Principles of effective verification/validation strategies for laboratory analytical methods and reagents

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IFCC Committee on Clinical Laboratory Management - http://www.ifcc.org/ifcc-education-division/emd-committees/c-clm/

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The what and why!

What are we trying to do in verification/validation studies?

- Establish foundation for analytical quality control
- Determine acceptability
- Identify issues/errors/weaknesses not identified by routine QC

Our testing environment is unique…Analyzers, Expertise, Staff, Workload, TAT requirements, Budgets, etc…

Why is it important?

- Test results inform medical decisions
- Erroneous test results cause diagnostic error

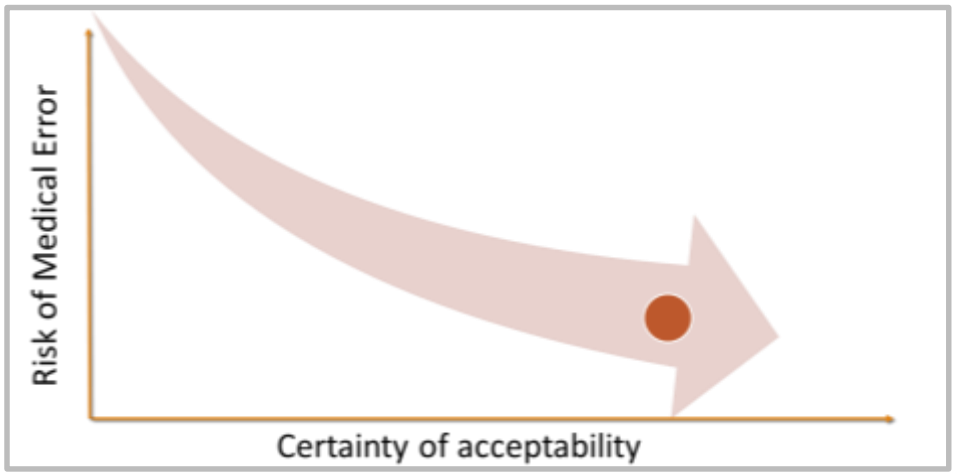
The Risk

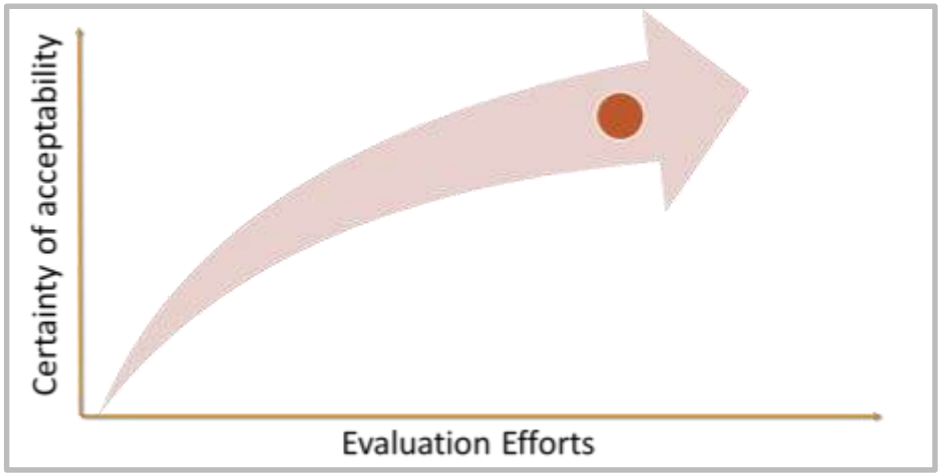
*Laboratory Error ….."**failure of planned action to be completed as intended, or use of a wrong plan to achieve an aim**, occurring at any part of the laboratory cycle, from ordering examinations to reporting results and appropriately interpreting and reacting to them"*

ISO/TS 22367 (2008)

