NKDEP Lab Working Group

IVD Manufacturer's Workshop

AACC Chicago, July 27, 2006

Neil Greenberg, PhD, DABCC
Member, NKDEP Lab Working Group and
Chair, IFCC WG-GFRA
Manager, Regulatory Affairs
Ortho Clinical Diagnostics
Rochester, NY

NKDEP Manufacturer's Workshop

Creatinine Standardization Program

- Key Objective:

- Improve accuracy & reproducibility of eGFR calculated from serum creatinine by ensuring optimal analytical performance of existing creatinine methods

NKDEP Manufacturer's Workshop

NKDEP LWG Strategic Plan:

1. Establish more stringent lab performance specifications (precision & bias) for routine creatinine measurements
   - *Total error not increasing variability in eGFR by more than 10% in critical creatinine range of 1.0-1.5 mg/dL (88-133 μmol/L).*
   - *Analytical performance in lower creatinine range (0.6-1.0 mg/dL or 53-88 μmol/L) comparable to performance >1.0 mg/dL (88 μmol/L)*

NKDEP Manufacturer's Workshop

NKDEP LWG Strategic Plan:

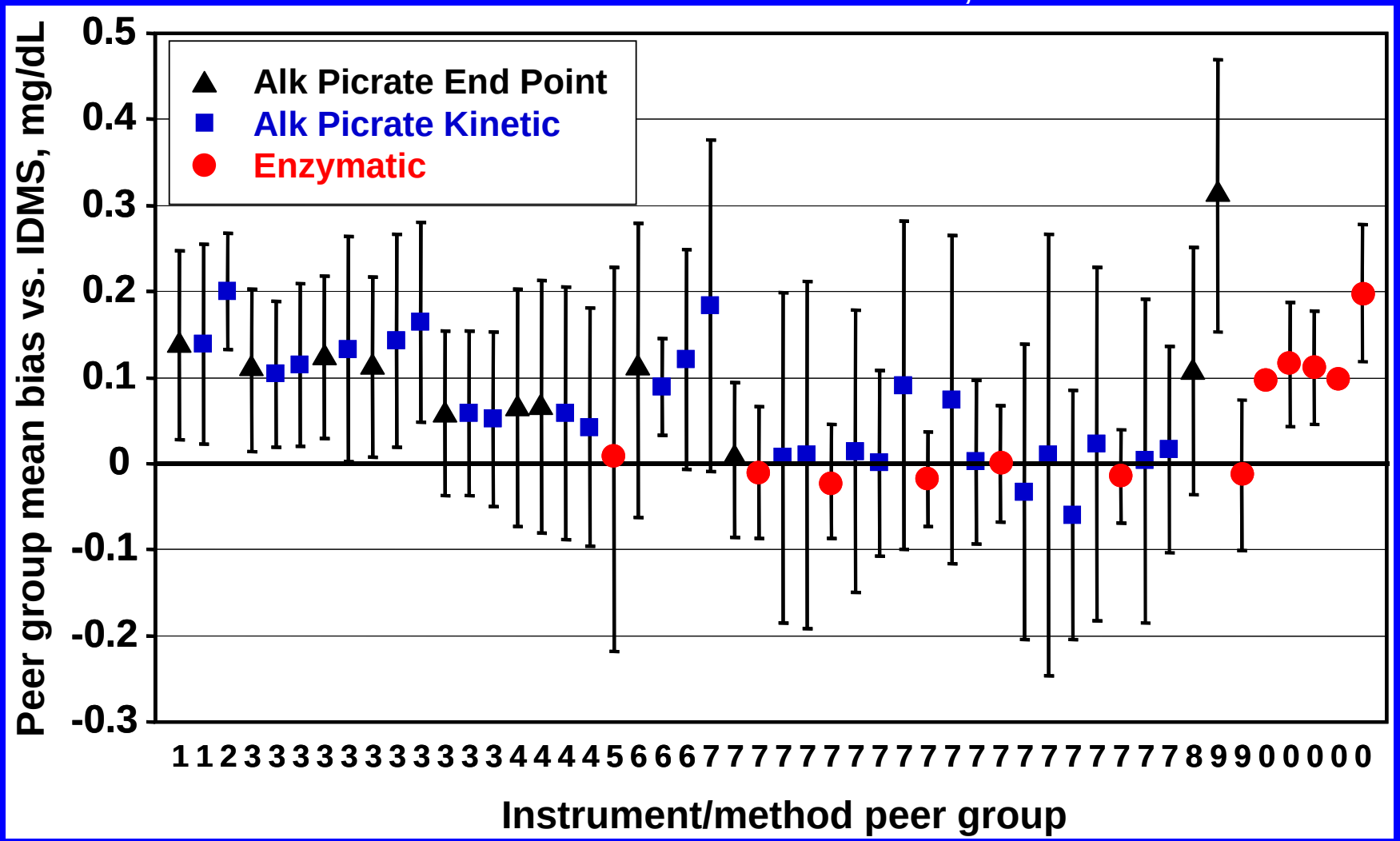
2. Close gap in calibration traceability infrastructure by supporting implementation of commutable certified matrix reference materials

