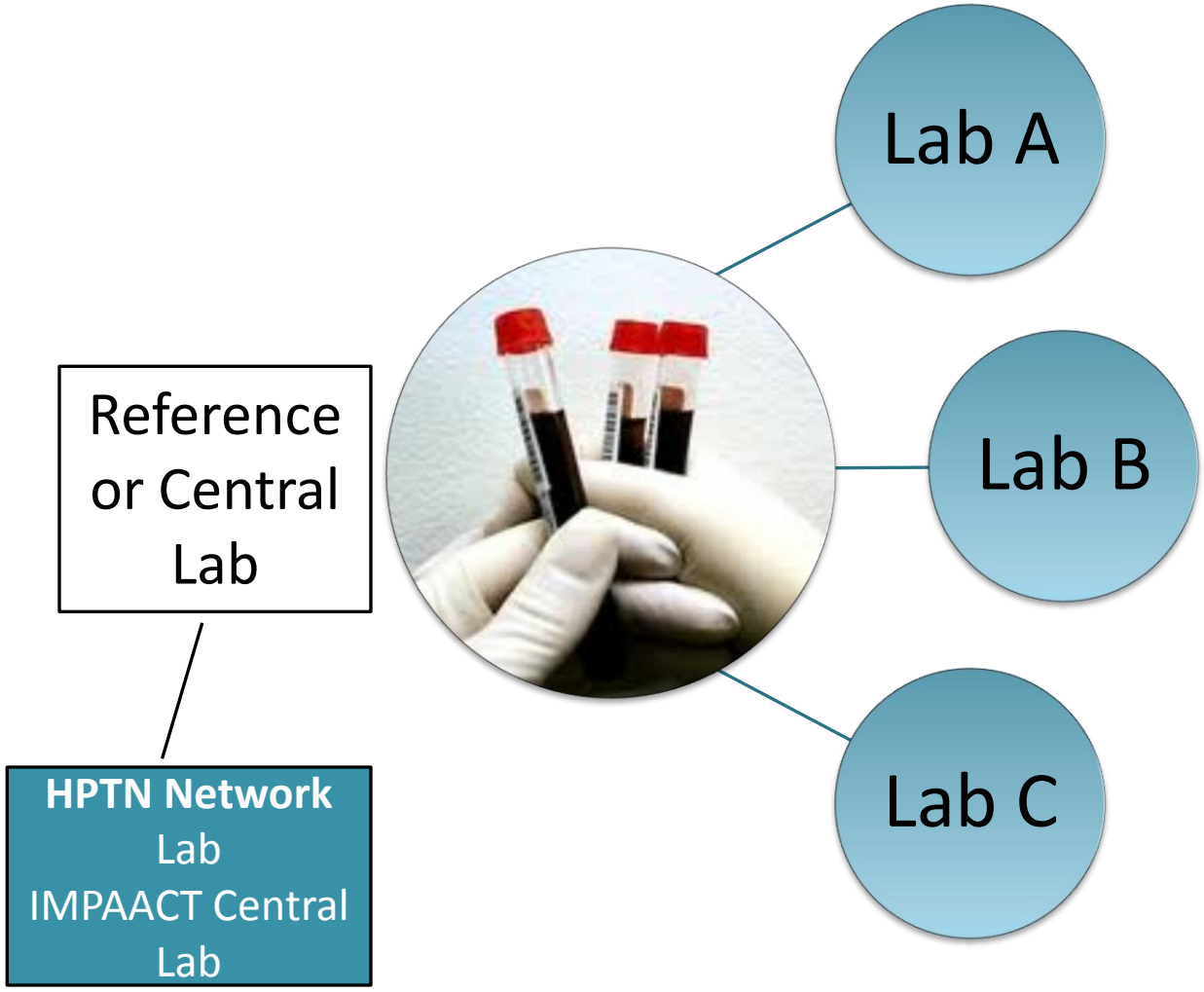
What are the CAP, CLIA, GCLP requirements for EQA of each method?

What are the advantages and disadvantages of using correlation to satisfy these requirements

Some Schemes Currently in Use

- Reference or Central Lab
- Shared EQA Panels
- Parent-Clinic Model

EQA Panels Made by a Reference Lab



How are the results evaluated?

Correlation

Between the reference lab and the local lab

Evaluation

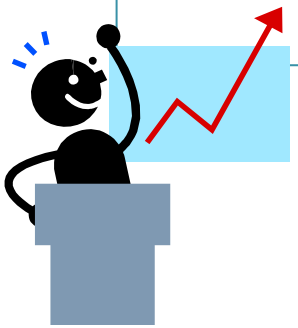
Using SMILE evaluation criteria (composite of CLIA, CAP and Accutest)

Challenges

Methods must be similar

Lack of peer group

Realistic only for qualitative samples



Shared EQA Panels

Commercial EQA

- Instrument 1 or Clinic 1
- Instrument 2 or Clinic 2
- Instrument 3 or Clinic 3

How are the results evaluated?

