Laboratory method harmonization/standardization - What a nephrologist needs to know

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What is harmonization

- Uniform results among different measurement procedures for the same laboratory test
  - Nomenclature
  - Patient preparation
  - Specimen collection and handling
  - **Result value**
  - Reporting units
  - Interpretive information

Today's topic
Terminology

- **Harmonization**: achieving comparable results among different measurement procedures
  - Usually implies there is no reference measurement procedure

- **Standardization**: achieving comparable results by having calibration traceable to a reference measurement procedure
What is the problem

- Many laboratory measurement procedures give different results for the same specimen.
Why does it matter

- Patients may get the wrong treatment
  - Many clinical decisions are informed by laboratory results
  - Many clinical guidelines use a fixed laboratory test value for treatment decisions
Why else does it matter

- Clinical studies may use a central lab with a single method
  - Guidelines from the study cannot be implemented until all other methods are harmonized to the central lab

- Clinical studies may use different methods
  - Data cannot be aggregated to develop guidelines until the results are harmonized
Diabetes and urine albumin

- Diabetics are tested annually to identify early kidney damage
- KDIGO (2012) and other guidelines recommend a decision value of 30 mg/g creatinine
- Results could differ as much as 70% in this concentration range among different measurement procedures
  - Based on assessment of 16 routine measurement procedures with 332 patient samples (manuscript submitted)
How to achieve uniform, and thus comparable, results

- Calibration of all measurement procedures is traceable to a common reference system

- All measurement procedures measure the same quantity
ISO 17511:2003

In vitro diagnostic medical devices - Measurement of quantities in biological samples - **Metrological traceability of values assigned to calibrators and control materials** (under revision)

➤ **CLSI: implementation guideline**
How is traceability credentialed

Joint Committee for Traceability in Laboratory Medicine (JCTLM)

- Reviews and lists reference system components based on conformance to ISO documents
  - Reference measurement procedures
  - Reference laboratories
  - Reference materials

http://www.bipm.org/jctlm/
Traceability (based on ISO 17511)

A reference system

Primary Reference Material
(NIST SRM 914a crystalline creatinine)

Primary Calibrator
(creatine in water)

Secondary Reference Material
(NIST SRM 967 creatinine in frozen human serum)

SI unit (mmol/L)

Primary Reference Measurement Procedure
(gravimetry, calibrated with NIST mass standards)

Secondary Reference Measurement Procedure
(IDMS)
Traceability (based on ISO 17511)

Primary Reference Material
(pure substance)

Secondary Reference Material
(matrix)

Mfr Working Calibrator

Mfr Product Calibrator

Patient sample result

SI unit
Reference Procedure
(e.g. IDMS)

Mfr Selected Procedure

Mfr Standing Procedure

Routine Procedure

Patient sample results are equivalent to the reference procedure results

Primary Reference Material

Secondary Reference Material
(calibrator)

Mfr Selected Procedure

Mfr Standing Procedure

Routine Procedure

SI unit
Reference Procedure
(e.g. IDMS)
Creatinine is standardized for most lab measurement procedures

Creatinine measurement still has issues: interfering substances in a specimen

<table>
<thead>
<tr>
<th>Subject group</th>
<th>n</th>
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<th>E2 Pos</th>
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<td>Protein, urine, 15 were 3-22 g/L</td>
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</tbody>
</table>

Creatinine measurement still has issues: imprecision, e.g. POCT
Measurands for which no reference procedures exist
- Cystatin C (ref material)
- Urine albumin
- PTH
- AKI biomarkers

Measurands for which reference procedures exist
- Creatinine
- Phosphate
- Calcium
A reference method may not ensure harmonized results

Phosphate at 3.2 mg/dL (1.0 mmol/L)

What happens when there is no reference measurement procedure
Traceability (based on ISO 17511)

Patient sample results are traceable to a reference material

Secondary Reference Material (matrix)

Mfr Working Calibrator

Mfr Product Calibrator

Mfr Selected Procedure

Mfr Standing Procedure

Routine Procedure

(calibrator)

