Laboratory Medicine Standardization Activity in Japan

National Institute Metrology of Japan (NMIJ)
Koichi Chiba
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Katsuhiko Kuwa
Japanese Committee of Clinical Laboratory Standards (JCCLS)

**Government Agencies:** 8
METI, MHLW, NMIJ/AIST, etc

**Professional Societies:** 32
- **JSCC** (Japan Society of Clinical Chemistry)
- **JSLM** (Japan Society of Laboratory Medicine)

**Other Clinical Societies**

**Industries:** 52

**Organizations:** JACRI*, JAIMA**

*JACRI: Japanese Association of Clinical Reagents Industry
**JAIMA: Japanese Analytical Instrument Manufacturers Association

Since 1985
Activities in JCCLS

1. Recommendation of Measurement Methods
2. Development of Matrix Reference Materials
3. External Quality Assessment
Activities in JCCLS

1. Recommendation of Measurement Methods
(by Japan Society of Clinical Chemistry)

- Ion Selective Electrode Measurement methods for Electrolytes; Na, K, Cl
- Measurement Methods for Enzymes; AST, ALT, CK, LD, γ-GT, ALP, AMY, ChE
- Enzymatic Measurement Methods; Glucose, Creatinine, Uric Acid, Total Cholesterol Triglycerides (Total Glycerides measurement)
- Measurement Method for Hemoglobin A1c
- Tonometry-based Measurement Methods for Blood Gases; pH, pCO2, pO2
Activities in JCCLS

2. Development of Multi-Analytes Reference Materials for Catalytic Concentration of Enzymes in Serum
(Japan Society of Clinical Chemistry)

- AST (holo type in cytosol)
- ALT (holo type in cytosol)
- CK
- LD
- γ-GT
- ALP
- AMY

(Underlined Items have been already listed in α-lists.)

They are produced from recombinants of human enzymes, except LD.

All analytes are in one bottle

(Freeze dried)
Activities in JCCLS

3. Development of Matrix Reference Materials
(by Japan Society of Clinical Chemistry)

- Electrolytes: \textit{Na, K and Cl for ISEs}
  Total Calcium & Total Magnesium
- Lipid: \textit{Total cholesterol for enzymatic analysis}
  HDL-Cholesterol for enzymatic analysis
  \textit{Triglycerides for enzymatic analysis}
- Glucose
- \textit{HemoglobinA1c}
- Creatinine
- Uric Acid
- Urea Nitrogen
- Blood Gases (pH, pCO$_2$, pO$_2$)

(Underlined Items have been already listed in $\alpha$-lists.)
Traceability System of Matrix CRMs

**Method**

- **Definitive Method**
  - Primary Reference Material
  - Reference Method
  - Secondary Reference Material
  - Field Method

- **Na, K, Cl**
  - IEG: Na
  - ID-MS: K, Cl
  - FAES: Na, K
  - Coulometry: Cl
  - 2nd Serum CRMs
  - ISE Method

- **Glucose**
  - 1st Serum CRMs
  - Hk-G6PD method
  - 2nd Serum CRMs
  - Enzymatic Analysis

- **Cholesterol**
  - 1st Serum CRMs
  - Abell-Kendall method
  - 2nd Serum CRMs
4. External Quality Control of Na, K and Cl Measurement by ISE Method

(EQA by Japan Medical Association)

Progress in Analytical Variation (CV)

Starting the Distribution of Serum CRM for ISE

- **Na**
- **K**
- **Cl**
Trueness Evaluation Using Uncertainty of Measured Value in Proficiency Testing

- Uncertainty (Cm)
- Bias (B)
- Mean Value (n=5) in Each Laboratory
- Target Value

\[ \text{Mean Value (n=5) in Each Laboratory} \]
K Measurement by ISE Method

Target Value: $4.96 \pm 0.01$ mmol/L
Allowable Limit: $\pm 0.1$ mmol/L including $B$

Mean (n=5)

Uncertainty ($C_m$)

Bias ($B$)

Target Value

Allowance limit

Participating Laboratories No.

In 2004

Sample H

Allowance limit

Mean (n=5)

+ $ts / \sqrt{n}$

- $ts / \sqrt{n}$
JOINT COMMITTEE for TRACEABILITY in LABORATORY MEDICINE (JCTLM)

Declaration of co-operation

A framework for international recognition of available higher-order reference materials, measurement procedures and reference measurement laboratories

Established in Sevres on 12 June 2002
New System of Developing and Providing Reference Materials in Japan

JCTLM: IFCC, ILAC, BIPM

NMIJ/AIST NMI

Government METI, MHLW

Profession
JSCC
JSLM
Others

Industry
JACRI
Others

Profession
JCCLS/Certification Committee

RM R&D Center (1)
RM R&D Center (2)

