Standardization of Creatinine Measurement

NKDEP Manufacturers' Forum

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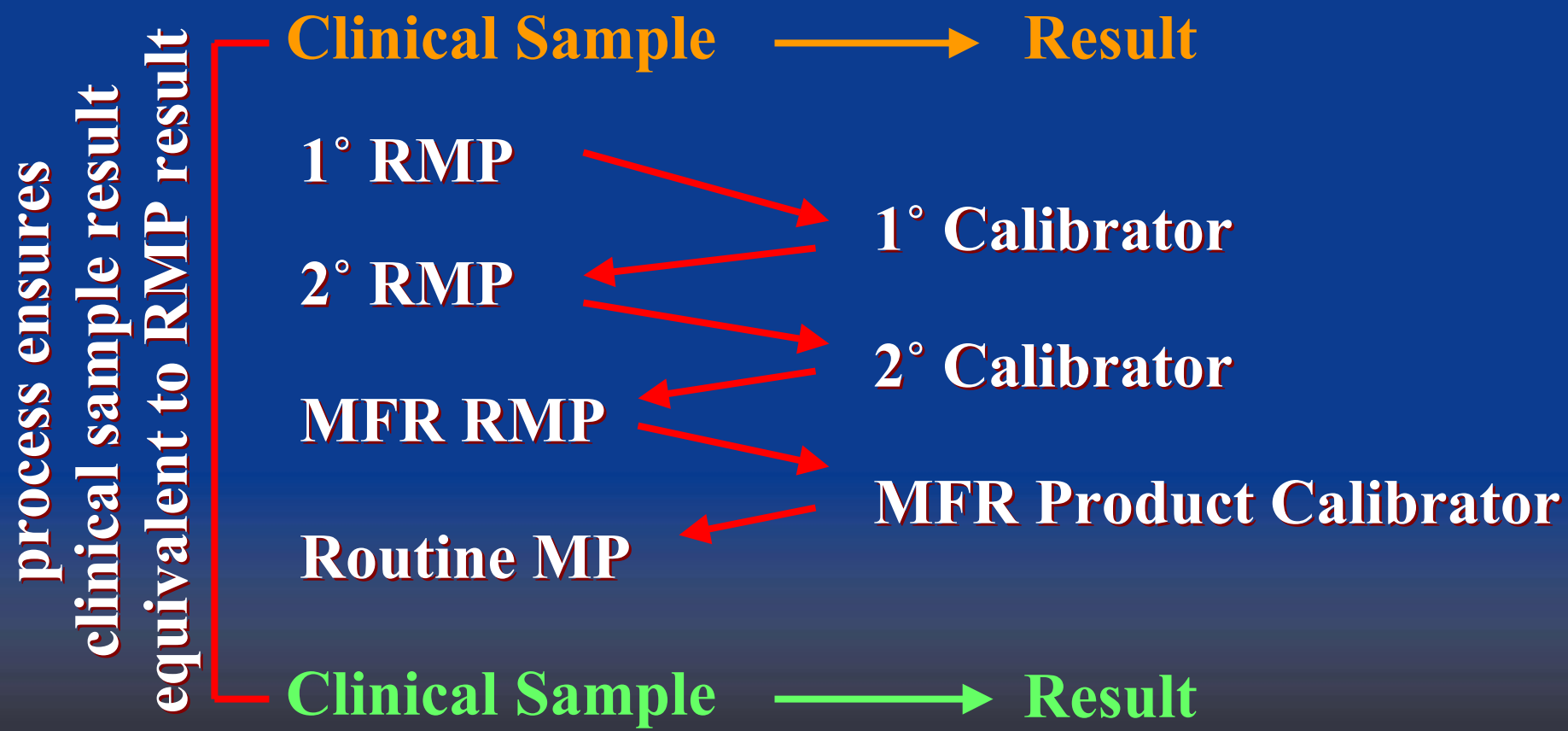
Why Standardize Serum Creatinine Measurement?