3. Promote use of more specific creatinine measurement procedures that minimize interferences affecting conventional methods.

NKDEP Manufacturer's Workshop

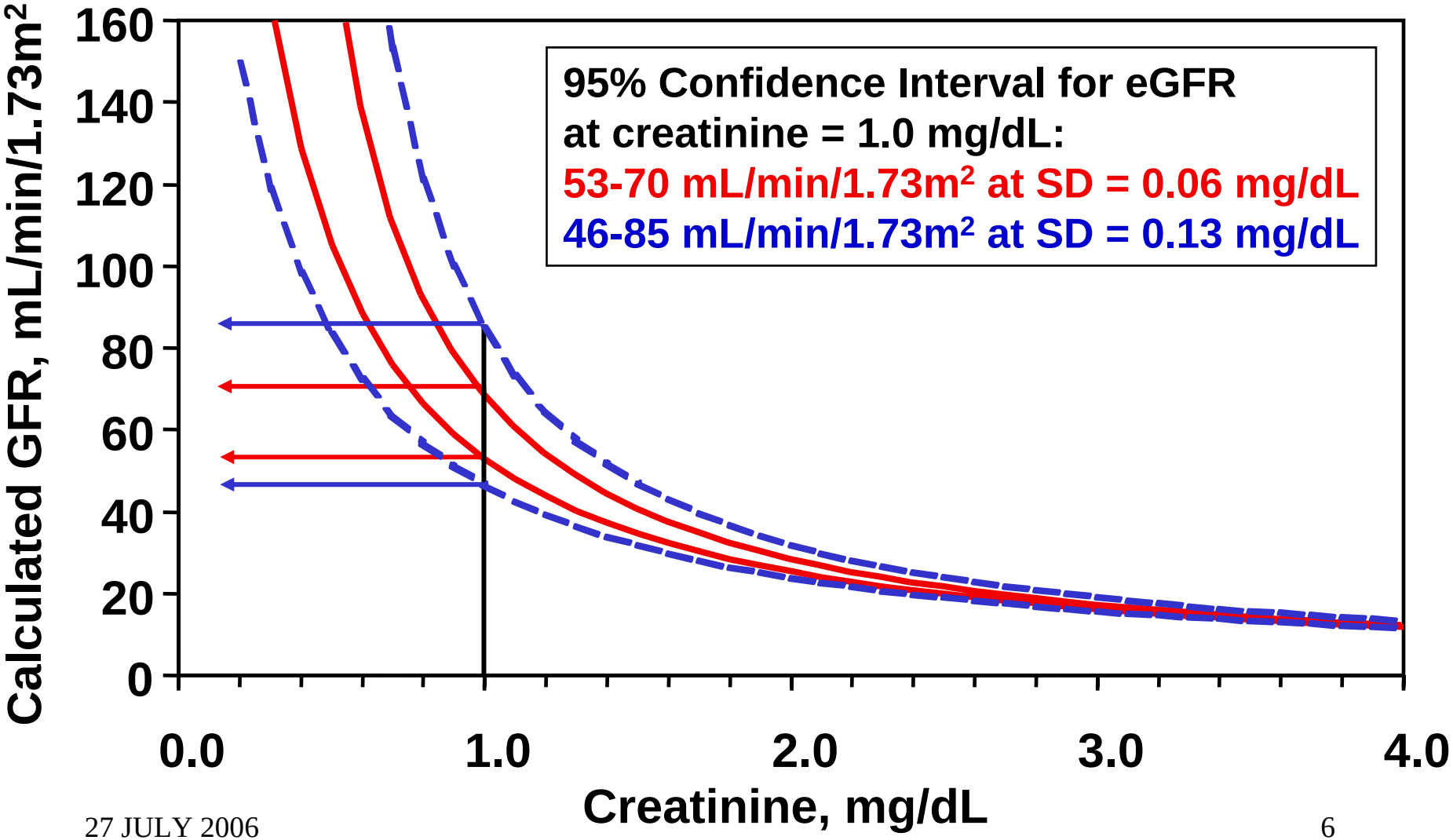
Lab performance specifications – Bias

Miller et al. Arch Pathol Lab Med 2005;129:297-304



NKDEP Manufacturer's Workshop

Imprecision Performance Specs



Myers et al. Clin Chem 2006;52:5-18

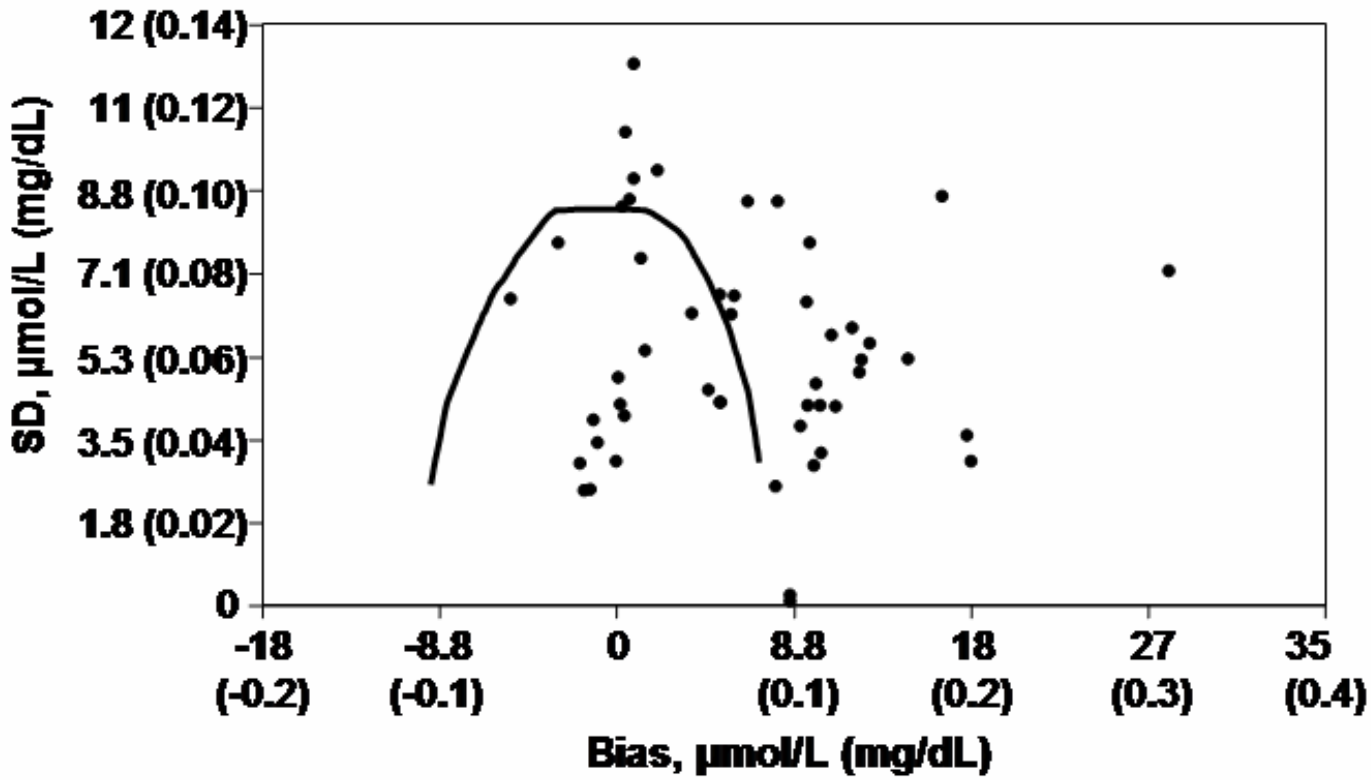
NKDEP Manufacturer's Workshop

Lab performance recommendations…

- Imprecision:
  - Standard Deviation <0.08 mg/dL (<7.1 µmol/L)
- Bias to IDMS reference method:
  - Bias <0.05 mg/dL (<4.4 µmol/L)

NKDEP Manufacturer's Workshop

Routine creatinine method performance vs. TE limit



Myers et al. Clin Chem 2006;52:5-18

NKDEP Manufacturer's Workshop

Field Performance Conclusions:

- Some methods demonstrate poor precision; most already meet or exceed required precision performance
- More than half of routine methods demonstrate unacceptable bias
- Short-term priority - minimize bias