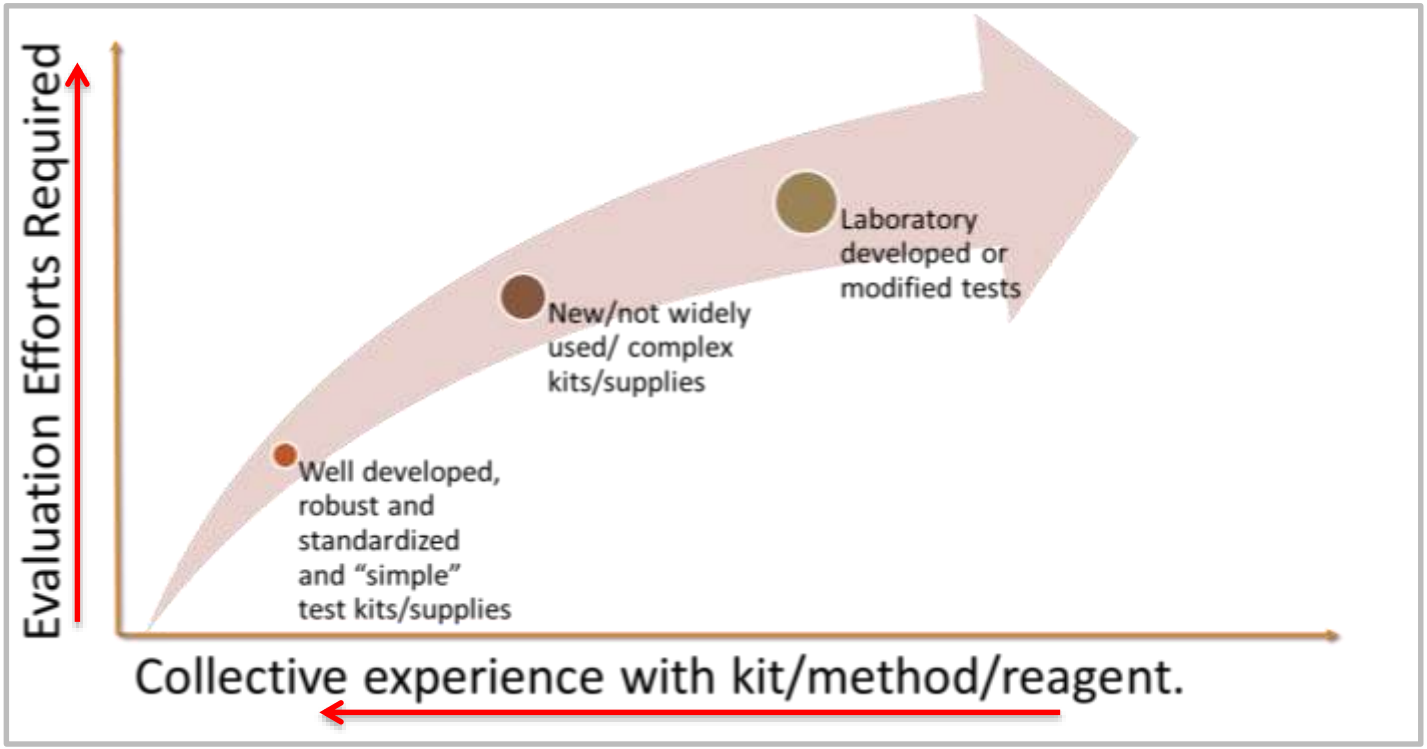
The Risk

Diagnostic Error and Laboratory Test Reagent/Method Acceptability

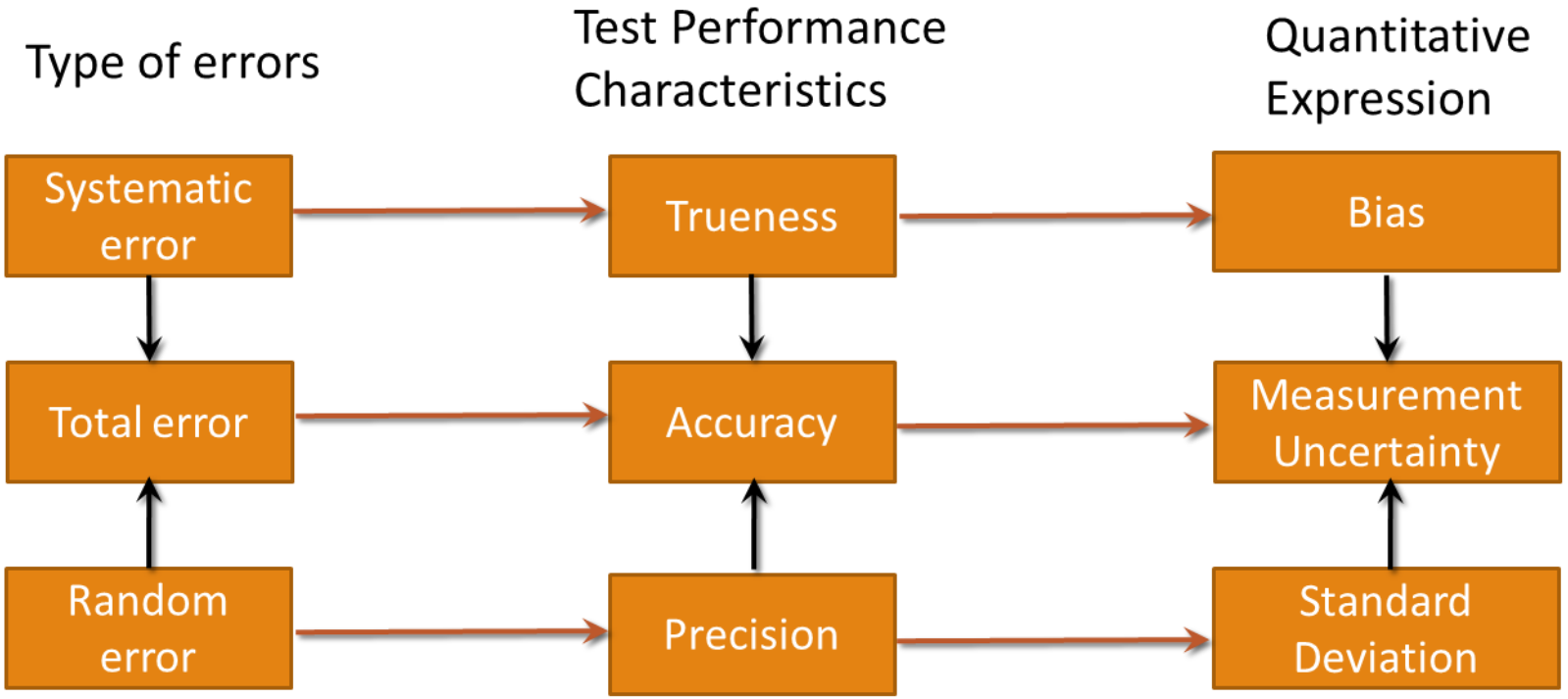




The Risk

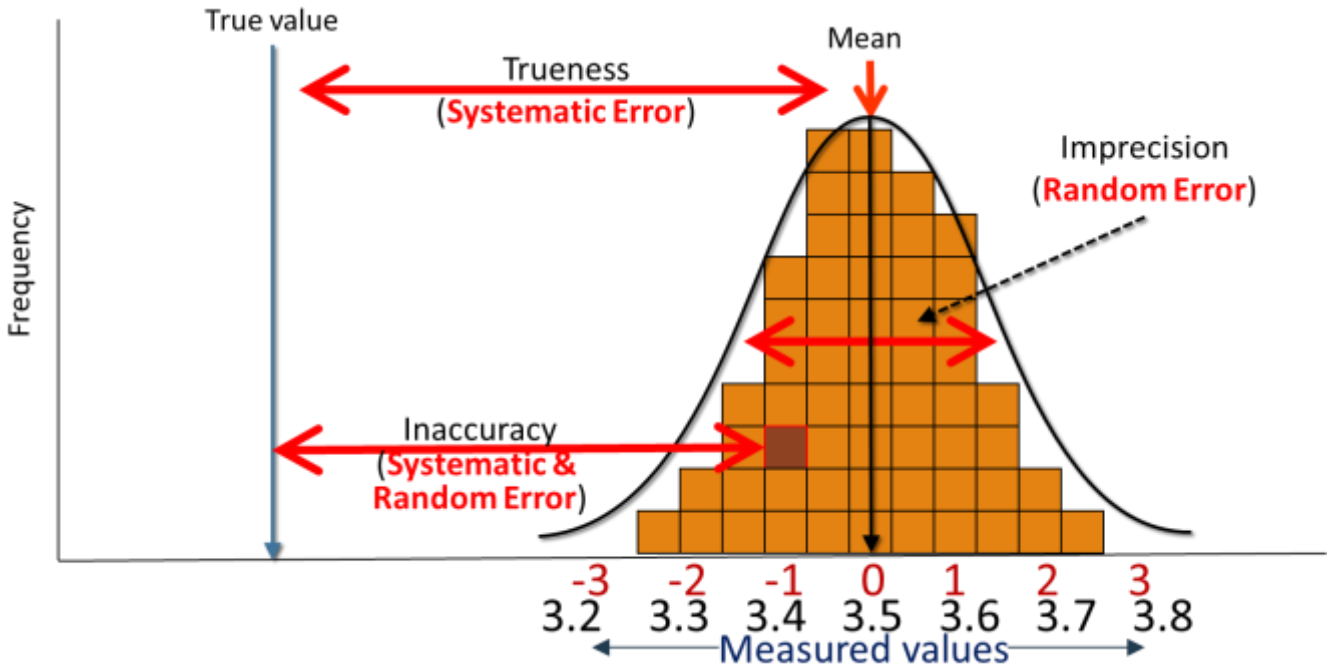

Evaluation Efforts Required
Laboratory developed or modified tests
New/not widely used/ complex kits/supplies
Well developed, robust and standardized and "simple" test kits/supplies
Collective experience with kit/method/reagent.

