CLIA ‘88: Blood Lead Laboratory Issues

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Lead Exposure and Prevention Advisory Committee (LEPAC)

Semi-Annual Meeting

December 2021

CLIA ‘88 Origins

- The Clinical Laboratory Improvement Amendments of 1988 (CLIA ‘88)
- Enacted in response to problems with laboratory accuracy and precision
- Laboratories testing human specimens and reporting patient-specific results must be compliant under the provisions of the Clinical Laboratory Improvement Amendments of 1988 (CLIA) (57 FR 7139, Sec. 493.1)
- Some states (currently NY and WA) operate their own lab regulatory programs which take the place of CLIA

CLIA ‘88 Certifications and Test Complexities

Facilities must be certified according to the complexity of tests used

- **High**
  - Graphite Furnace Atomic Absorption Spectrometry (GFAAS)[1]
  - Inductively Coupled Plasma Mass Spectrometry (ICP-MS)[1]
- **Moderate**
  - LeadCare Ultra [2]
  - LeadCare Plus [2]
- **CLIA-waived**
  - LeadCare II [2]

[1] Laboratory developed test (LDT)
[2] FDA 510(k) approved

Laboratory Developed Tests (LDT) for Blood Lead

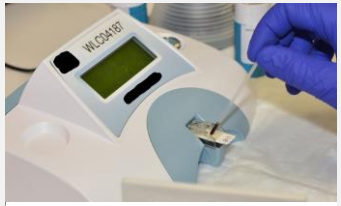
- A type of in vitro diagnostic test that is designed, manufactured and used within a single laboratory
  - e.g., GFAAS and ICP-MS blood lead tests
- FDA[1] has generally not enforced premarket review and other applicable FDA requirements
- CLIA certifications and requirements apply
- Test specifics are unique to each laboratory
  - limits of detection are calculated, and updated, by each lab using a statistical approach they choose
  - Limits of reporting are policy decisions by each lab

Images provided by CDC

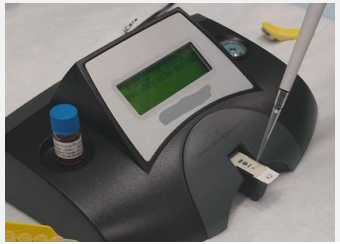
[1] https://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/laboratorydevelopedtests/default.htm

FDA 510(k) Approved Tests for Blood Lead

- The LeadCare II, Plus and Ultra are FDA 510(k) approved for marketing instruments.
- "In vitro diagnostic products are those reagents, instruments, and systems intended for use in diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease." [21 CFR 809.3]
- CLIA certifications and requirements apply
- Test specifics are fixed, as approved by FDA



LeadCare II



LeadCare Plus

LeadCare Ultra

Images provided by CDC

Blood Lead Proficiency Testing (PT) Requirements

CLIA blood lead proficiency testing requirements have been in place since 1988.

- **Participation**
  Required for high and moderate complexity tests
  Not Required for CLIA-waived tests

- **Acceptable performance for blood lead testing**
  ±4 µg/dL or ±10% (which ever is greater)

Proposed Change for Criteria for Acceptable Performance in PT

- **2009-2010:** the Lab Workgroup of ACCLPP determined that 87-90% of labs could maintain successful participation in PT at ±2 µg/dL or ±10% criteria
- **2011:** the Advisory Committee for Childhood Lead Poisoning Prevention (ACCLPP) recommended this criteria change by letter to the Secretary of the Health and Human Services (HHS).
- **2019:** Centers for Medicare and Medicaid Services (CMS) published proposed changes to acceptable performance for >100 regulated analytes in the Federal Register[1]
  - **proposed ±2 µg/dL or ±10% (which ever is greater) for blood lead**
  - currently there is no proposed date for implementation.

[1] Federal Register Vol. 84, No 23, 2/4/2019, page 1536. https://www.federalregister.gov/d/2018-28363

Acknowledgements

Dr. Jerry Thomas

For more information, contact NCEH/ATSDR
1-800-CDC-INFO (232-4636)
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Backup Slides

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."

Best estimates[1] of precision of blood lead measurements between 3.0 to 4.1 µg/dL

Lab Test Type	95% confidence interval (µg/dL)	N
LeadCare II[2]	± 1.8	1028
GFAAS[3]	± 1.6	673
ICP-MS[3]	± 0.83	915

[1] Calculations by NCEH / DLS using 2010-2019 PT data from six programs.