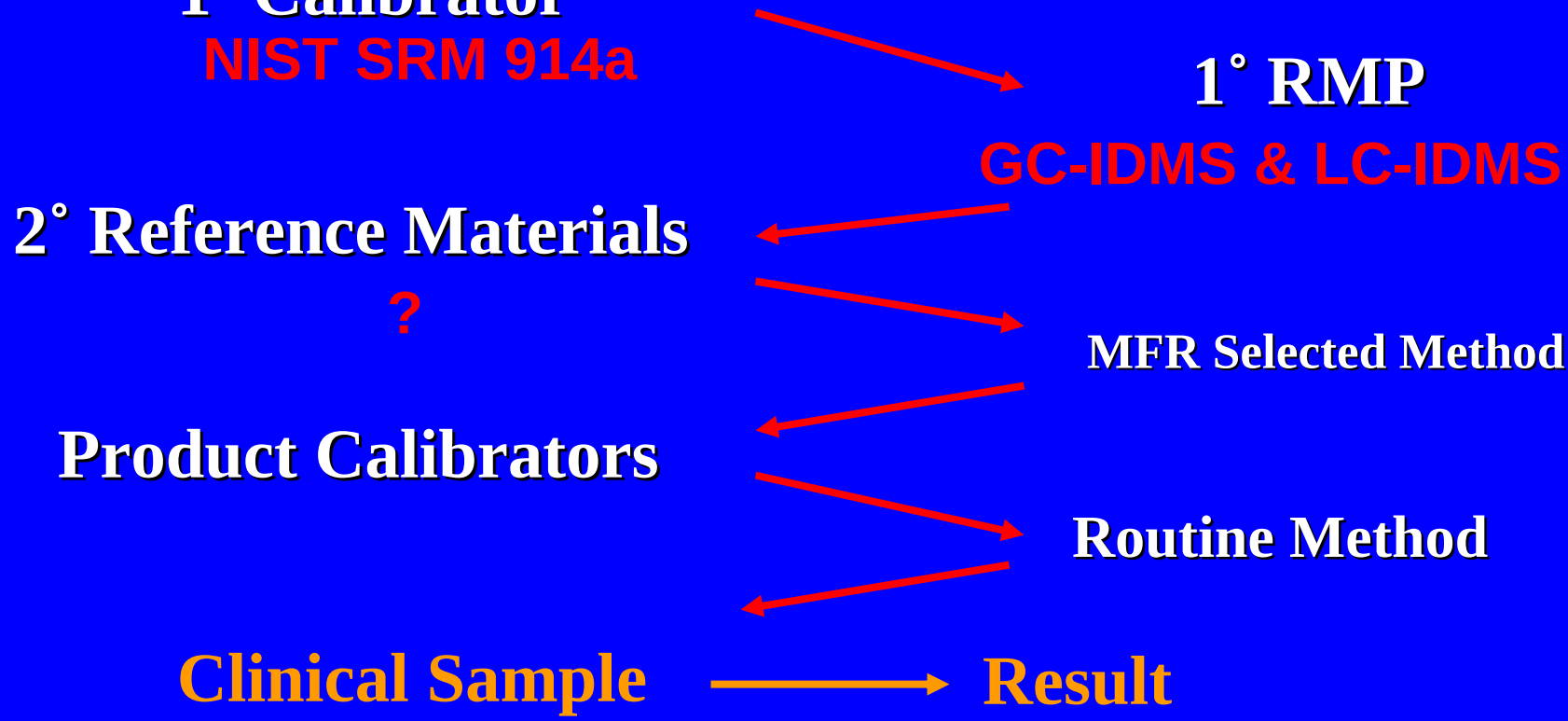
NKDEP Manufacturer's Workshop

NKDEP calls on all manufacturers of IVD reagents and systems for creatinine to eliminate calibration bias.