A Few Definitions



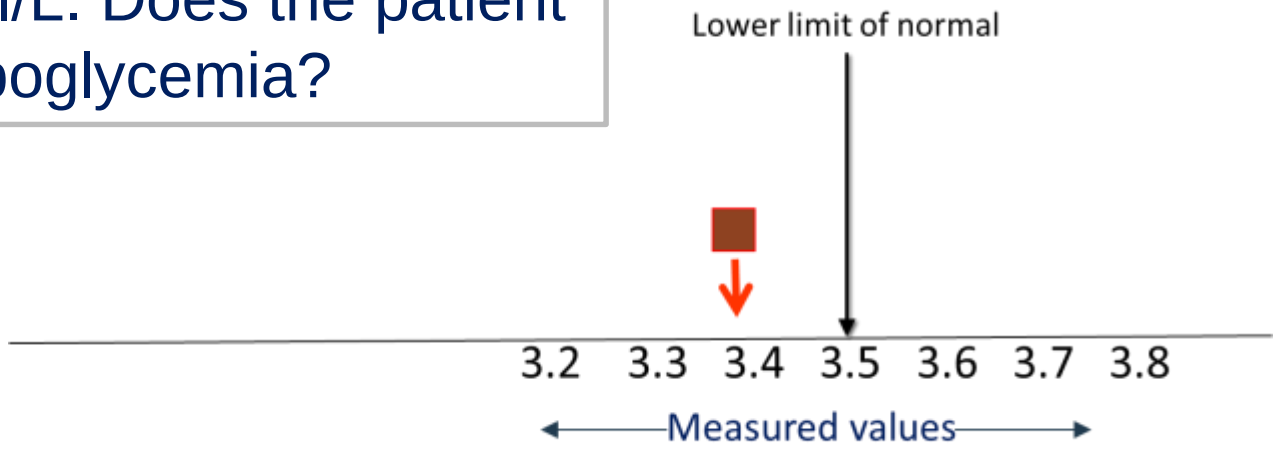
Adapted from: Accred Qual Assur (2006) DOI 10.1007/s00769-006-0191-z

Total Error


True value
Mean
Trueness
(Systematic Error)
Imprecision
(Random Error)
Frequency
Inaccuracy
(Systematic &
Random Error)
-3 -2 -1 0 1 2 3
3.2 3.3 3.4 3.5 3.6 3.7 3.8
Measured values

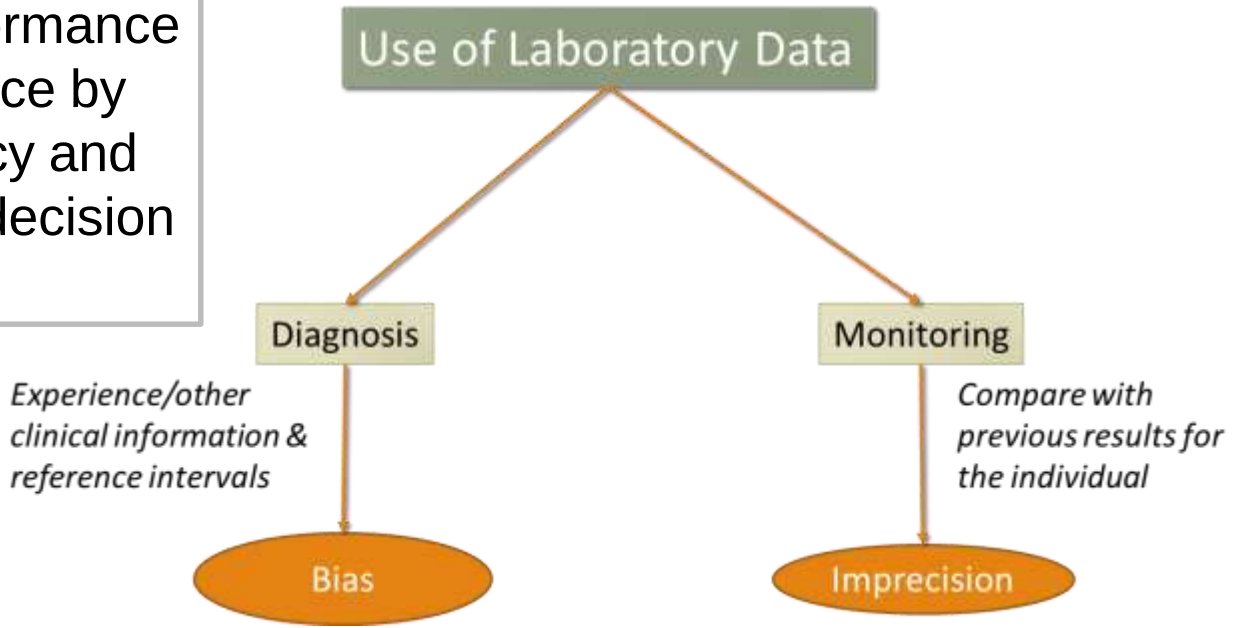
The Clinical Implication

A clinician orders a glucose and the lab reports a value of 3.4 mmol/L. Does the patient have hypoglycemia?



Inaccuracy & Imprecision

Analytical error & performance relates to clinical practice by the impact of inaccuracy and imprecision to clinical decision making.



Diagnostic Test Characteristics

Analytical

- Accuracy
- Precision
- Reportable Range
- Analytical Sensitivity
- Analytical Specificity
- Carry-over
- Others

Clinical

- Diagnostic Sensitivity
- Diagnostic Specificity
- Reference Ranges
- Positive/Negative Predictive Value
- Likelihood Ratios
- ROC Curve
- Others

Evaluation, Verification & Validation

Evaluation – A global term applied to determining analytical and clinical performance characteristics of a new test to a laboratory.

