Blood Lead Measurement Challenges

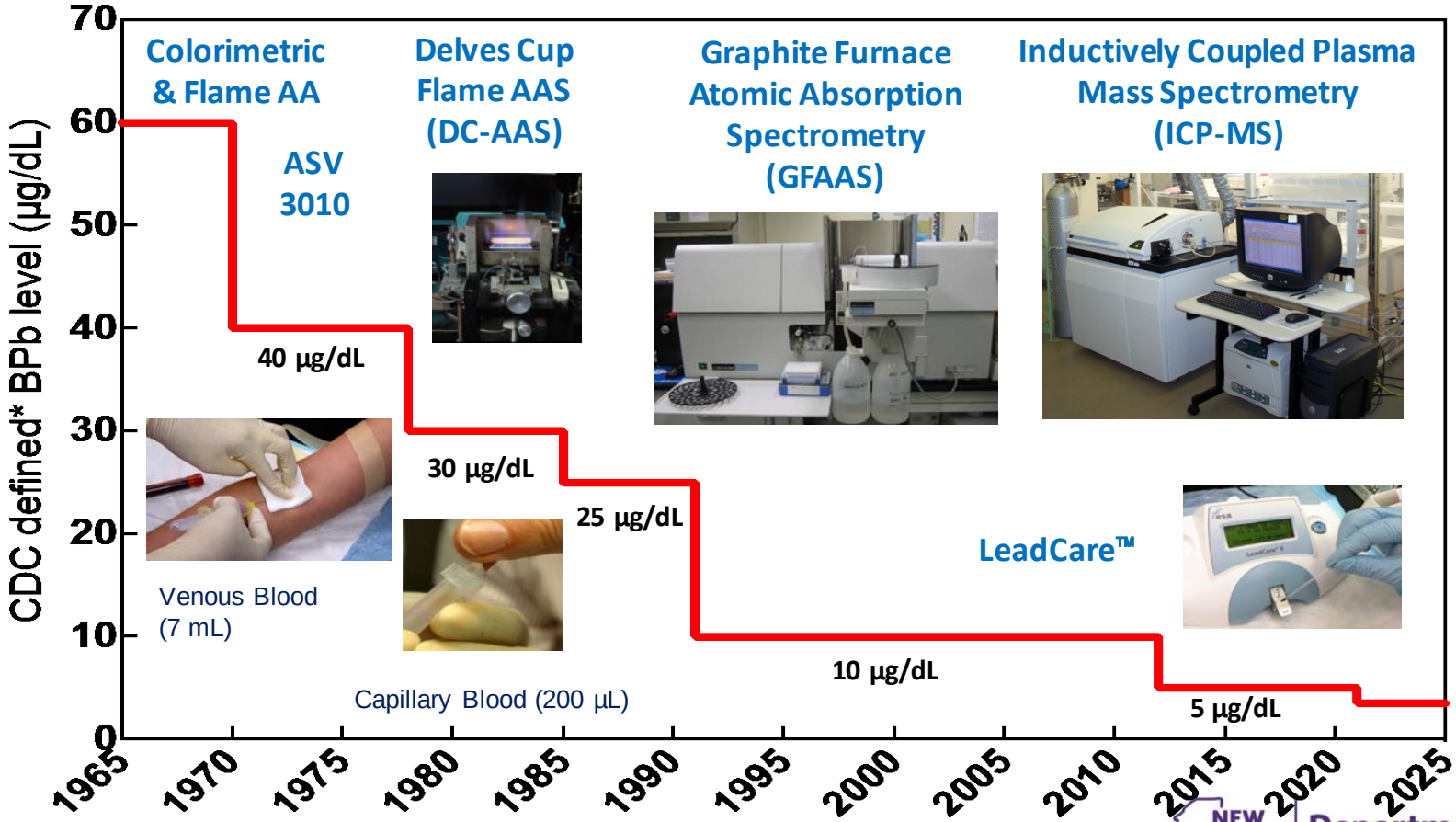
Patrick J. Parsons, PhD

June 2, 2022

Blood Lead Measurement Challenges

Patrick J. Parsons, PhD
Director, Division of Environmental Health Sciences, and
Chief, Laboratory of Inorganic and Nuclear Chemistry

Since 1986 Director, Lead Poisoning Laboratory…



*definitions:
BLL of concern
BLL action level
Elevated BLLs

60 years of Analytical Methods for Blood Lead

NEW YORK STATE Department of Health | Wadsworth Center

Lab Performance at Low Blood Lead Concentrations

The following slides are reproduced (with permission) from a presentation given at the Semi-Annual Meeting of the NCEH/ATSDR LEPAC, October 2020.