- **Set calibration of all routine methods traceable to IDMS reference methods**

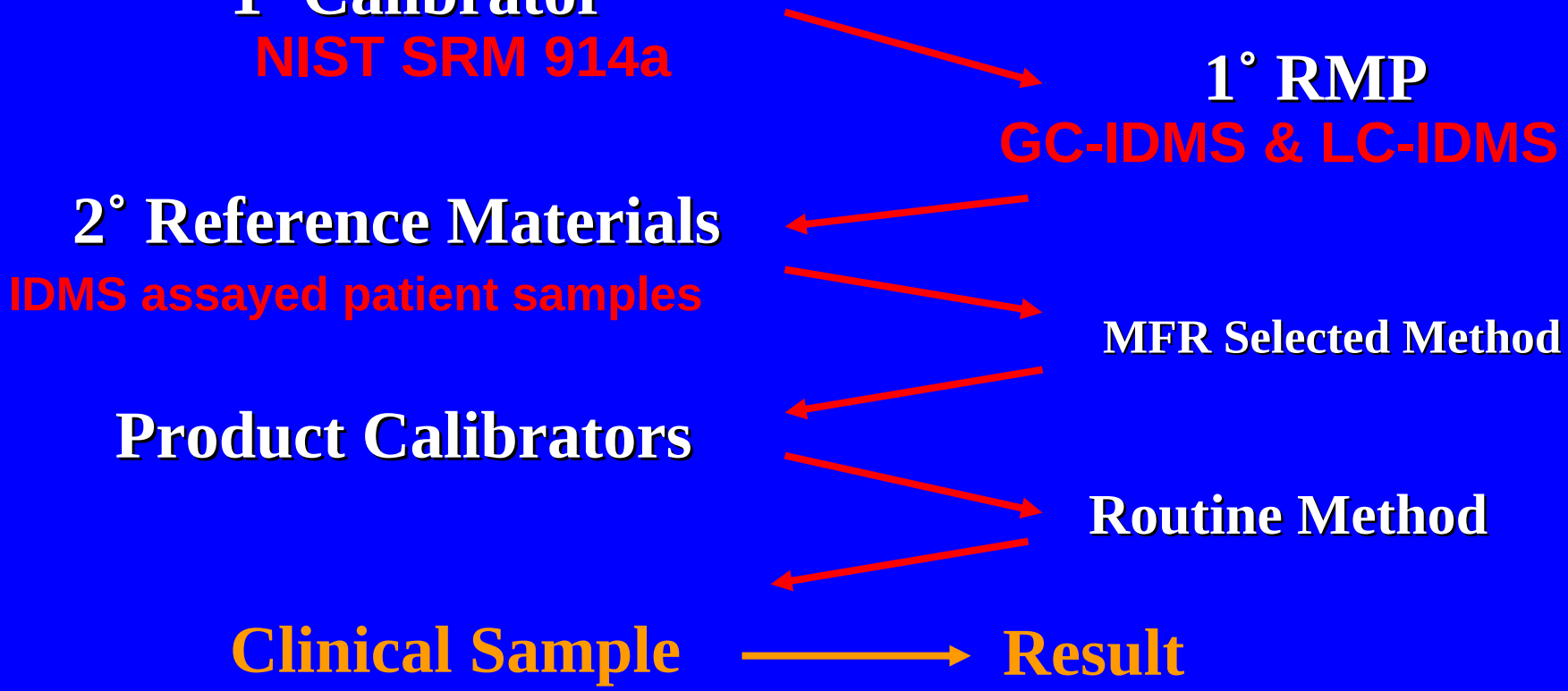
NKDEP Manufacturer's Workshop

Calibration Traceability - Routine Serum Creatinine Methods



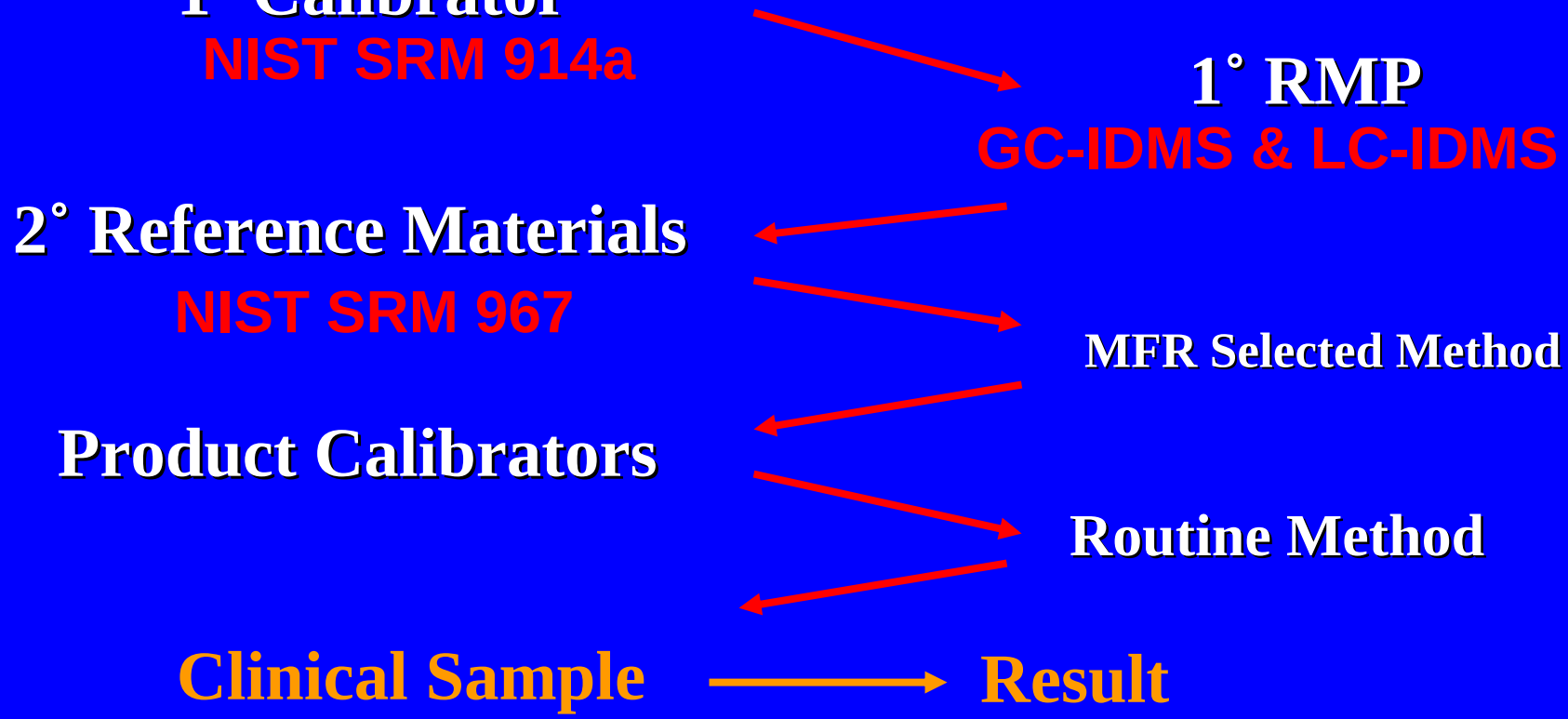
NKDEP Manufacturer's Workshop

Calibration Traceability - Routine Serum Creatinine Methods



NKDEP Manufacturer's Workshop

Calibration Traceability - Routine Serum Creatinine Methods



NKDEP Manufacturer's Workshop

Next steps for manufacturers…

1. Update calibrator assigned values if needed
2. Notify customers and EQAS/Proficiency program providers of intentions and timeline to implement new calibrations
   - Provide customers with adequate transition time, since communications and training around the changes may be complex
   - NKDEP, IFCC and EC4 will provide jointly signed custom letters and templates to support manufacturers with communications

NKDEP Manufacturer's Workshop

Recommendations for Manufacturers

- Use NIST SRM 967 (release fall 2006)

OR