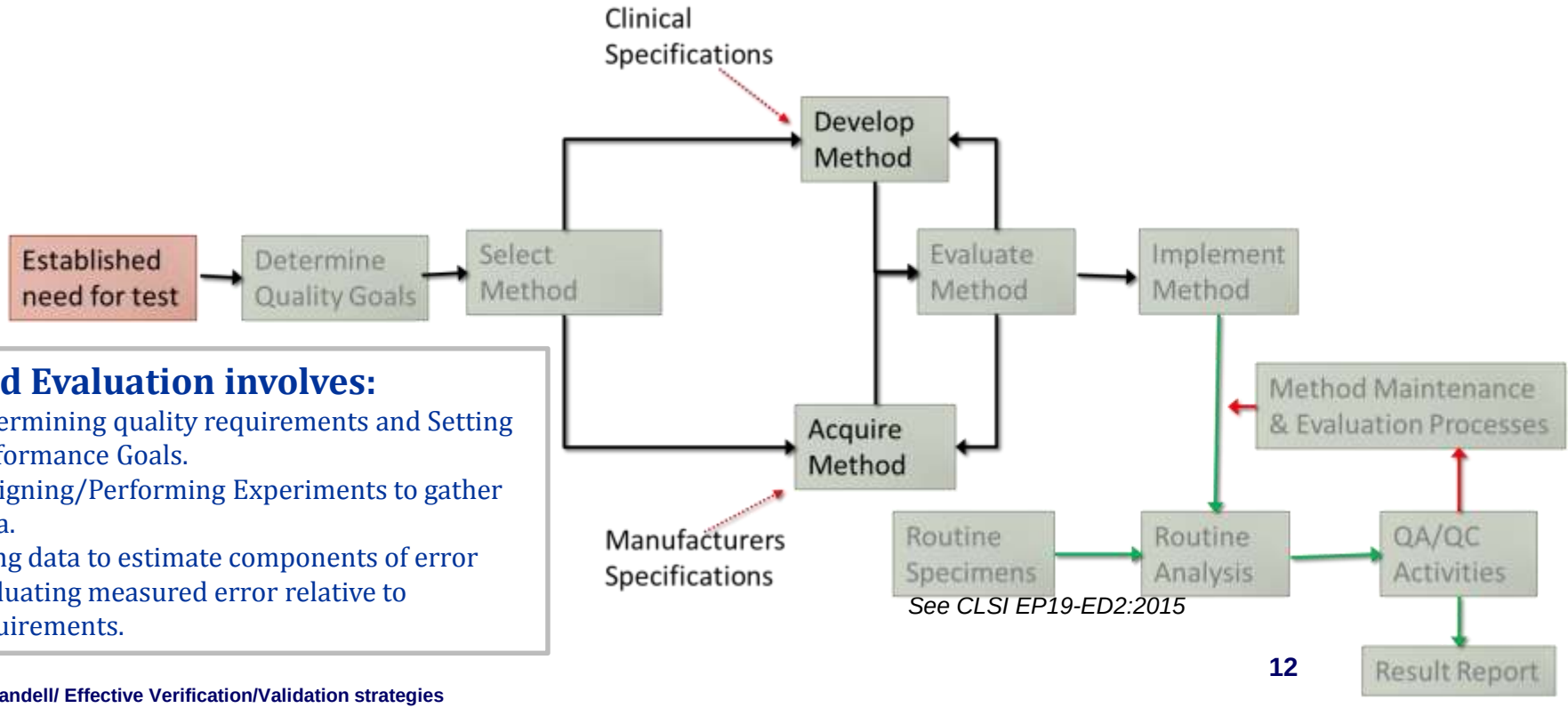
Verification – "*Provision of objective evidence that a given item fulfills specified* ***requirements****."* (JCGM 200:2012)

→ Confirms claimed specifications

Validation – "*verification, where specified requirements are adequate for* ***intended use****."* (JCGM 200:2012)

→ Confirms performance Fit for Purpose

The Evaluation Process



Method Evaluation involves:

1. Determining quality requirements and Setting Performance Goals.
2. Designing/Performing Experiments to gather Data.
3. Using data to estimate components of error
4. Evaluating measured error relative to requirements.

See CLSI EP19-ED2:2015

Diagnostic Test Characteristics

Analytical

- Accuracy
- Precision
- Reportable Range
- Analytical Sensitivity
- Analytical Specificity
- Carry-over
- Others

→

- **Method Comparison**
- **Standard Reference Materials**
- **Reference Methods**

"…Established by comparing results to a definitive or reference method, …verified by comparing results to an established comparative method. "

CAP Laboratory Accreditation Program Checklist.

Diagnostic Test Characteristics

Analytical

- Accuracy
- **Precision**
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- Analytical Specificity
- Carry-over
- Others

- **Within Run**
- **Between Run**
- **Between Day**

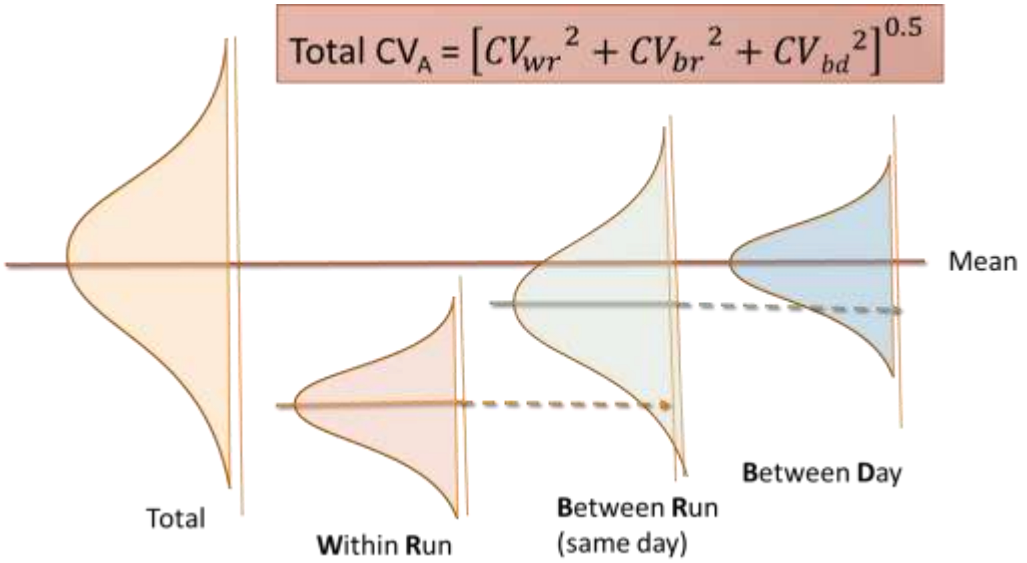
"Established by repeat measurement of samples at varying concentrations or activities within-run and between-run over a period of time."

CAP Laboratory Accreditation Program Checklist.

Deconstructing imprecision

The total within laboratory imprecision is a composite of three different aspects of random variation. Also by:

- Reagent lot
- Calibrator lot
- Calibration frequency
- Operator
- Instrument
- Laboratory



Diagnostic Test Characteristics

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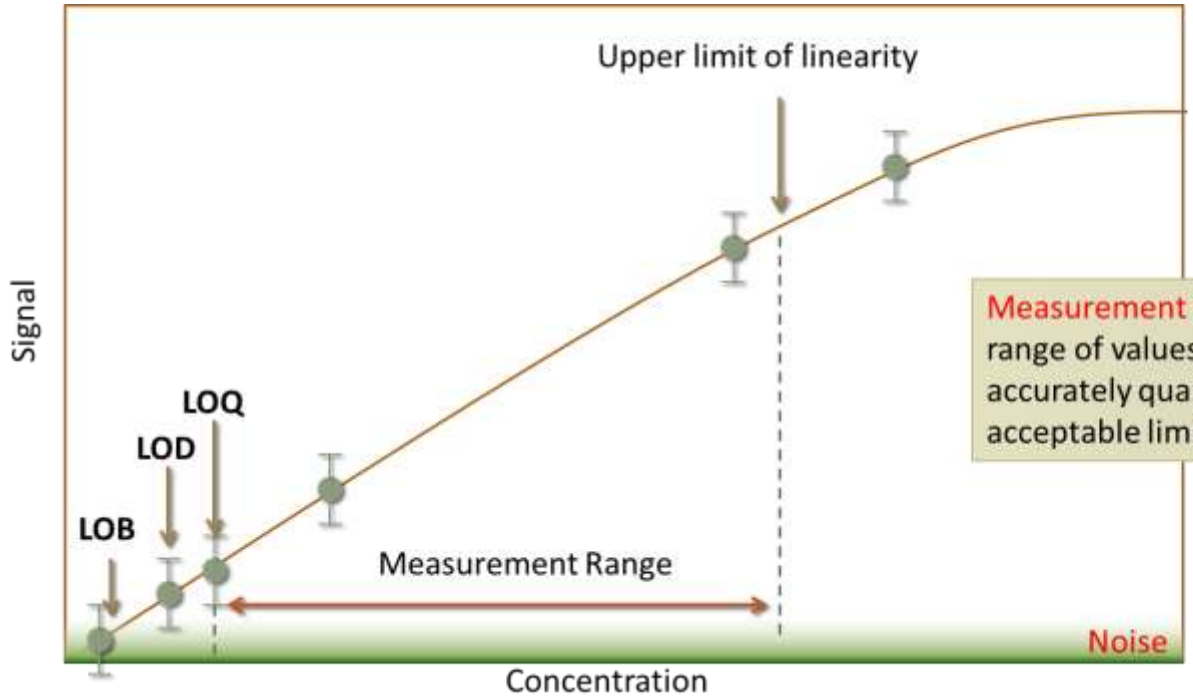
- Carry-over
- Others