To improve and normalize serum creatinine results used in prediction equations so that estimates of glomerular filtration rates (GFR) are accurate and comparable regardless of when or where tests are performed

Standardization is accomplished by establishing traceability to reference measurement procedures of higher order

Traceability in Laboratory Medicine



Joint Committee on Traceability in Laboratory Medicine

Formed in June 2002 with the purpose to improve comparability of test results by establishing traceability to reference standards

Two Working Groups formed:

- **Working Group 1 – Reference Materials & Procedures - Establish criteria for acceptance of materials/procedures & produce lists of such items**
- **Working Group 2 – Reference Laboratories - Establish criteria for accreditation of reference laboratories at the calibration level**

Reference Measurement Procedures

Approved by JCTLM for Creatinine Measurement

Method	Institution
GC-IDMS	NIST, Gaithersburg, MD
GC-IDMS	University of Ghent, Belgium
GC-IDMS	DGKC, Bonn, Germany

Candidate Reference Measurement Procedures under Consideration by JCTLM for Creatinine Measurement

Method	Institution
LC-IDMS	NIST, Gaithersburg, MD
LC-IDMS*	LGC, Ltd, Middlesex, UK**

* Comparison with traditional GC-IDMS gave a bias of <0.2%

** Nominated in the JCTLM cycle II for consideration as a Reference Measurement Procedure

Reference Materials Approved by JCTLM for Creatinine Measurement

Primary Reference Material

Name	Form	Available From
SRM 914a	Crystalline creatinine 99.7±0.3 mass%	NIST

Reference Materials Approved by JCTLM for Creatinine Measurement

Secondary Reference Materials

Name	Form	Concentration	Source
BCR 573	lyophilized serum	0.78±0.16 mg/dL	IRMM[1]
BCR 574	lyophilized serum	1.19±0.015 mg/dL	IRMM
BCR 575	lyophilized serum	4.57±0.08 mg/dL	IRMM
SRM 909b-1	lyophilized serum	0.64±0.006 mg/dL	NIST
SRM 909b-2	lyophilized serum	5.29±0.061 md/dL	NIST

[1] Institute for Reference Materials and Measurements, Geel, Belgium

CAUTION!! CAUTION!!

The Secondary Reference Materials from IRMM and NIST have not been evaluated for commutability with field methods, therefore they may be unsuitable for direct use in field measurement procedure calibration.

Comparison of performance between the IRMM and NIST materials has not been performed, therefore interchange of materials for assessing trueness is not recommended.

Commutable Reference Material for Creatinine Measurement

- Collaboration between NKDEP, CAP and NIST
- Fresh-frozen human serum pools prepared according to NCCLS C-37A
- Two levels: approximately 0.8 mg/dL and 4.0 mg/dL
- Elevated level prepared using supplementation with crystalline creatinine
- Materials will be value assigned by NIST GC-IDMS and LC-IDMS methods
- Materials will be designated NIST SRM 967