- Work with JCTLM listed reference lab offering IDMS measurements on sample panels
  - JCTLM has approved 3 GC-IDMS methods and 1 LC-IDMS reference method
  - JCTLM Website: www.bipm.fr/en/committees/jc/jctlm/

NKDEP Manufacturer's Workshop

Recommendations for Manufacturers

- Proactively guide customers on calibration issues.
  - Provide labs with mathematical relationship between results from the IDMS-calibrated method (new) compared to results for a previous conventionally calibrated method
  - May be critical to enable labs and/or pharmacies to adjust IDMS-traceable creatinine results to support conventional drug dosing schedules based on clinical data established using creatinine methods with traditional calibration
- Communicate with PT/EQA providers
- Address imprecision and non-specificity (longer term)

Support Letter for Manufacturers

Dear Customer:

We are writing on behalf of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC); the National Kidney Disease Education Program (NKDEP), an initiative of the National Institutes of Health (USA); and the European Communities Confederation of Clinical Chemistry (EC4) to introduce you to our Creatinine Standardization Program and highlight its implications for clinical laboratories. The effort is part of a larger worldwide initiative to help health care providers better identify and treat chronic kidney disease (CKD) in order to prevent or delay kidney failure and improve patient outcomes.

Reliable serum creatinine measurements are critical to increasing the diagnosis and treatment of CKD. Until now, inter-laboratory variability in serum creatinine measurement rendered all equations for estimating glomerular filtration rate (GFR), including the Modification of Diet in Renal Disease (MDRD) Study equation, less accurate in the slightly elevated range of serum creatinine concentrations [<133 µmol/L (1.5 mg/dl)]—the relevant range for detecting CKD (<60 mL/min/1.73 m^2). The Creatinine Standardization Program is intended to reduce inter-laboratory variation in creatinine assay calibration and provide more accurate estimates of GFR.