HECTEF SRC

IVD Manufacturers

Clinical Laboratories

NMIJ/AIST

National Metrology Institute of Japan
Collaboration System for Standardization of Clinical Chemical in Japan

1. Clinical Chemistry Organization
   - JSCC (Clinical Chemistry)
   - JSLM (Laboratory Medicine)
   - JAMT (Medical Technologists)
   - JRCLA (Registered Clinical Laboratory)

2. Metrology Organization
   - NMIJ/AIST

3. IVD Industry Organization
   - JACRI
   - JAIMA

4. Accreditation Organization
   - JAB
   - NITE

5. Authorities
   - METI
   - MHLW

JCTLM (International) and Domestic Standardization
Structure of Clinical Chemistry Standardization

Clinical Chemistry Organization
- JSCC
- JSLM
- JAMT
- JRCLA

Collaboration

WG1: Reference Materials/Reference Measurement Procedures
- National Standards
- Higher Order Reference Materials
- Matrix Reference Materials for Working Standards
- Reference Methods and Recommended Methods
- Standardization of Routine Methods

WG2: Harmonization for Measurement Values
- Standardization of Protocol for Internal Quality Control in a Lab.
- External Quality Control in each Area or Group
- Nationwide Standardization – Patchwork Standardization (Nationwide External Quality Control)

JCCLS

NMIJ/AIST

JACRI

Authorities
- METI
- MHLW

Fund from NEDO

Fund from METI
Development Program of Clinical CRMs in Japan

**NMIJ:** *Pure Material Type of CRMs*
- SI Traceable CRMs

**JCCLS:** *Higher Order Matrix CRMs*
- Metabolite and Substrates
- Blood Gases
- Electrolytes
- Hormones
- Lipids
- Proteins/Enzymes

**JACRI:** *Feasibility Study on Standardization of Clinical Chemical Reagents*
- Standardization of Working Standard Level of Calibrators
1. Development Program of Clinical CRMs by NMIJ

- Development of SI Traceable CRMs -

Metabolites
- Cholesterol
- Creatinine
- Uric Acid
- Urea
- Triglycerides

Hormones
- Progesterone
- Estradiol
- Testosterone
- Cortisol

Proteins
- Albumin (ALB)
- C-reactive protein
- PSA
- Insuline
- C-peptide (CPR)

BIPM & NMIJ Joint Research
NMIJ CRM 6001-a Cholesterol

Pure Cholesterol
Purity : 99.9 ± 0.1%

Certification Method:
Freezing-point depression method

Certified on March 2005
2. Development Program of Clinical RM by JCCLS

**Metabolite and Substrates**
- Glucose
- Creatinine
- Uric acid
- Urea
- Hemoglobin A1C
- Glycoalbumin

**Blood Gases**
- Blood gases

**Electrolytes**
- Ionized calcium
- Total calcium
- Total magnesium

**Hormones**
- Cortisol
- Insulin
- C-peptide (CPR)

**Lipids**
- HDL-cholesterol
- LDL-cholesterol

**Proteins/Enzymes**
- Secondary CRM of Albumin
- Serum albumin
- Urine albumin
- Pancreatic amylase
- Serum CRM for CRP
- Cholineesterase
- Lipase
3. Feasibility Study of Standardization of Clinical Reagents by JACRI

<table>
<thead>
<tr>
<th>Urine sodium (Na)</th>
<th>Digoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine potassium (K)</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Urine chloride (Cl)</td>
<td>β 2 — microglobulin</td>
</tr>
<tr>
<td>Urine magnesium (Mg)</td>
<td>Estradiol</td>
</tr>
<tr>
<td>Urine calcium (Ca)</td>
<td>Progesterone</td>
</tr>
<tr>
<td>Urine urea nitrogen (UN)</td>
<td>Testosterone</td>
</tr>
<tr>
<td>Urine uric acid (UA)</td>
<td>Thyroid stimulating hormone</td>
</tr>
<tr>
<td>Urine creatinine (Cre)</td>
<td>Thyroxine</td>
</tr>
<tr>
<td>Urine amylase (AMY)</td>
<td>β -human choriogonadotropin</td>
</tr>
<tr>
<td>Urine glucose (GLU)</td>
<td>Fibrinogen degradation products (FDP)</td>
</tr>
<tr>
<td>Urine inorganic phosphorus (IP)</td>
<td>D-dimer</td>
</tr>
<tr>
<td>Serum inorganic phosphorus (IP)</td>
<td>Carcinoembryonic antigen (CEA)</td>
</tr>
<tr>
<td>Serum prostate specific antigen</td>
<td>Alpha-feto protein (AFP)</td>
</tr>
<tr>
<td>Serum antinuclear antigen</td>
<td>Carbohydrate antigen 125 (CA125)</td>
</tr>
<tr>
<td>Serum lithium (Li)</td>
<td>Ferritin</td>
</tr>
</tbody>
</table>
GW2: Patchwork Standardization for Nationwide

Global Harmonization

Higher Order CRM:
BIPM & NMIJ

International Standard:
JCCLS & IFCC

Establishment of the Nationwide Standardization

Higher Order CRM

Consensus Domestic Standard

Nationwide Harmonization

Net work Lab

Standardization in Nationwide

Feasibility Study of Patchwork Standardization
- *Intra-* and *Inter-*Laboratory Variation -

Participants; 40 Labs.