• Value assignment
• Commutability

Patient sample result
Approaches to value assignment

⇒ Arbitrary units, e.g. U/L

⇒ A nominal concentration based on a pure substance (e.g. purified or recombinant protein)
   • may not be the same as the clinical measurand
   • may contain reactive impurities or aggregated forms

⇒ By a designated comparison procedure, or mean of a group of procedures (e.g. cystatin C)
Consensus values are adequate

- The actual quantity value (e.g. concentration) may not be known
- Harmonization can be achieved
- Clinical guidelines can be implemented
Traceability to a Reference Material

Secondary Reference Material (calibrator)

Procedure 1

Procedure 2

Procedure 3

Procedure n

Must be commutable with patient samples for all measurement procedures with which it will be used

Patient Samples

Results 1

Results 2

Results 3

Results n
Commutable: same relationship for clinical samples and reference materials
Non-commutable: different relationship for clinical samples and reference materials
Calibration with non-commutable materials

Causes patient sample results to be incorrect
The Problem

Many secondary reference materials are not commutable with native clinical samples for routine clinical laboratory procedures
Many secondary reference materials are not commutable with native clinical samples for routine clinical laboratory procedures.

- Historically, commutability of reference materials was not validated for use with routine clinical laboratory measurement procedures.
The manufacturer’s procedures used for value assignment may be the same as the routine procedure.

- Secondary Reference Material (matrix)
- Mfr Working Calibrator
- Mfr Product Calibrator
- Patient result

Why commutability matters
Many secondary reference materials are not commutable with native clinical samples for routine clinical laboratory procedures. This breaks the traceability chain.
The Problem

Many secondary reference materials are not commutable with native clinical samples for routine clinical laboratory procedures.

- Even though manufacturers show traceability, the process fails to provide equivalent results for patient samples when different measurement procedures are used.
Publishers: Variability Between Methods

Almond A, Ellis AR, Walker SW
Current parathyroid hormone immunoassays do not adequately meet the needs of patients with chronic kidney disease.


**PTH concentration (pmol/L) in a single patient.**

**Treatment variation caused by comparing highest and lowest PTH concentrations in 18 patients.**
Must change practice to require commutability validation for reference materials intended for use with:

- Manufacturer’s standing procedures
- Routine clinical laboratory procedures

IFCC Working Group on Commutability
(established March 2013)

• Operating procedures for the formal assessment of commutability
• Criteria for commutability taking into account the intended use of a reference material
• Standard terminology to describe commutability characteristics
• Information to be provided regarding commutability
• Education of manufacturers, laboratories, end users
Standardization of Cystatin C

- A certified reference material is available (ERM-DA471/IFCC in 2010)
  - Commutability is validated

- Some method manufacturers are now establishing calibration traceability to this new reference material

- Standardized values are not universally implemented
Cystatin C

• eGFR equations based on large populations and standardized cystatin C are being published

• Equations cannot be universally applied until the standardization is completed
What happens when there is both:

- no reference measurement procedure
- no reference material
Traceability (based on ISO 17511)

- There is no common calibrator
- Method specific reference intervals or decision values are used

Mfr Working Calibrator
Mfr Product Calibrator

Routine Procedure
Mfr Standing Procedure

Patient sample result

Patient sample results are not traceable to any international reference
Examples: traceable to a manufacturer’s working calibrator
(no reference material nor reference measurement procedure)

- Urine albumin (being addressed by NKDEP)
- NGAL
- KIM 1
- Many biomarkers discussed at this conference
Possible approaches to achieve harmonization when no RMP nor RM

- Based on a panel of patient samples
  - Traceable to an all methods mean (outliers removed)
  - Traceable to a designated measurement procedure (arbitrary, but one which has good correlation with clinical outcome)
Calibration traceability does not ensure accuracy

- Measurement procedure may not be specific for the measurand
  - Interfering substances may influence the result

- Measurand may not be well defined
  - Molecular form(s) of clinical interest may not be understood
Urine protein

- Many different proteins may be present – the measurand is not defined
- Different methods measure different proteins in the mix
- Not possible to harmonize results
- Cannot compare values from different methods used in different laboratories
Heterogeneity

Protein biomarkers may be different in health and disease

- Post-translational modifications
- Molecular complexes
- Ligands may bind
- Fragments may exist (truncation, proteolysis)
Albumin Forms – what is measured?
- what should be measured?