Correlation

Between the local lab and the peer data collected by EQA provider

Evaluation

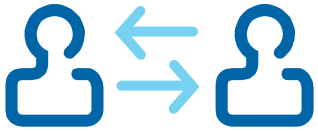
EQA provider's criteria

CLIA TEa criteria

Challenges

Adequate sample volume

Parent-Clinic Model



Parent Lab

Must be participating in commercial EQA

Clinic 1

Clinic 2

Clinic 3

Clinic 4

How are the results evaluated?

Correlation

Between the main (parent) lab and clinics

Evaluation

Acceptability criteria set by the main lab

SMILE suggests using historical CV or 50% of CLIA (quantitative)

Challenges

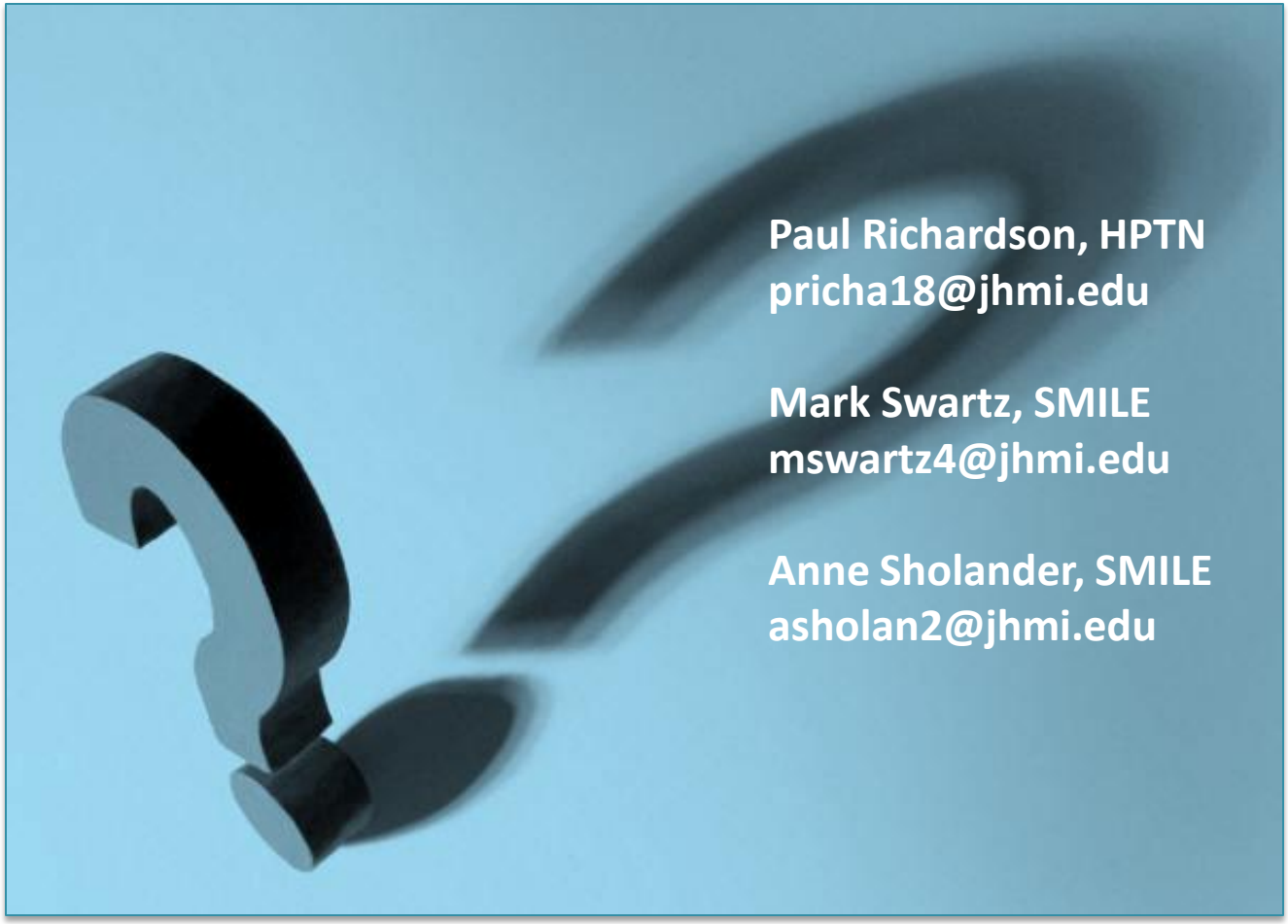
Finding appropriate samples

Stability of samples

In Conclusion….

- Define correlation testing
- Explain why correlation is necessary
- Explain when correlation testing is required
- Define the recommended frequency of correlation
- Explain how to develop acceptability criteria for correlation
- Troubleshoot failed correlation
- Explain applications for correlation testing as an alternative to commercial EQA panels

Questions



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