Testing Items
1. Biochemical Analytes: 26
2. CBC (Blood Counts and Hemoglobin): 5

Assay Procedure
1. Intra-laboratory variation
   (1) Single assay: Biochemical analytes
       Assay is performed at morning and evening.
   (2) Double assay: CBC
       Assay is performed at morning.
2. Inter-laboratory variation
   Comparison of mean values
### Intra-laboratory Variation on Biochemical Analytes

<table>
<thead>
<tr>
<th>Analytes</th>
<th>Abnormal Pooled Serum</th>
<th>Normal Pooled Serum</th>
<th>Data Trol</th>
<th>Aalto</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Bilirubin</td>
<td>mg/dL</td>
<td>5.43</td>
<td>0.69</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>CV(%)</td>
<td>0.61~3.41</td>
<td>0~7.15</td>
<td>0~5.75</td>
</tr>
<tr>
<td>Glucose</td>
<td>mg/dL</td>
<td>353.7</td>
<td>94.7</td>
<td>90.9</td>
</tr>
<tr>
<td></td>
<td>CV(%)</td>
<td>0.21~2.85</td>
<td>0.34~1.73</td>
<td>0.39~1.42</td>
</tr>
<tr>
<td>Urea Nitrogen</td>
<td>mg/dL</td>
<td>65.9</td>
<td>13.9</td>
<td>15.6</td>
</tr>
<tr>
<td></td>
<td>CV(%)</td>
<td>0.44~3.16</td>
<td>0.81~3.03</td>
<td>1.01~3.01</td>
</tr>
<tr>
<td>Creatinine</td>
<td>mg/dL</td>
<td>6.74</td>
<td>0.76</td>
<td>1.11</td>
</tr>
<tr>
<td></td>
<td>CV(%)</td>
<td>0.46~3.35</td>
<td>1.32~5.04</td>
<td>0~2.32</td>
</tr>
</tbody>
</table>
**Inter-laboratory variation on Biochemical Analytes**

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Abnormal Pooled Serum</th>
<th>Normal Pooled Serum</th>
<th>Data Trol</th>
<th>Aalto</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Bilirubin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD(mg/dL)</td>
<td>0.16</td>
<td>0.05</td>
<td>0.04</td>
<td>0.14</td>
</tr>
<tr>
<td>CV(%)</td>
<td>2.87</td>
<td>7.33</td>
<td>5.27</td>
<td>4.14</td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD(mg/dL)</td>
<td>5.12</td>
<td>1.06</td>
<td>1.19</td>
<td>3.11</td>
</tr>
<tr>
<td>CV(%)</td>
<td>1.45</td>
<td>1.12</td>
<td>1.30</td>
<td>1.13</td>
</tr>
<tr>
<td>Urea Nitrogen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD(mg/dL)</td>
<td>1.73</td>
<td>0.51</td>
<td>0.37</td>
<td>1.88</td>
</tr>
<tr>
<td>CV(%)</td>
<td>2.62</td>
<td>3.68</td>
<td>2.38</td>
<td>3.47</td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD(mg/dL)</td>
<td>0.13</td>
<td>0.04</td>
<td>0.04</td>
<td>0.09</td>
</tr>
<tr>
<td>CV(%)</td>
<td>1.93</td>
<td>4.77</td>
<td>3.32</td>
<td>1.90</td>
</tr>
</tbody>
</table>
Medical and Economic Impact of JCTLM

**Impact**

- Diagnosis and Preventative Medicine Based on an Individual Specificity
- Development of Medicines, IVDs, Diagnosis Tools
- Study on Medical Science and Preventative Medicine
- Long Term Individual Record of Clinical Laboratory Data
- Improving Medical Treatment, Consultation, Medication, etc.
- Effective Use of Laboratory Data in Nationwide

**Clinical Chemistry**

- Standardization of Diagnosis Procedure and Criteria
- Database of Clinical Chemistry
- Standardization of Health Status
- Comparability of Clinical Chemical Data in Laboratory

**Standardization By JCTLM and JCCLS**

- International Standardization of SOP
- External Quality Control
- Link Labs.

- Development of National and International Reference Materials
- International Comparison
Thank you for your Attention!!