Glycated forms are a greater proportion in urine - attributed to differential uptake in the tubules.

Many ligands bind and are concentrated in urine.

Protease activity and chemical reactions occur in plasma and urine.

Unpaired cysteine-34 can form albumin dimers and other covalent modifications.

C and N terminal truncation occurs.

Large (>5 kDa) and small (500-5000 Da) fragments have been identified in plasma and urine.

Slide courtesy of David Bruns
IDMS measured a complete albumin molecule in urine

Bias between concentrations of trypsin cleavage peptides from urine albumin measured by LCMS for 340 urine samples

<table>
<thead>
<tr>
<th>Normalized</th>
<th>Fragment</th>
<th>Bias between pairs</th>
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<td>0.991</td>
<td>QTALVELVK</td>
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</table>

Near amino terminus – aa 13
Near carboxy terminus – aa 534 of 585

Heterogeneity may still be present

- Trypsin cleavage peptides could be formed from altered albumin molecular forms
- Immunoassays react with epitopes in the albumin molecule
- IDMS and immunoassay may not measure the same quantity
Immunoreactivity with modified albumin

Method A | Method B
---|---

Sample 1
Albumin (mg/L) | 0 | 200 | 400<br>Total Protein (mg/L) | 0 | 250 | 500<br>2.0 g/L

Sample 2
Albumin (mg/L) | 0 | 200 | 400<br>Total Protein (mg/L) | 0 | 60<br>1.6 g/L

Sample 3
Albumin (mg/L) | 0 | 200 | 400<br>Total Protein (mg/L) | 0 | 60<br>0.6 g/L

Samples stored for 3 years at -20°C

Specimen specific influences on UA measurement procedures

CV due to specimen specific influences for 332 urine samples:

- 0-7% for 13 of 16 commercial methods
- 12-14% for 3 of 16 methods (same manufacturer)
- Many methods were minimally affected by urine matrix or albumin molecular forms
- Some methods were more sensitive to such influences

Bachmann et al. (manuscript submitted)
Bias was the major problem for 16 commercial methods for UA

Bachmann et al. (manuscript submitted)
In development for urine albumin

- **Reference materials**
  - NIST SRM 2925 pure albumin
  - NIST SRM 3666 albumin in frozen human urine
  - NIST SRM 3667 creatinine in frozen human urine
  - **Diluted** IRMM DA470k/IFCC serum proteins RM

- **Reference measurement procedure**
  - NIST and Mayo Clinic based on LC-IDMS
Molecular size, and opportunity for heterogeneity, in kidney biomarkers

Creatinin
About the size of 1 aa
Muscle

Cystatin C
120 aa
All tissues

IL-18
157 aa
Multiple tissues

Kim-1
359 aa
Transmembrane protein

NGAL
178 aa
Widely expressed

Albumin
585 aa

Thanks to David Bruns for some of the images.
Example: NGAL

- Monomeric, homodimeric and heterodimeric forms
- Free vs. NGAL/MMP9 complex
- Immunoassays target different epitopes
- No reference material for calibration
- At the stage of method specific interpretation

What do we do?
International Forum organized by AACC in October, 2010

90 participants from 12 countries

Representing 62 organizations & manufacturers
Challenges for harmonization

- Materials are labeled as “reference materials” that have not been validated to be commutable for the intended measurement procedures.
- Inadequate understanding of the measurand – the quantity intended to be measured.
- Inadequate analytical specificity for the measurand.
Challenges for harmonization

- Lack of a systematic process to identify and prioritize measurands in need of harmonization