I gratefully acknowledge: Robert Jones PhD, Jeff Jarrett MS, Matt Karwowski, MD, MPH, Jim Pirkle MD PhD and Po-Yung Cheng PhD.

National Center for Environmental Health
Agency for Toxic Substances and Disease Registry
CDC

Three main methods to measure blood lead

- **ICP-MS** – Inductively coupled plasma mass spectrometry
- **GFAAS** – Graphite furnace atomic absorption spectroscopy
- **Leadcare II** – Point-of-care (POC) portable blood lead instrument

LeadCare FDA Safety Recall Issue

FDA Safety notice: *"FDA Warns Against Using Magellan Diagnostics LeadCare Testing Systems with Blood Obtained from a Vein: FDA Safety"*

"The FDA is warning facilities such as laboratories or health clinics that Magellan Diagnostics' LeadCare Testing Systems may underestimate BLLs and give inaccurate results when processing **venous** blood samples."

https://www.fda.gov/medical-devices/safety-communications/fda-warns-against-using-magellan-diagnostics-leadcare-testing-systems-blood-obtained-vein-fda-safety

Request from the 2017 NCEH/ATSDR Board of Scientific Counselors, Lead Poisoning Prevention Subcommittee

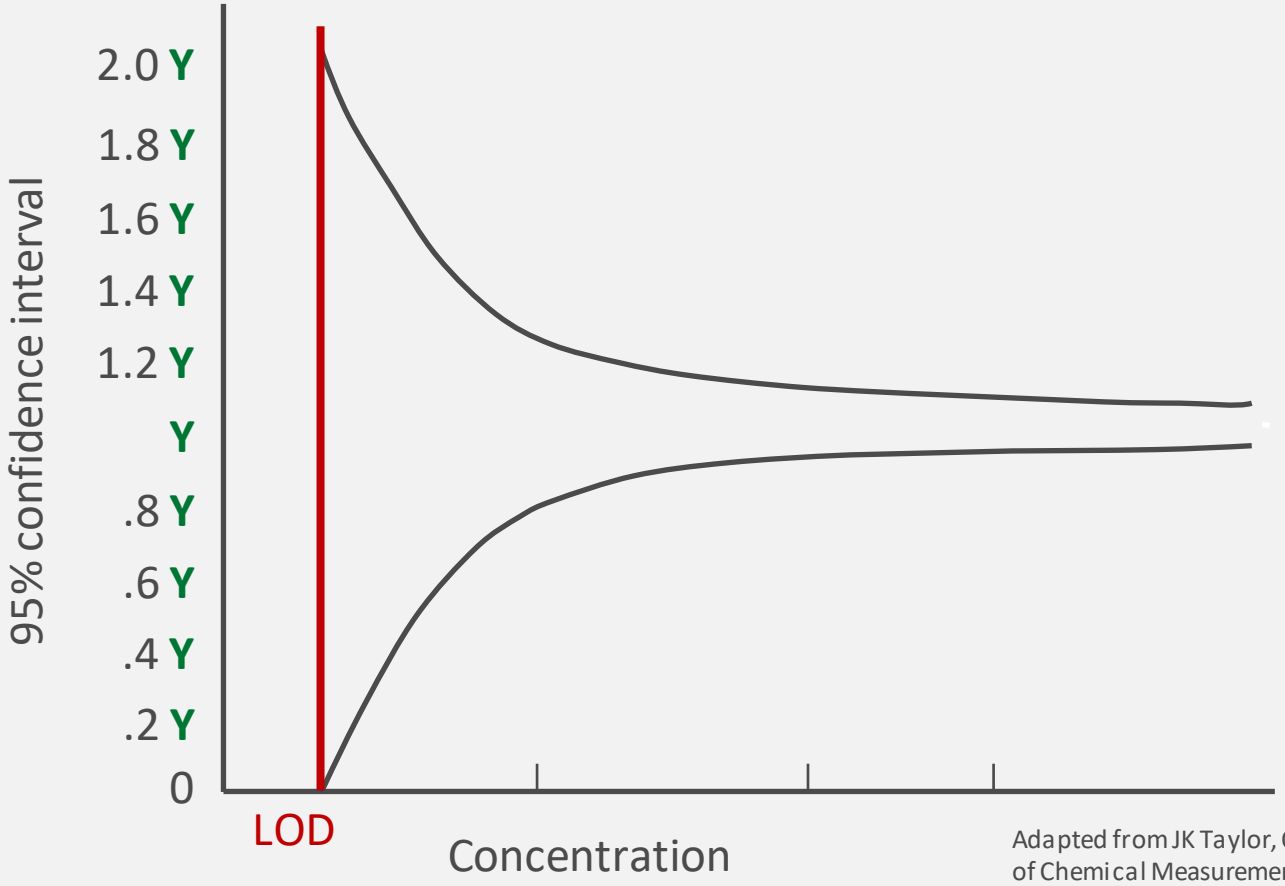
"Examine the implications of the level of quantitation and precision of the three primary laboratory methods (ICP-MS, GFAAS, and POC – LeadCare II) for the positive and negative predictive value of blood lead tests obtained in the setting of a possible revised reference value (RV) of 3.5 µg/dL."