Creatinine Accuracy-based Linearity Survey

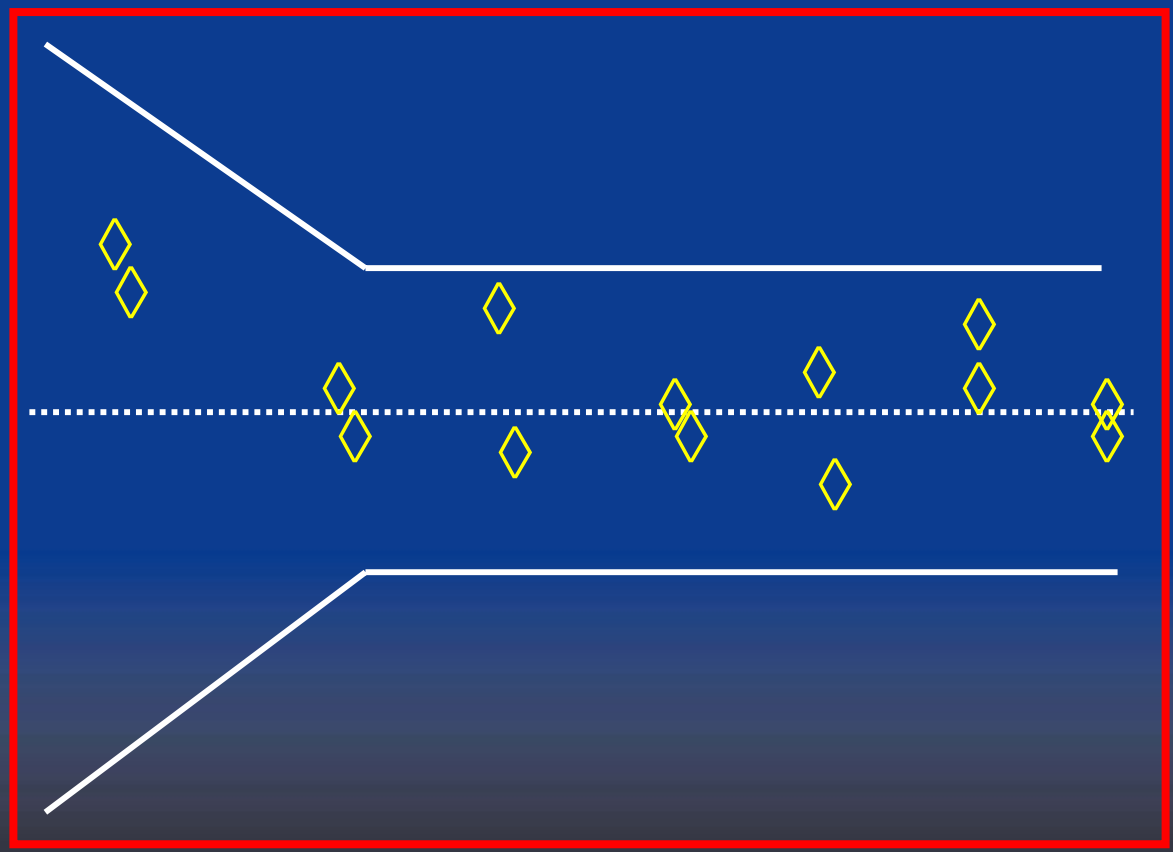
- Product designation: LN24
- Suitable for assessing calibration of routine field methods
- Prepared from fresh female off-the-clot serum

LN24-01	0.5008 mg/dL
LN24-02	0.7390 mg/dL *
LN24-03	1.3942 mg/dL
LN24-04	2.0494 mg/dL
LN24-05	2.7046 mg/dL
LN24-06	3.3598 mg/dL
LN24-07	4.0150 mg/dL *