- **Limit of Blank**
- **Limit of Detection**
- **Limit of Quantification**
- **Analytical Measurement Range**
- **Clinical Measurement Range**

Important for quantitative methods

Analytical Sensitivity and Reportable Range



Measurement Range is the range of values we can accurately quantify within acceptable limits.

Diagnostic Test Characteristics

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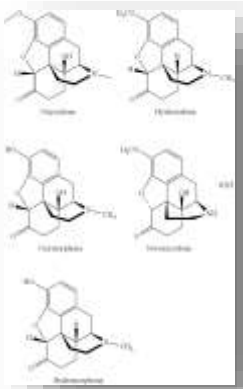
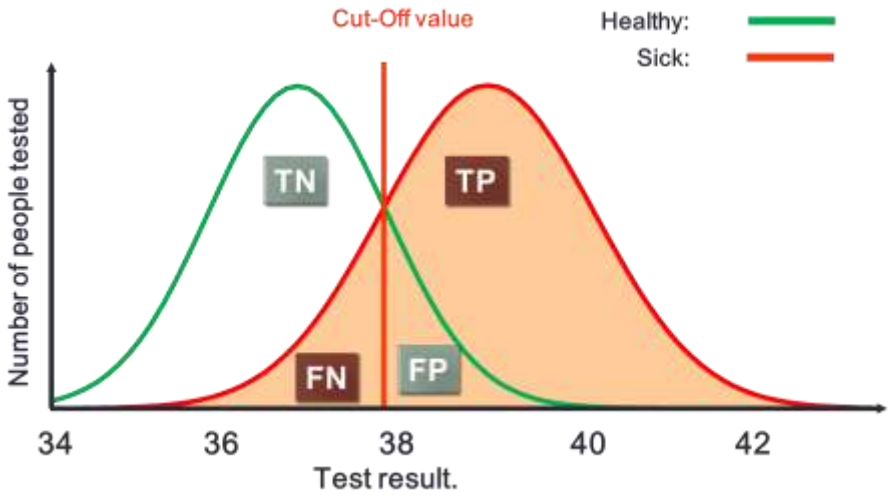


- Interferences
- Cross-reactivity

Related to systematic error (Trueness)

Diagnostic Test Characteristics



		Sickness	
		Present	Absent
Test	+	True Positive	False Positive
	-	False Negative	True Negative

Clinical

- Diagnostic Sensitivity
- Diagnostic Specificity
- Reference Ranges
- Positive/Negative Predictive Value
- Likelihood Ratios
- ROC Curve
- Others

Diagnostic Test Characteristics

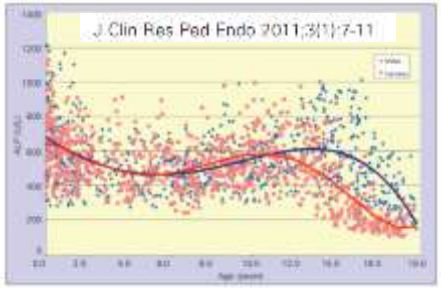
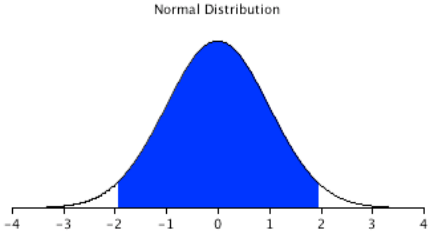
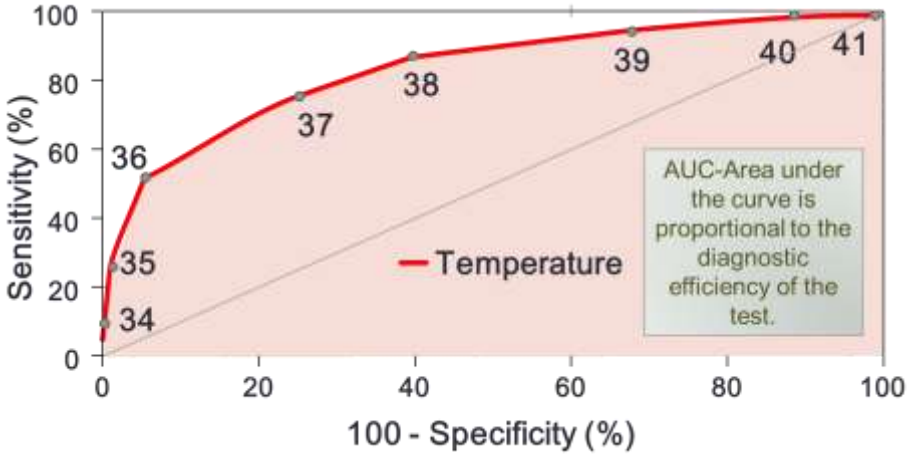


Figure 1. Serum ALP levels according to age showing a tetraphasic course from birth to adulthood