Summary of measurement issues

- **Sensitivity**
  - For each of the three methods, is 3.5 µg/dL above the limit of detection (LOD)?

- **Precision**
  - For each of the three methods, is the precision of measurement at 3.5 µg/dL adequate for clinical use?

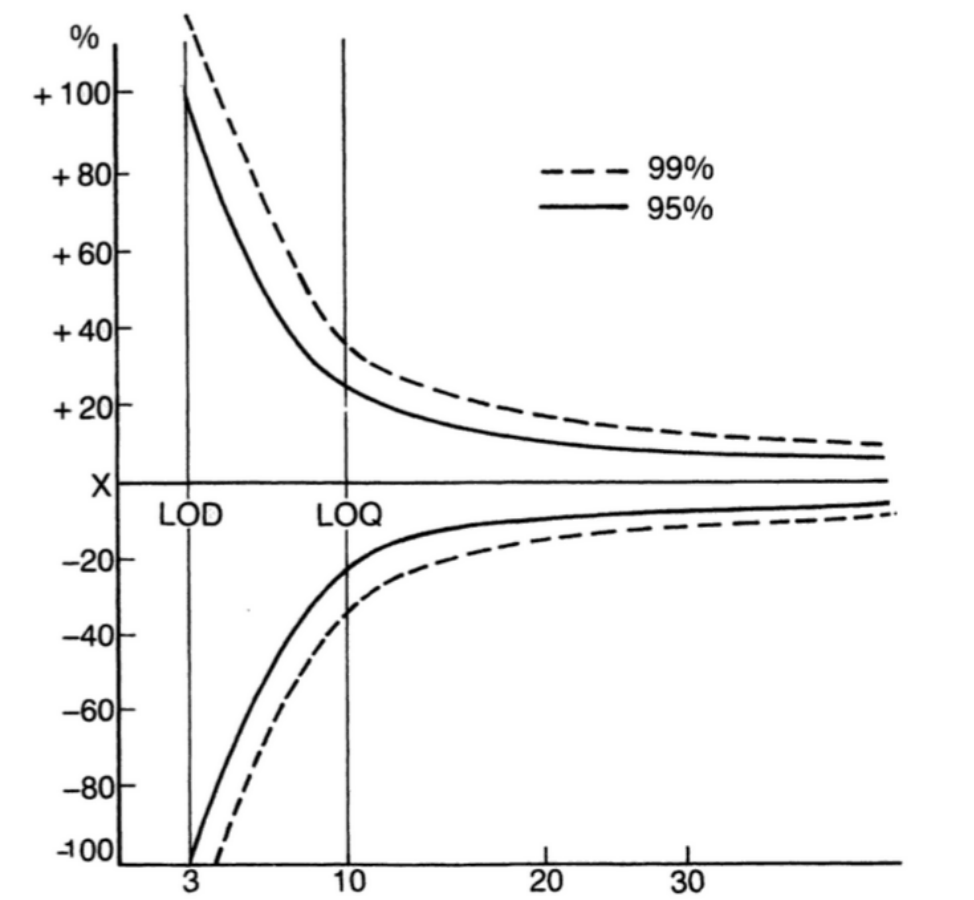
Imprecision increases non-linearly near the limit of detection



Adapted from JK Taylor, Quality Assurance of Chemical Measurements, 1987.