* measured by LC-IDMS at NIST; all others were calculated

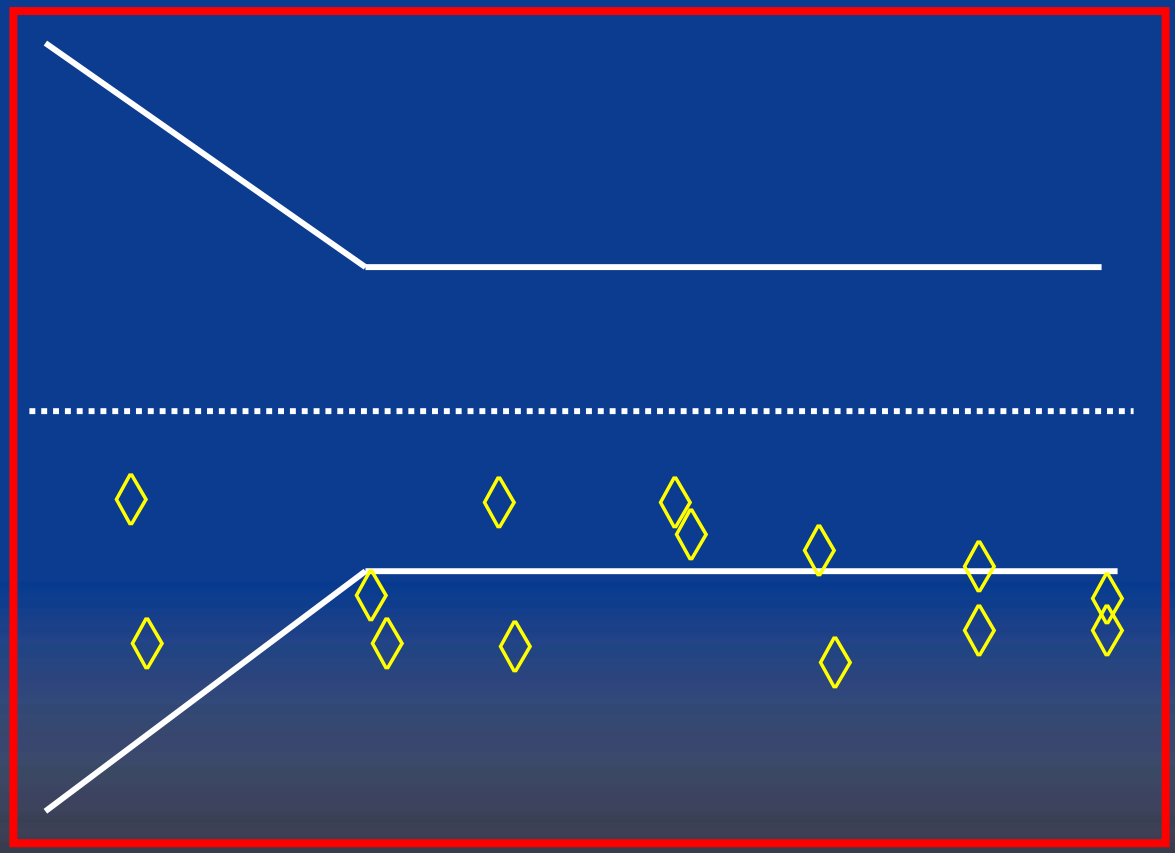
Acceptable Calibration Verification

% Difference between Participant Results and NIST Value



Non-Calibrated Evaluation

% Difference between Participant Results and NIST Value



CAP 2004 LN24-A
All-Laboratories (n=18) Results

Sample ID	Mean (mg/dL)	CV (%)	NIST (mg/dL)	Diff (mg/dL)	Diff (%)
LN24-01	0.540	16.4	0.5008	+0.039	7.8
LN24-02	0.805	2.0	0.7390*	+0.066	8.9
LN24-03	1.448	5.4	1.3942	+0.054	3.9
LN24-04	2.097	4.4	2.0494	+0.048	2.3
LN24-05	2.752	4.8	2.7046	+0.047	1.7
LN24-06	3.415	4.7	3.3598	+0.055	1.6
LN24-07	4.041	4.0	4.0150*	+0.026	0.65

Recommendations for Standardizing Creatinine Measurement

- Develop a reference material for serum creatinine with proven commutability with individual patient serum. - NIST SRM 967 is expected to fulfill this need.

- Develop a high level reference method with high throughput (e.g. LC/IDMS) which is accepted by JCTLM that manufacturers can use to validate assay trueness. - The two LC-IDMS methods developed by NIST and LGC, Ltd (Stokes) will fulfill this need.

- Establish high level/high throughput reference method (LC-IDMS) in several labs (including at least one US lab) capable of providing reference services with <1 month turnaround time and at reasonable cost.

Recommendations for Standardizing Creatinine Measurement (Continued)

- Introduce a regularly recurring fresh frozen serum-based PT program that is traceable to a reference measurement procedure that manufacturers can use to assess calibration of field methods. - The new CAP LN24 Creatinine Accuracy Calibration Verification/Linearity Survey has these attributes.

- Coordinate introduction of traceability of creatinine to IDMS with PT/EQAS providers to ensure that appropriate participant grading is made during the transition between calibration schemes. - CAP has agreed to dual grading.

Recommendations for Standardizing Creatinine Measurement (Continued)

- Determine the differences in clinical decision criteria that may result when implementing traceability of serum creatinine assays to IDMS. Coordinate method re-calibration with equation revision.
- Develop guidelines to assist manufacturers in providing effective communication to end users, addressing: change in serum creatinine reference range; change in creatinine clearance values and reference range; change in creatinine values that will impact drug dose adjustment; and adjustment of coefficients in the equation used to estimate GFR.

Standardization does not correct for non-specificity problems. Non-specificity issues must be addressed by IVD manufacturers.