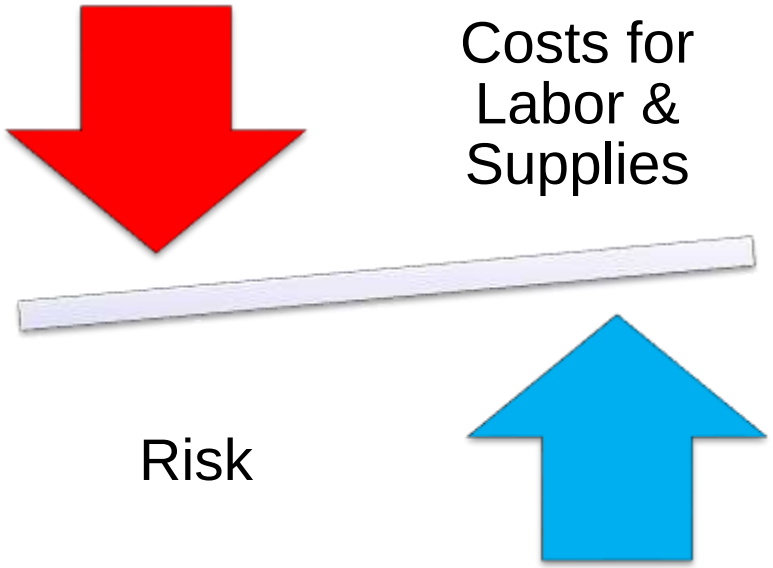


Clinical

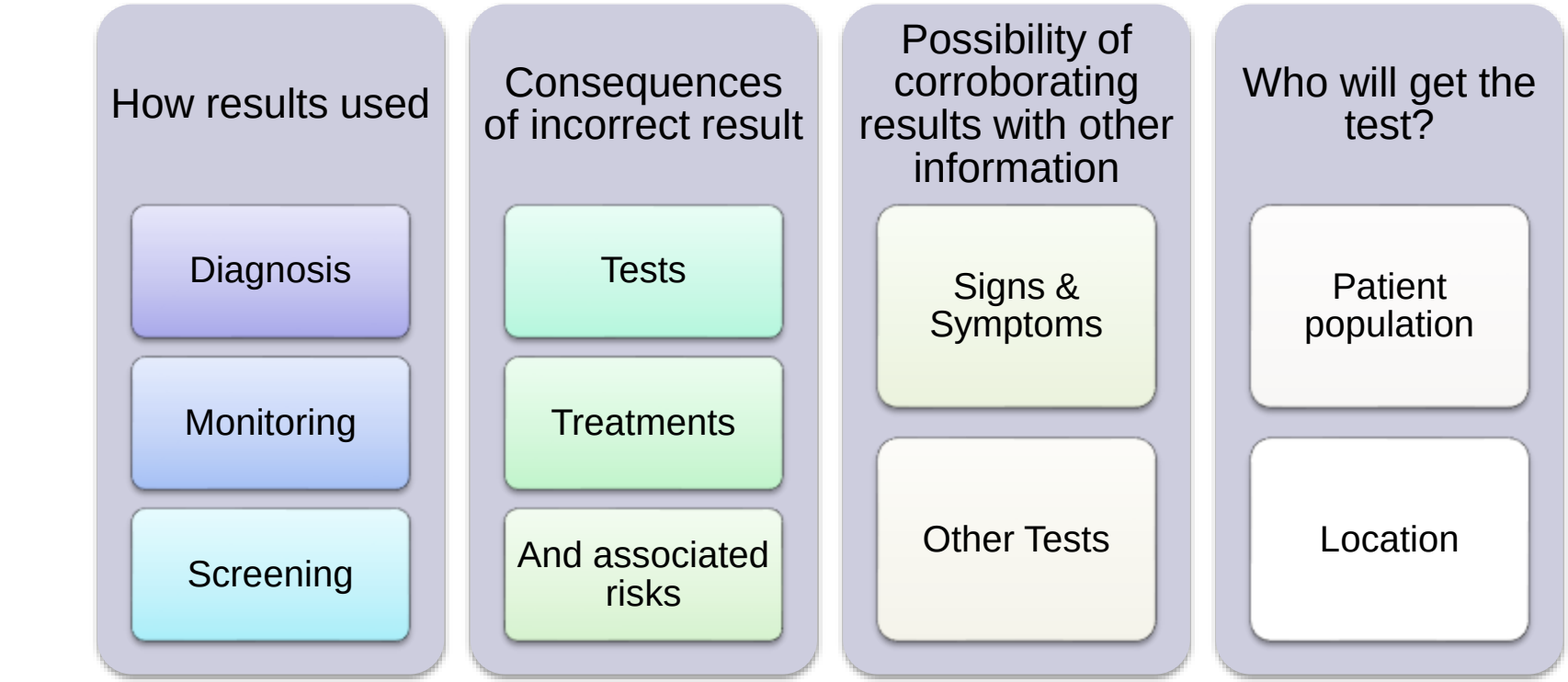
- Diagnostic Sensitivity
- Diagnostic Specificity
- **Reference Ranges**
- Positive/Negative Predictive Value
- Likelihood Ratios
- **ROC Curve**
- Others

How much evaluation?

- Purpose of Test
- Environment
- Quantitative vs. qualitative
- Validation vs. verification
- Available information
- Experience with test
- Implications of error