- Lack of systematic procedures to implement harmonization, in particular:
  - when there is no reference measurement procedure
  - when there is no reference material
Challenges for harmonization

- Despite many organizations in many countries working to improve harmonization:
  - The work is not coordinated to prevent
    - Duplication of effort
    - Different approaches by different groups
  - People do not know what others are doing
Challenges for harmonization

- Regulatory requirements
  - Changing calibration requires regulatory approval
  - Does the clinical benefit justify the cost to meet regulatory requirements?
  - Can regulatory guidance be modified to lower the cost?
The Roadmap

Develop an infrastructure to coordinate harmonization activities worldwide to include:

1. Prioritization of measurands
2. Coordination of work by different organizations
3. Developing technical processes to achieve harmonization
4. Surveillance of success of harmonization
Focus technical work on measurands for which no reference measurement procedure exists

- Measurands in this category have been technically challenging
- There have been few effective procedures implemented for harmonization of these measurands
Cooperation

- With other organizations already working to improve standardization / harmonization
- Provide a communications portal among organizations to prioritize and coordinate standardization / harmonization activities
- Maintain an open and transparent process
AN INFRASTRUCTURE FOR HARMONIZATION

International Consortium for Harmonization of Clinical Laboratory Results

- Review and Recommend
- Strategic Partners Group
- Council
- Governance, Administration
- Harmonization Oversight Group
  - Harmonization Implementation Groups
  - Special Working Groups
- Operations Management
- Work Groups

Secretariat/Host - AACC
ICHCLR: Council members

AACC

Korean Society of Clinical Chemistry

Chinese Association for Clinical Laboratory Management

College of American Pathologists
Strategic Partners Group

Key stakeholders:

Clinical practice groups
Laboratory practice groups
IVD manufacturers
Public health organizations

Metrology Institutes
Standards organizations
Regulatory organizations
PT/EQA organizations
Strategic Partners Group (Stakeholders):
- Clinical practice groups
- Laboratory practice groups
- IVD manufacturers
- Public health organizations
- Metrology Institutes
- Standards organizations
- Regulatory organizations
- PT/EQA organizations

Harmonization Oversight Group

Communication

Evaluate measurand proposals

When no RMP
- Solicit champion and funding
  - Clinically affected entity
  - Economically affected entity

Special Working Group
- Review priority and technical feasibility
- Recommendation to Harmonization Oversight Group

Harmonization Implementation Group
- Technical plan
- Surveillance plan
- Implement the plans
- Achieve JCTLM listing

Coordination / Cooperation
- If work is underway, refer to that group
- If RMP is possible, refer to another group
- If interest by another group, coordinate
Strategic Partners Group

Members of the Strategic Partners Group have the opportunity to support the program by submitting measurands in need of harmonization and to nominate experts for consideration to serve on the Harmonization Oversight Group. Members will receive project plans and milestone updates from Harmonization Implementation Groups for review and comment. Stakeholders who are committed to harmonization of clinical laboratory results (e.g. clinical laboratory and medical organizations, IVD manufacturers, metrology institutes, standard-setting organizations, public health organizations, regulatory agencies and individuals) may become members of the Strategic Partners Group. The annual membership fee for a Strategic Partners Group member is $500. Subscription to the Strategic Partners Group during 2013 will carry a Strategic Partner’s membership status forward through December of 2014 to coincide with an annual membership period.

Click here for more information on the operation of the International Consortium for Harmonization of Clinical Laboratory Results.

Join the Strategic Partners Group
Measurands

This section provides information on the status of harmonization or standardization of measurands. Information on reference measurement procedures and reference materials under development is provided when such information is available as well as information on commutability of existing reference materials where information exists. Links to organizations actively addressing harmonization of particular measurands are provided for inquiry on additional information on those projects. For measurands not yet harmonized, information is provided on the priority and technical feasibility for harmonization determined by the Harmonization Oversight Group.

Submit a Measurand

Review my Submissions
Questions / Comments

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