Uncertainty of measurement close to the limit of detection (LOD)

% relative uncertainty



X = analyte concentration (denoted as a multiple of the SD)

Limits of Detection and Quantitation

Limit of Detection (LOD)

- the lowest level at which the magnitude of the measurement is greater than the uncertainty of the measurement
- at the limit of detection, measurement uncertainty is ~±100 %

Limit of Quantitation (LOQ)

- is the lowest level the lab decided is quantitatively meaningful or is their lower reporting level based on “policy” decisions

Limits of laboratory-developed tests vary by lab and over time

- ICP-MS, GFAAS

Limits of manufacturer-developed tests are fixed (FDA cleared)

- LeadCare 1, LeadCare II, LeadCare Ultra, LeadCare Plus

Limits of Detection (LOD) and Lower Reporting Limits, µg/dL

Reported by Labs	ICP-MS	GFAAS	LeadCare II	LeadCare Ultra LeadCare Plus
Published LOD	0.05 – 1.06	0.08 – 1.5	Fixed at 3.3**	Fixed at 1.9
Lower reporting limits*	0.02 – **5**	0.1 – **5**		

* Examples reported to WSLH and CDC LAMP programs during testing events

** LeadCare II LOD determined by using non-laboratory trained personnel (CLIA Waived criteria)

Summary of measurement issues

- **Sensitivity**
  - For each of the three methods, is 3.5 µg/dL above the limit of detection (LOD)?

    Yes
- **Precision**
  - For each of the three methods, is the precision of measurement at 3.5 µg/dL adequate for clinical use?

    Yes (PP well, depends on the lab..)

Blood lead proficiency testing program data sources

- Wisconsin State Laboratory of Hygiene (WSLH)
  - Blood Lead Regulatory PT Program
  - Laboratory Response Network – Chemical (LRN-C)
- New York State Department of Health (NYSDOH) Wadsworth's Trace Elements in Blood PT Program
- CDC's Lead and Multielement Program (LAMP)
- Centre de toxicologie du Québec (CTQ)
  - PCI: Interlaboratory Comparison Program
  - QMEQAS: Quebec Multielement External Quality Assessment Scheme

Blood lead proficiency testing CLIA requirements

- 5 unknown samples sent 3 times per year
- Required for
  - ICP-MS, GFAAS, LeadCare I, LeadCare Ultra, LeadCare Plus
- Not required for LeadCare II

Number of participating labs by method by provider

	WSLH	NYS DOH	CDC LAMP	CTQ
ICP-MS	20 – 45	15 – 30	~40	10 – 40
GFAAS	~40	1 – 45	~30	0 – 50
LeadCare II	~350	0 – 10	~10	0

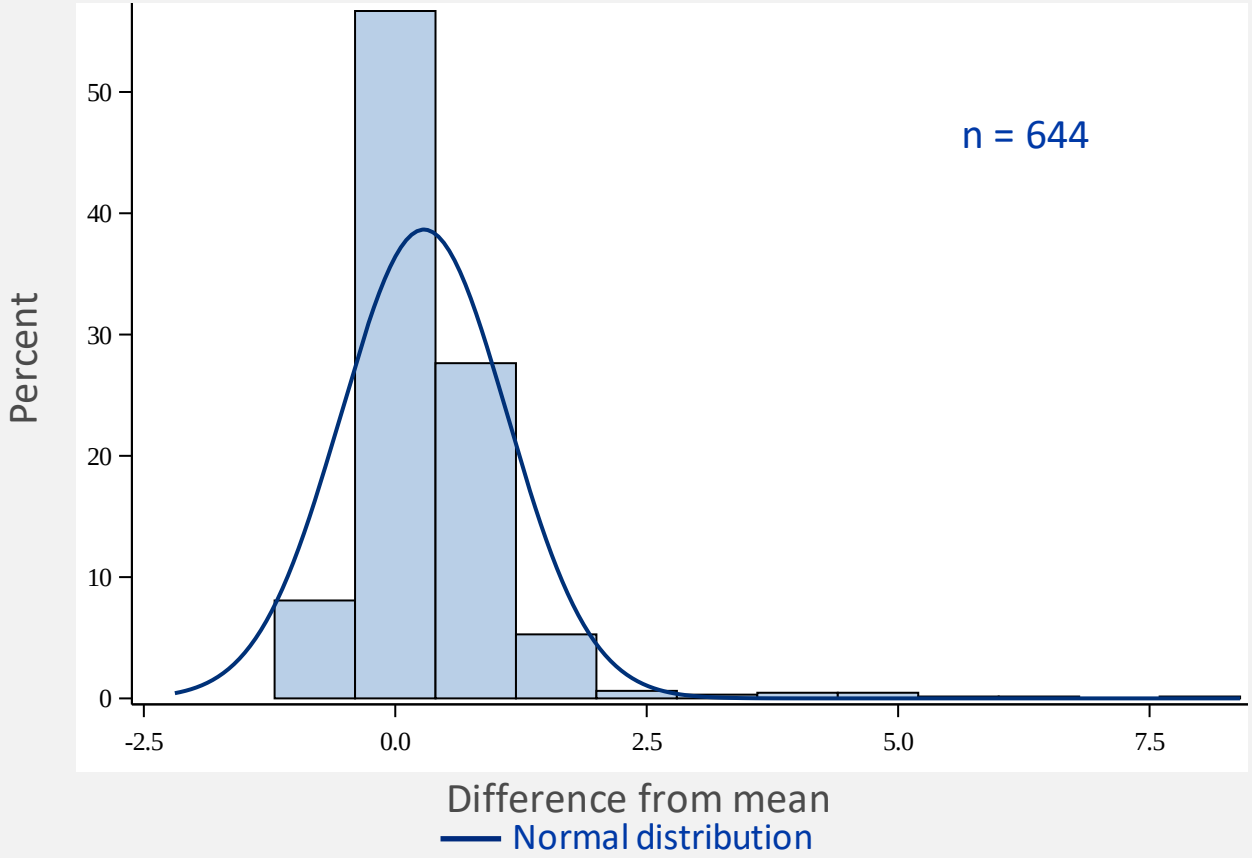
Data selection from proficiency testing (PT) programs