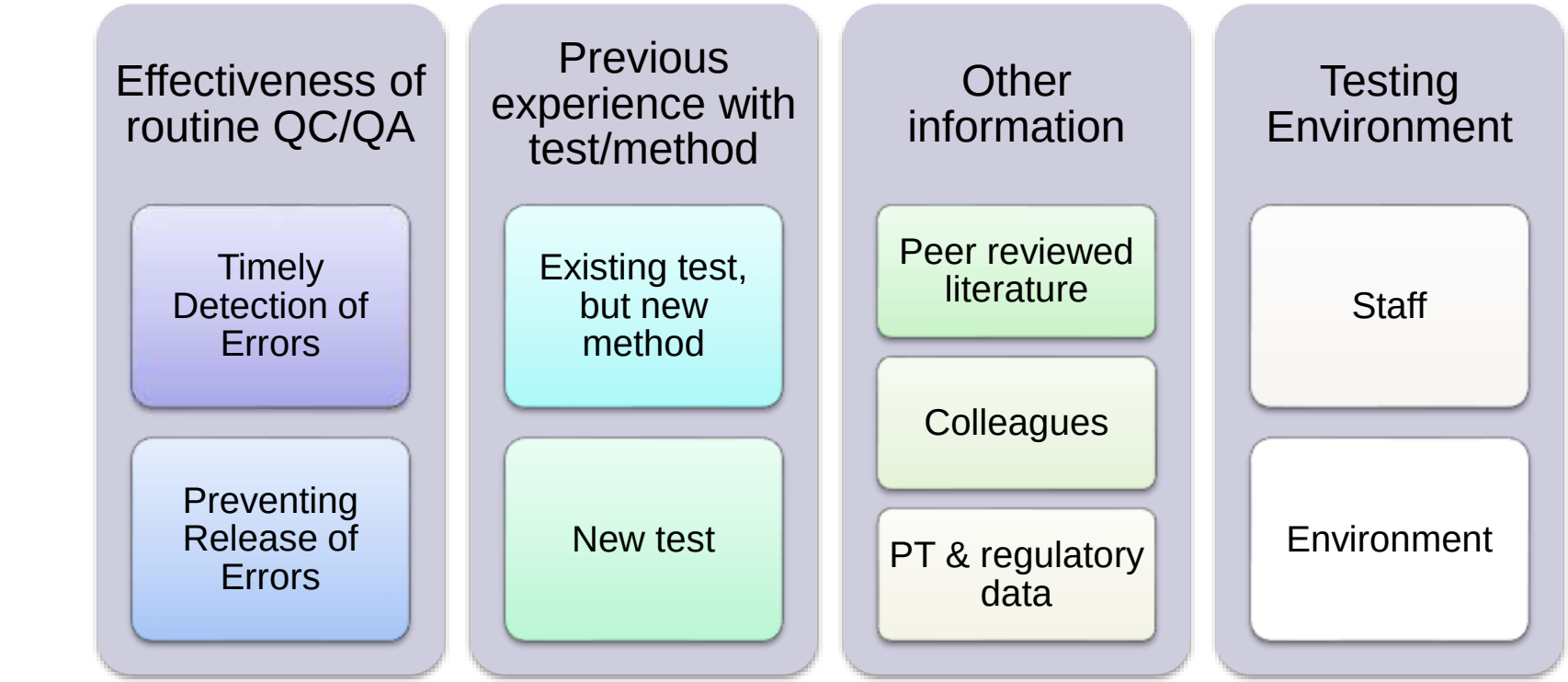


Clinical Use Considerations for New Method



Ref. CLSI EP17-A: 2012

Laboratory Considerations for New Method



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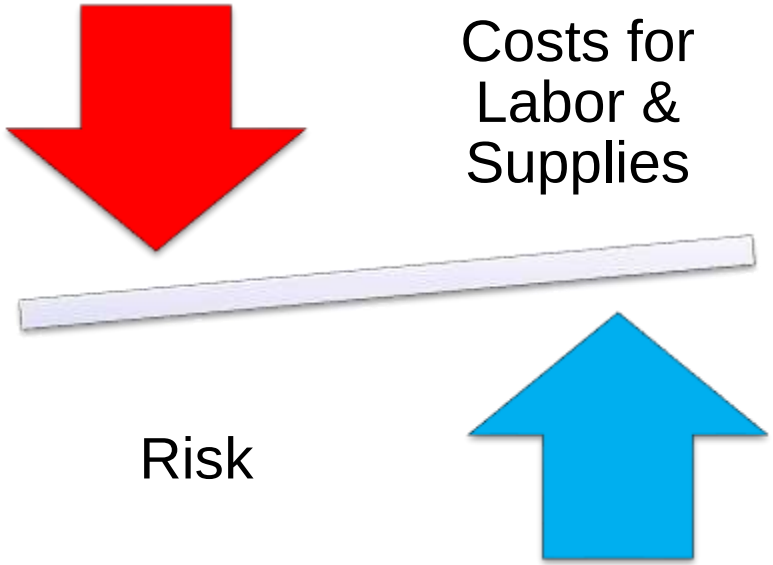
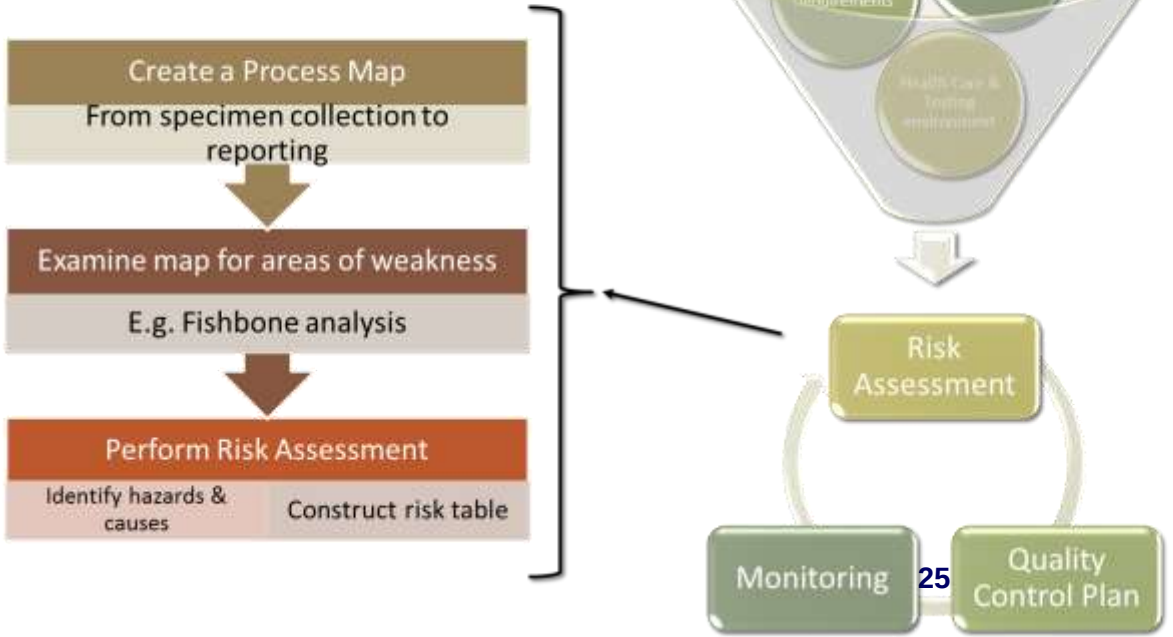
How much evaluation?



How much evaluation?

Careful risk assessment with consideration of both clinical and laboratory factors is helpful is determining the magnitude of evaluation study.



How much evaluation?

