UNDERSTANDING MEASUREMENT UNCERTAINTY

UBC POLQM Conference
November 25, 2019

Dan Tholen

WHY MEASUREMENT UNCERTAINTY ?

- Three phases in conducting a medical laboratory test
  - "Pre-analytic" – gathering, sending, receiving the patient sample
  - "Analytic" – making THE MEASUREMENT (follow manufacturer's instructions)
  - "Post-analytic" – reporting and interpreting the measurement result
- Determination of mu for the analytic phase is required by ISO 15189 and by many experts in the measurement sciences, including experts in medical laboratory testing.
- Pre-analytic and post-analytic sources of error are addressed separately in ISO 15189
- The uncertainty of test measurements is often the smallest factor leading to the probability of an incorrect decision resulting from a lab test

WHY MEASUREMENT UNCERTAINTY ?

- MU might not seem to be important for approved IVDD assays, when use as approved or validated.
- But MU is essential for the inner workings of those IVD Devices – measurements of extremely small changes of electrical transmissions, changes in light intensity or spectra, of microliters of precipitate, of micromiters in cell size – or errors in temperature or pH or pressure and flow can profoundly affect chemical reactions. Patient results and medical decisions can be affected by small variances in basic measurements of voltage, colors, mass, temperature, and length
- Fortunately the medical lab doesn't need to be concerned about MU at this level, in most cases. But what about use of modified methods, or lab-developed methods?

ISO 15189:2012

- **5.5.1.4 Measurement uncertainty of measured quantity values**
- The laboratory shall determine measurement uncertainty for each measurement procedure in the examination phase used to report measured quantity values on patients' samples. The laboratory shall define the performance requirements for the measurement uncertainty of each measurement procedure and regularly review estimates of measurement uncertainty
  - NOTE 1 The relevant uncertainty components are those associated with the actual measurement process, commencing with the presentation of the sample to the measurement procedure and ending with the output of the measured value.

ISO 15189:2012

- **5.5.1.4 Measurement uncertainty of measured quantity values…**
- The laboratory shall consider measurement uncertainty when interpreting measured quantity values. Upon request, the laboratory shall make its estimates of measurement uncertainty available to laboratory users.
- Where examinations include a measurement step but do not report a measured quantity value, the laboratory should calculate the uncertainty of the measurement step where it has utility in assessing the reliability of the examination procedure or has influence on the reported result.

ANALYTIC MEASUREMENT UNCERTAINTY ?

- Within run precision – differences between results for the same sample in the same run
- Between run precision – differences between results for the same sample in different runs
  - Different time (within requirements for hold time)
  - Different technicians
  - Different equipment – any differences between platforms that might be used (or other equipment such as balances, pipettes, thermometers, etc.).
- Bias or systematic error – relative to some reference (e.g., SRM, reference method). Or differences in reagent lots.

WHAT IS MEASUREMENT UNCERTAINTY ?

VIM:

- **measurement uncertainty** the dispersion of the quantity values being attributed to a measurand, based on the information used
  - *Definition, equipment (platform), technician, time*

- **definitional uncertainty** component of measurement uncertainty resulting from the finite amount of detail in the definition of a measurand

RELEVANT DOCUMENTS

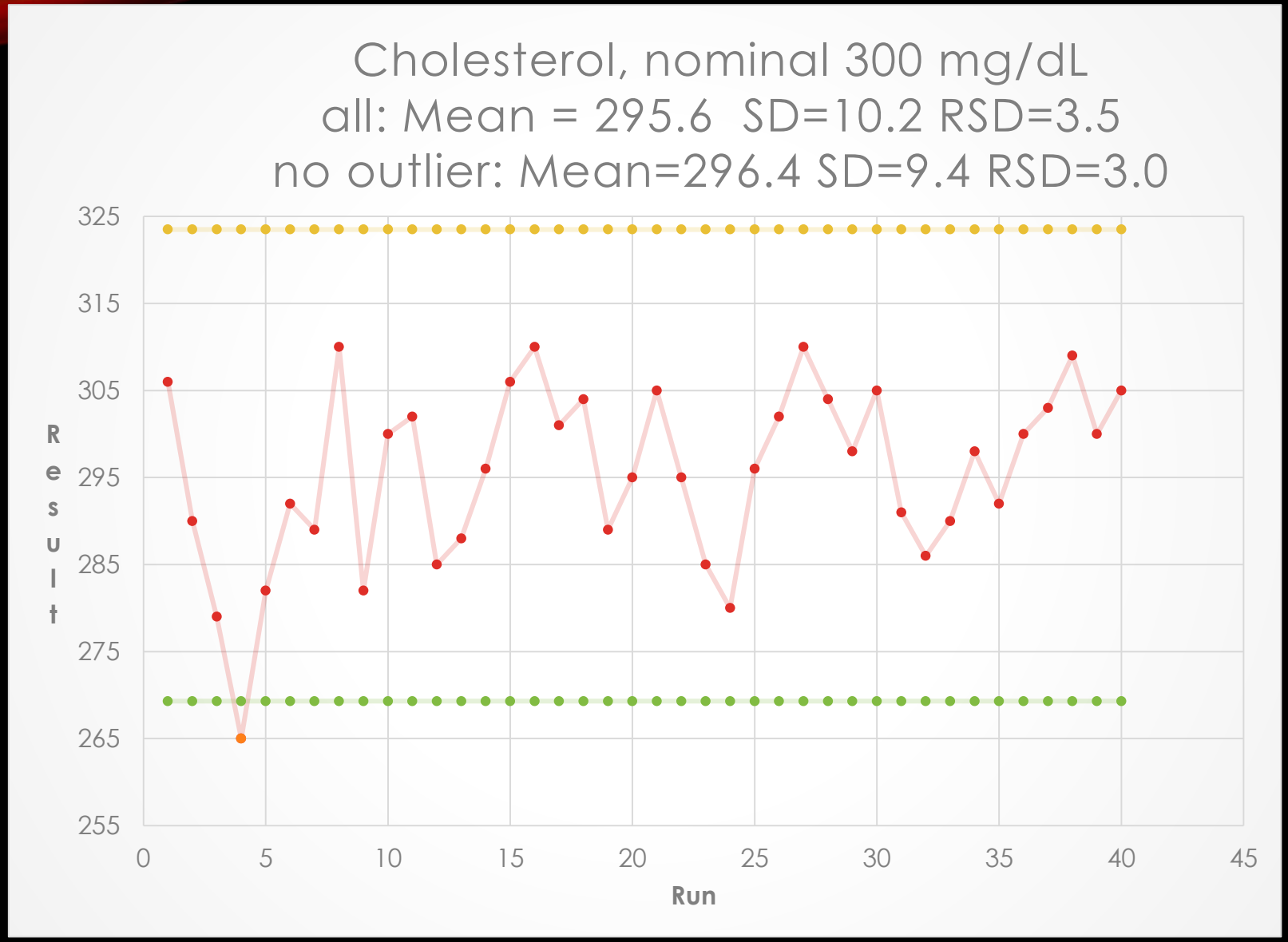
- **ISO 15189:2012** Medical laboratories — Requirements for quality and competence
- **ISO/IEC 17025**:2017 General requirements for the competence of testing and calibration laboratories
- **ISO/TS 20914:2019** Medical laboratories — Practical guidance for the estimation of measurement uncertainty
- **ISO 21748:2017** Guidance for the use of repeatability, reproducibility and trueness estimates in measurement uncertainty evaluation
- **A2LA P903:2019** (draft) Policy on Estimating Measurement Uncertainty for ISO 15189 Testing Laboratories
- **A2LA P103b:2018** Policy on Estimating Measurement Uncertainty for Life Sciences Testing Labs