- Blood pools used in 2010 - 2019 PT challenge events
- Blood lead concentration means are 3.0 – 4.1 µg/dL
- LeadCare II data from 3 samples (92% of submitted results)
- Calculated difference of each result from pool mean
- Excluded outliers based on 4 sigma criteria

Data by test type

	# submitted results	<LOD (%)	N >LOD
LeadCare II	1028	37%	644
GFAAS	690	2.5%	673
ICP-MS	942	2.9%	915

LeadCare II – difference in measurements from pool mean for PT samples (3.5 – 4.1 µg/dL)

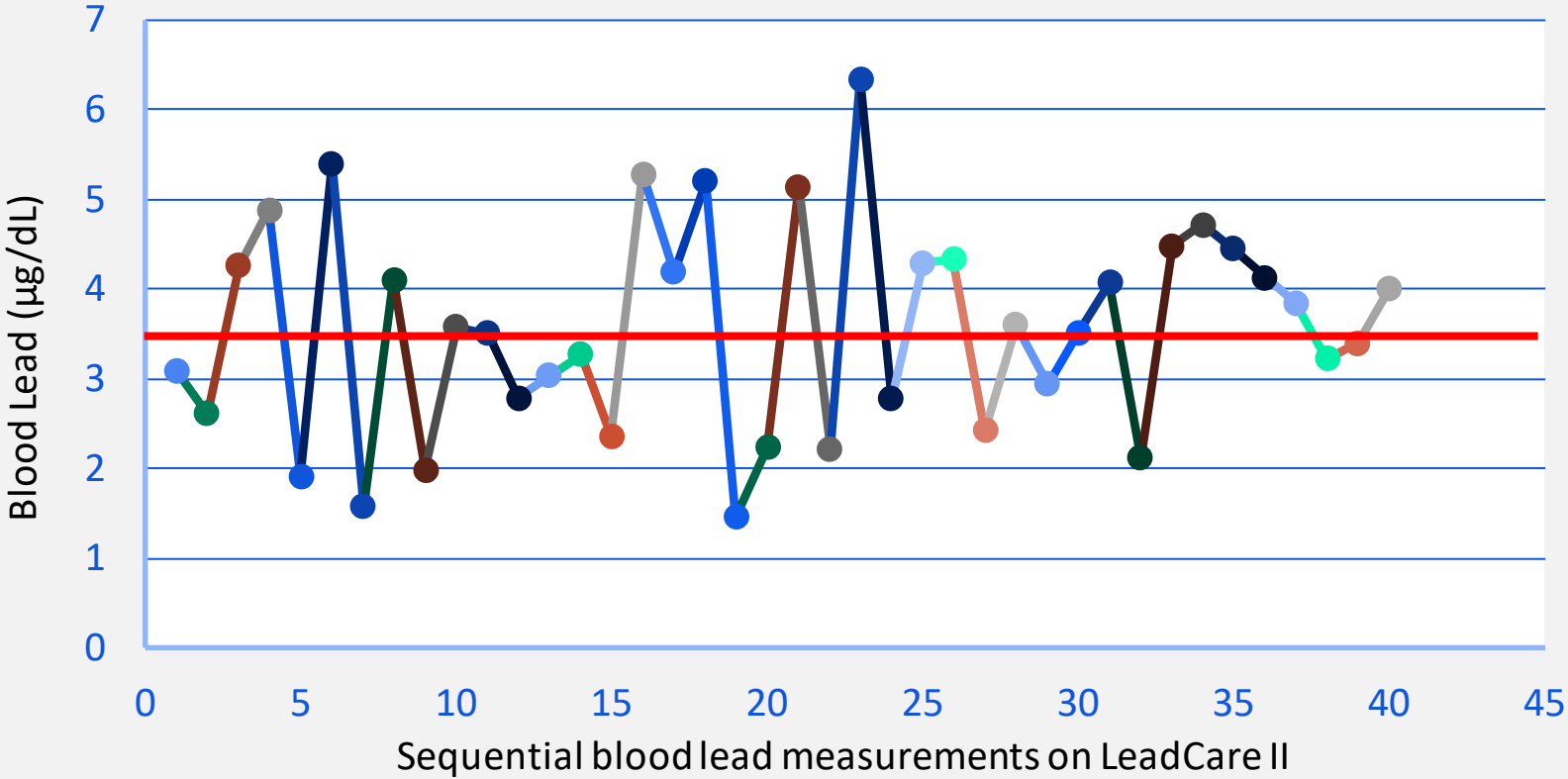


Best estimates of precision of blood lead measurements between 3.0 to 4.1 µg/dL

	95% confidence interval (µg/dL)	N
LeadCare II*	± 1.8	1028
GFAAS**	± 1.6	673
ICP-MS**	± 0.83	915

*<LOD treated as zero. SD estimated from proc-univariate as (97.5th - 50th percentile)/2.
** <LOD excluded

Simulation of sequential blood lead measurements for a person with constant, true blood lead of 3.5 µg/dL using the LeadCare II



NHANES Blood Lead Percentiles for Children age 1-5 years

NHANES	Sample Size	Geometric Mean	50th	75th	90th	95th	97.5th
2011-2014	1531	0.86 (0.80-0.93)	0.82 (0.75-0.89)	1.21 (1.09-1.32)	1.90 (1.64-2.24)	2.57 (2.26-3.05)	3.48 (2.65-4.29)
2 cycles each							
2015-2018	1419	0.71 (0.66-0.77)	0.65 (0.60-0.71)	1.04 (0.94-1.16)	1.66 (1.49-1.86)	2.41 (1.9-3.01)	3.44 (2.68-4.22)

Summary

- Precision estimates are based on pools from Proficiency Testing providers with blood lead mean concentrations between 3.0 and 4.1 µg/dL