[2] Data from 3 samples (92% of submitted results). <LOD treated as zero. SD estimated from proc-univariate as (97.5th - 50th percentile)/2.

[3] <LOD excluded

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

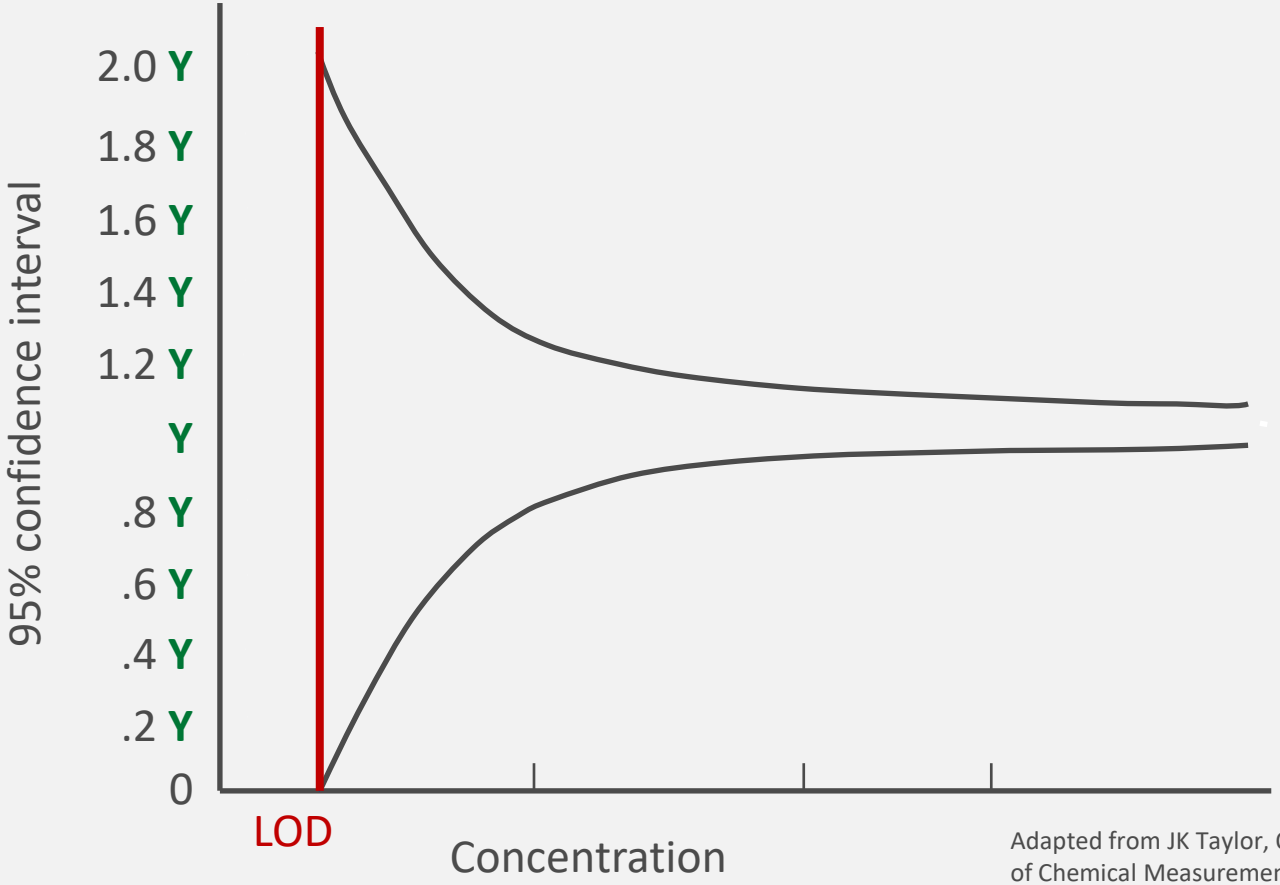
Limits of Detection (LOD) and Lower Reporting Limits, µg/dL

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**	Fixed at 3.3**	Fixed at 1.9

* Examples reported to the Wisconsin State Laboratory of Hygiene (WSLH) PT program and CDC's Lead and Multielement Program (LAMP) during blood lead testing events.