ISO/TS 20914:2019 Medical laboratories — practical guidance for the estimation of measurement uncertainty

- **Scope:** This document provides practical guidance for the estimation and expression of the measurement uncertainty (MU) of quantitative measurand values produced by medical laboratories.
- Quantitative values produced near the medical decision threshold by point-of-care testing systems are also included in this scope
- This document also applies to the estimation of MU for results produced by qualitative (nominal) methods which include a measurement step. It is not recommended that estimates of MU be routinely reported with patient test results, but should be available on request.

ISO/TS 20914:2019

- Procedure: Use routine QC variation as an evaluation of measurement uncertainty
  - Over time, technicians, equipment
  - Covers all relevant steps in measurement process
- Standard Deviation of QC results can be used as an estimate of measurement uncertainty
  - Appropriate for level of analyte (concentration)
  - If QC covers all major sources of uncertainty
- If a correction is made for bias, then there is some additional uncertainty due to the correction $u = \sqrt{(s^2_{QC} + u^2_b)}$


Cholesterol, nominal 300 mg/dL
all: Mean = 295.6 SD=10.2 RSD=3.5
no outlier: Mean=296.4 SD=9.4 RSD=3.0
325
315
305
295
285
275
265
255
Result
0
5
10
15
20
25
30
35
40
45
Run

A2LA POLICY P903 (revised)

- Policy for implementation of ISO 15189 per ILAC MRA
  - Also approved for USA CLIA ‘88 requirements
- Revision is in draft stage – approved unanimously by Medical Technical Advisory Committee (MEDTAC), awaiting formal approval by A2LA internal process for policy approval.
- Original policy is 28 pages, consistent with full GUM (bottom-up approach) and with various top-down approaches

- Revision 10 pages, consistent with ISO/TS 20914, ISO 21748, A2LA P103b

A2LA POLICY P903 (revised)

- Policy classifies test methods
- Depending on classification, various approaches can be used to evaluate measurement uncertainty
  - Standard deviation (or RSD) from routine QC
  - Reproducibility of validated test method (e.g., IVDD test kit information)
  - Bottom-up approach (i.e., GUM) involving mathematical modelling and propagation of uncertainty components

A2LA POLICY P903 (revised)

- Policy classifies test methods
- **Category I**: Test Methods that are reported on a qualitative basis, or on a categorical or nominal scale.
- **Category II**: Well-recognized test methods - those methods that specify limits to the values of the major sources of uncertainty of measurement (usually as considerations in the instructions) and specify the form of presentation of calculated results. This category includes methods or devices approved by the US FDA (not modified methods)
- **Category III**: All other methods (including modified methods)

A2LA POLICY P903 (revised)

- Approaches to use for different classifications of methods
- **Category I**: No uncertainty evaluation needed (could have information of false positive and false negative rates, or sensitivity).
- **Category II**: Evaluation of uncertainty from available data
  - Precision data from an interlaboratory comparison per ISO 5725-2
  - Internal validation study or QC data over a period of time
- **Category III**: Can use available data as for Category II when available. If not available then use GUM model (mathematical model, influence factors, propagation of uncertainty)

WHY MEASUREMENT UNCERTAINTY?

- Understanding Measurement uncertainty completes the circle of QC
- A method might have QC "in control" – but are the control limits tight enough so that when results "pass QC", are errors small enough that a medical decision would not be affected?
- A method can be operating within its claimed precision performance (repeatability and reproducibility), but could medical decisions be affected within that reproducibility?
- And it is always important to have an understanding of variability in results caused by common factors – differences between technicians, reagent lots or support equipment.

THANK YOU FOR YOUR ATTENTION