- Precision for measurements made at between 3.0 and 4.1 µg/dL are similar to estimates reported previously for 4.0 to 6.0 µg/dL
- Blood tube manufacturers should consider offering blood tubes < 0.2 µg/dL blood lead equivalent (CDC criteria is 0.1 µg/dL)
- Improving precision of methods continues to be important

Based on the CDC lab group's analysis of blood lead PT data, there some important implications for routine blood lead testing in NYS

LC II	95% CI at 3.5 µg/dL is ±1.8 µg/dL	1.7 – 5.3 µg/dL
GFAAS	95% CI at 3.5 is ±1.6 µg/dL	1.9 – 5.1 µg/dL
ICP-MS	95% CI at 3.5 is ±0.83 µg/dL	2.7 – 4.3 µg/dL

Measurement uncertainty must include contamination bias…
Previously set at no more than 0.5 µg/dL in 1990s

NYS standards tightened to no more than 0.2 µg/dL in 2020

Current federal PT performance criteria were last set in 1992

±4 µg/dL or ±10%, whichever is greater

Change in federal PT performance criteria were proposed in 2012…

±2 µg/dL or ±10%, whichever is greater…. Not yet implemented

Measurement uncertainty must include contamination bias…
Previously set at no more than 0.5 µg/dL in 1990s

NYS standards tightened to no more than 0.2 µg/dL in 2020

Venous blood – gold standard, with blood lead confirmed by GFAAS or ICP-MS

Capillary blood – acceptable for screening purposes, but contamination bias will always an issue

Questions?