To that end, the Creatinine Standardization Program encourages IVD manufacturers to adjust the calibration of routine serum creatinine methods to be traceable to the internationally accepted reference system (reference materials, methods, and laboratories) described in ISO 17511 and CLSI X5R and approved by the JCTLM (www.bipm.org). The Program also encourages manufacturers to work with clinical laboratories to coordinate this calibration adjustment with the introduction of a revised GFR estimating equation appropriate for use with standardized creatinine methods.

and other concerned IVD manufacturers are responding to the need for standardization, while recognizing the challenge to and patience required of its customers when implementing the new calibration. will be communicating with you regarding their timeline for full implementation. Once completed, the clinical laboratory community's efforts will dramatically help to improve CKD detection.

Please visit the laboratory professionals section of the NKDEP website http://www.nkdep.nih.gov/labprofessionals to learn more about the Creatinine Standardization Program, find useful materials and resources, and sign up to receive free email updates so we can help you stay abreast of creatinine standardization activities.

We wish to thank and their customers for their efforts and patience during this transition period. Please do not hesitate to send us your questions or comments at csp@info.niddk.nih.gov.

Communication to EQAS/PT Providers

Dear Proficiency Testing (PT)/External Quality Assessment Schemes (EQAS) Providers:

We are writing on behalf of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC); the National Kidney Disease Education Program (NKDEP), an initiative of the National Institutes of Health (USA); and the European Communities Confederation of Clinical Chemistry (EC4) to introduce you to our Creatinine Standardization Program and highlight its implications for PT/EQAS providers.

The NKDEP, in collaboration with the IFCC and EC4, has launched the Creatinine Standardization Program to reduce inter-laboratory variation in creatinine assay calibration and provide more accurate estimates of glomerular filtration rate (GFR). The effort is part of a larger NKDEP initiative to help health care providers better identify and treat chronic kidney disease in order to prevent or delay kidney failure and improve patient outcomes….

….Specifically, IFCC, NKDEP and EC4 are asking PT/EQAS providers to:

1) Advise participant laboratories that you will be collaborating with IVD manufacturers, IFCC, NKDEP and EC4 to ensure appropriate grading of PT/EQAS data during a transition period for implementation of the Creatinine Standardization Program, to ultimately improve the worldwide performance of GFR estimates based on standardized serum creatinine values.

2) Make accommodations in participant grading within your respective survey programs during the transition of routine creatinine methods from traditional calibrations to IDMS-traceable calibrations. It is anticipated that bimodal distributions of survey results within a method may be observed. When this occurs, it will most likely be the result of groups of laboratories independently transitioning to new creatinine calibrations for a particular method, and it should not be a cause for a given laboratory to fail a PT/EQAS challenge. Thus, it may be necessary for the PT/EQAS providers to collaborate with IVD manufacturers to create new instrument/method peer groups for their participants that reflect the calibration status of each method that is undergoing a calibration transition (traditional or IDMS-traceable) for both serum and urine creatinine values.


Photo courtesy of Bob Rej, NYS DOH
MANN MUNK
MED. PROFESSOR
DER UNIVERSITÄT
UND
LIED DER AKADEMIE
WISSENSCHAFTEN
ZU
BERLIN
3. FEBRUAR 1839
IN POSEN
T. 1. OKTOBER 1912
IN BERLIN
MAX JAFFÉ

NKDEP Manufacturer's Workshop

References

1. Clinical Chemistry 2006; 52:5-18
2. www.nkdep.nih.gov/labprofessionals

Acknowledgement: Gary Myers, CDC, for allowing me to liberally borrow his material.

Thank You!