Verification

At least

- Accuracy
- Precision
- Reportable Range
- Reference Range

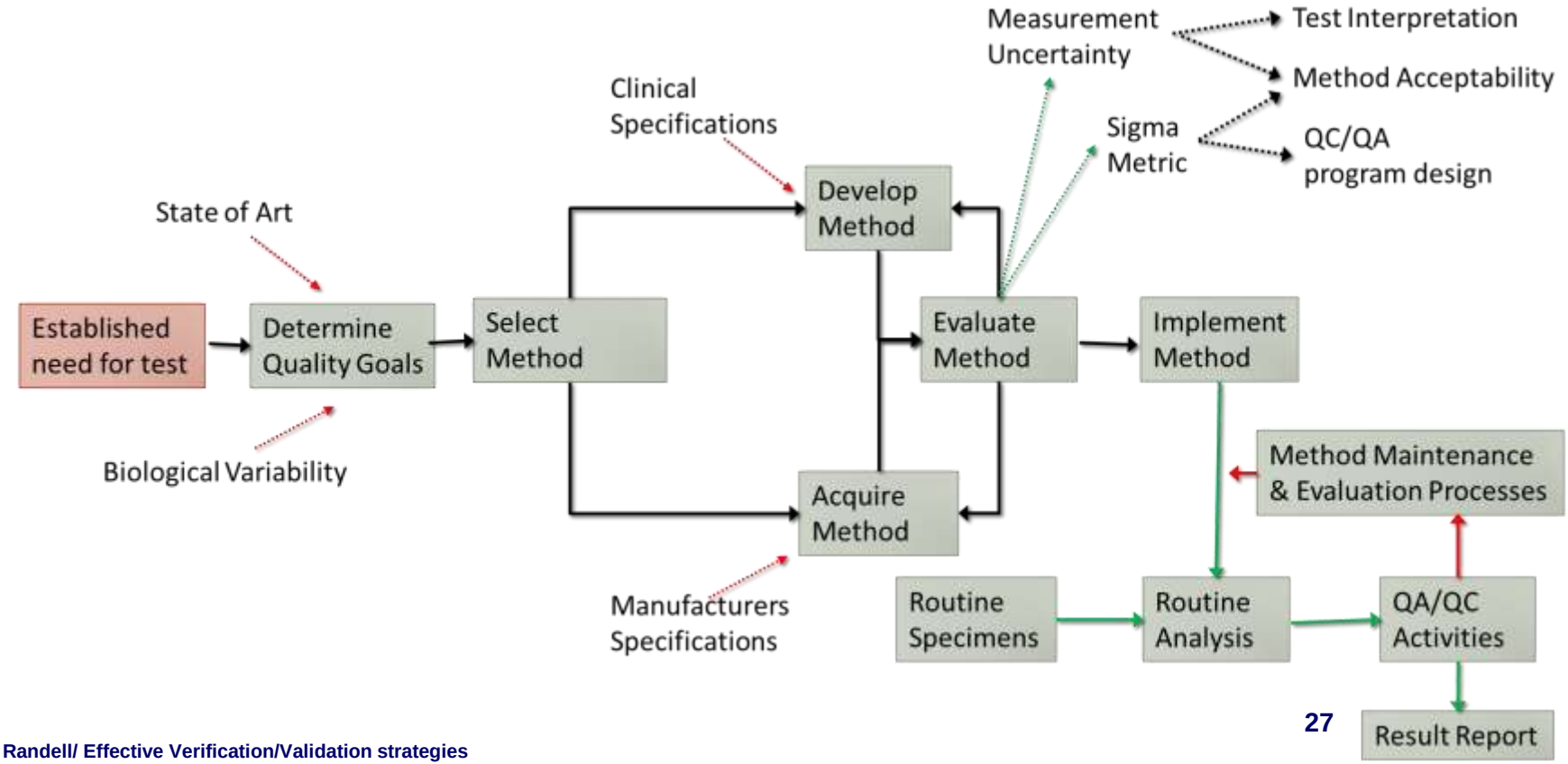
Validation

As much as necessary to confirm suitability for intended use.

Include consideration of:

- Measurement trueness
- Measurement accuracy
- Measurement precision
- Measurement uncertainty
- Analytical specificity
- Analytical sensitivity
- Measurement Range
- Diagnostic specificity & sensitivity
- Reference Range

The Evaluation Process



Lot number Evaluation: The what and why!

Lot number change can change performance.

- Change or instability in component materials (Trueness)
- Transportation and storage (Trueness)
- Incorrect calibration (Trueness)

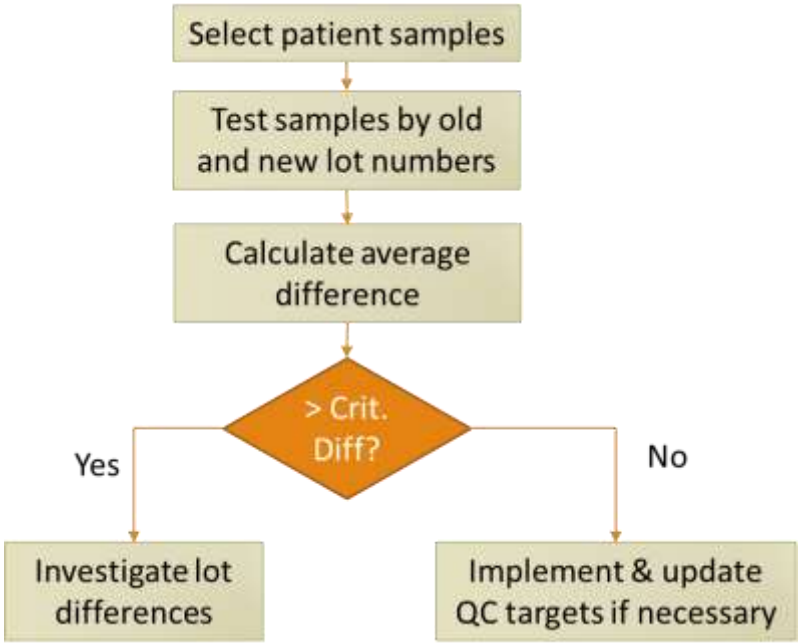
Lot number change can affect QC result only, patient result only, or both.

Why is it important?

- Detect significant changes that may impact PATIENT CARE
- Confirm patient sample result consistency

Lot number evaluation

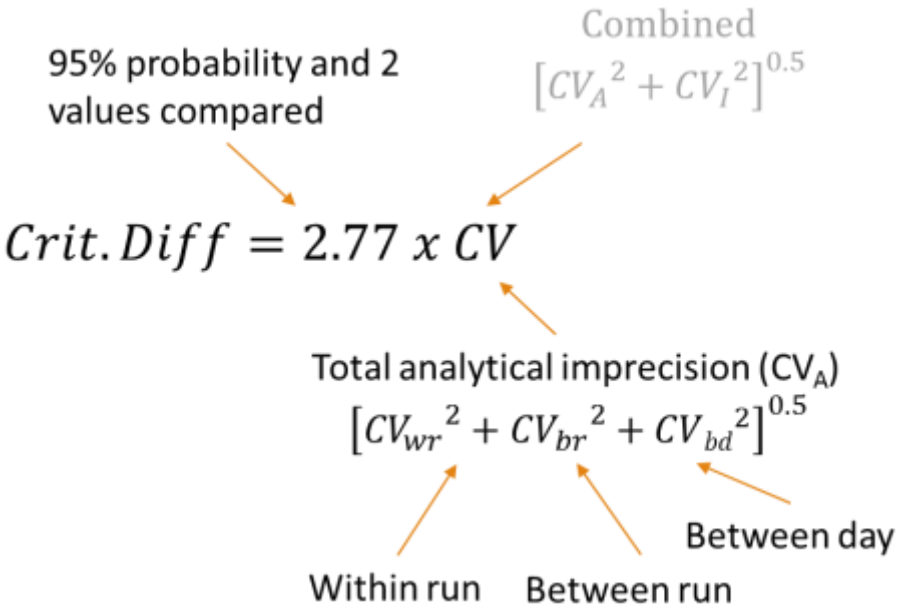
- Rejection criteria is based on:
  - Critical difference
  - Performance goals
- For affiliated hospitals the verification needs only be done once –QC checks sufficient
- New shipment of verified lot - QC checks sufficient.



Ref: CLSI EP26 A:2013

Lot number evaluation

- No universally accepted acceptance criteria.
- Analyte specific
- Based on performance goals
- Be aware of Statistical Power
  - α usually ≤5% (proportion false rejection)
  - ß usually 5 to 20% (proportion false acceptance)
  - Power=1-ß (Desirable is 90 to 95%)
- Increasing statistical power requires more samples and/or more replicates. (i.e. 3 samples with 5 replicates gives same power as 15 samples)



Ref: CLSI EP26 A:2013

Summary

- Validation studies most confirm Fitness for Purpose
- Verification studies must confirm Manufacturers Specifications
- Determining acceptability by validation and verification studies involves assessment of analytical and clinical performance.
- Selection of specific studies depends on consideration of risk and local clinical and laboratory factors.
- Reagent lot number verification is mainly based on determining bias within acceptable limits using patient data .

Useful Resources

Instrument/Method Verification

- https://www.eurachem.org/images/stories/Guides/pdf/MV_guide_2nd_ed_EN.pdf
- http://clsieclipseua.org/