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

Imprecision increases non-linearly near the limit of detection



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

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

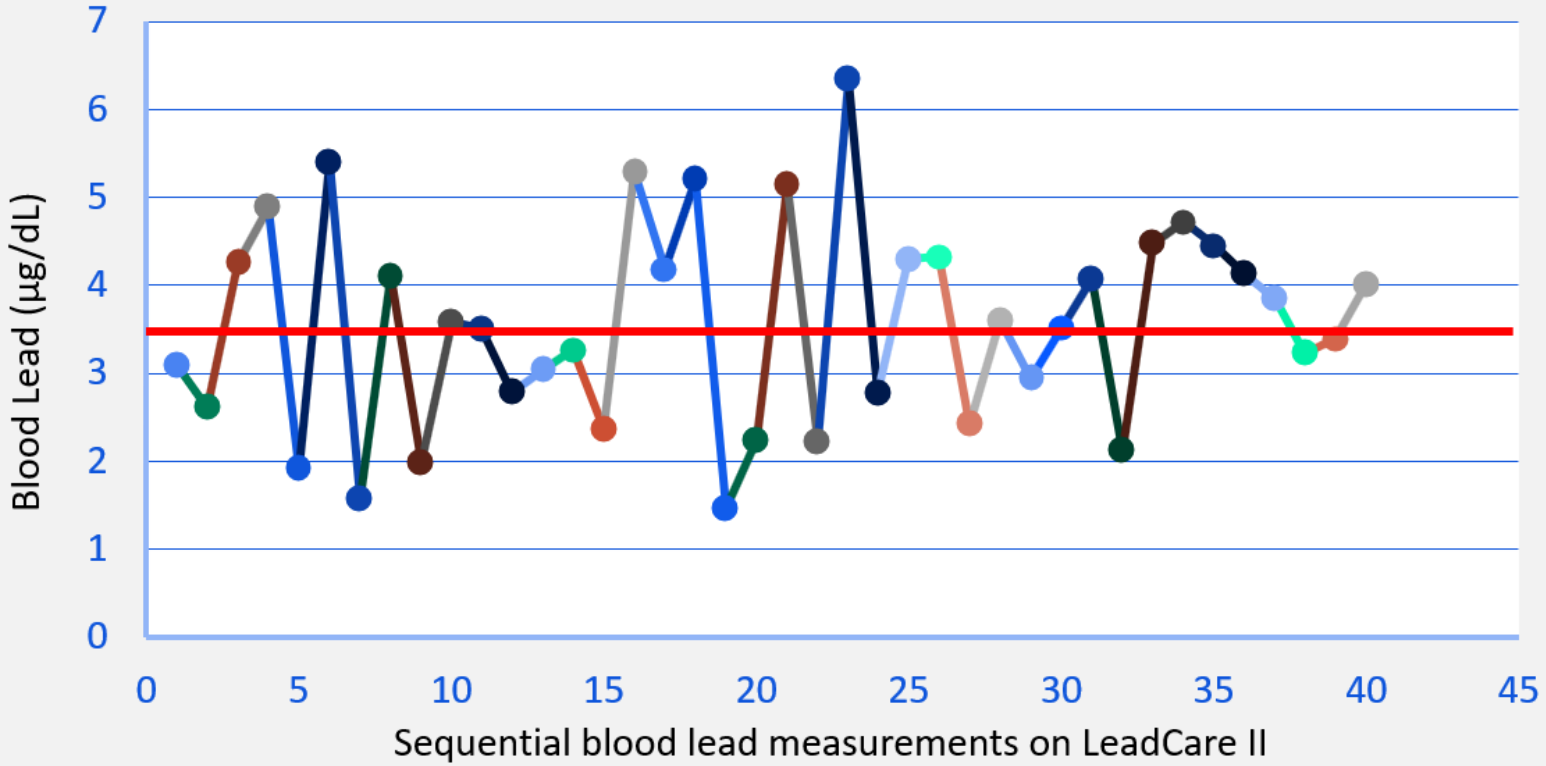
Limits of laboratory-developed tests vary by lab and over time

- ICP-MS, GFAAS

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

- LeadCare, LeadCare II, LeadCare Ultra, LeadCare Plus

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



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