Post analytical variation: impact of difference in reference intervals

Dr. Miranda van Berkel, General Clinical Chemistry EQA
Radboudumc Nijmegen
The speaker has no financial relationship with any IVD industry
Clinical decision making

Clinical decisions are rightfully made when doctors...

- Ask the right questions
- Order the right tests
- Get the right results
- Interpret results to the right decision limits
- Take the right corresponding action

Guidelines
Good Clinical Practice

Standardization

Evidence-based medicine

Harmonisation
Evaluation of test results:

- Interpretative comments
- Appropriate calculation
- Reference intervals & decision limits
- Reporting units
- Critical values
- Turnaround time
5.6.3 Interlaboratory comparisons

5.6.3.1 Participation

The laboratory shall participate in an interlaboratory comparison programme(s) (such as an external quality assessment programme or proficiency testing programme) appropriate to the examination and interpretations of examination results. The laboratory shall monitor the results of the interlaboratory comparison programme(s) and participate in the implementation of corrective actions when predetermined performance criteria are not fulfilled.

NOTE The laboratory should participate in interlaboratory comparison programmes that substantially fulfil the relevant requirements of ISO/IEC 17043.

The laboratory shall establish a documented procedure for interlaboratory comparison participation that includes defined responsibilities and instructions for participation, and any performance criteria that differ from the criteria used in the interlaboratory comparison programme.

Interlaboratory comparison programme(s) chosen by the laboratory shall, as far as possible, provide clinically relevant challenges that mimic patient samples and have the effect of checking the entire examination process, including pre-examination procedures, and post-examination procedures, where possible.
My opinion of including post analytical phase in EQA program

A. It is **of no added value** for interpretation of patient results
B. It is **suited** for harmonisation of interpretation of patient results
C. Already in place, I use it regularly for interpretation of results
D. Only some elements (eg units and reference intervals) are useful
What can be learned from other EQA organisers?

Patient Report Comments

Case Details

<table>
<thead>
<tr>
<th>Case Details</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>135 (136-145) mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.7 (3.5-5.1) mmol/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>100 (98-107) mmol/L</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>8 L (22-29) mmol/L</td>
</tr>
<tr>
<td>Urea</td>
<td>2.7 L (3.2-7.3) mmol/L</td>
</tr>
<tr>
<td>Creatinine</td>
<td>73 (62-106) mmol/L</td>
</tr>
<tr>
<td>Glucose</td>
<td>6.4 H (3.5-5.4) mmol/L</td>
</tr>
<tr>
<td>Lactate</td>
<td>1.6 (0.5-1.6) mmol/L</td>
</tr>
<tr>
<td>eGFR</td>
<td>&gt;90 (&gt;90) ml/min/1.73m2</td>
</tr>
<tr>
<td>Osmolality</td>
<td>335 H (280-300) mmol/kg</td>
</tr>
</tbody>
</table>

Participant No.

Your Comment
Severe metabolic acidosis with a high anion and osmolar gap. Methanol toxicity. Suggest ethanol level and ABG. Requires urgent management.

Your Key Words
Severe metabolic acidosis Pref
High Anion Gap Metabolic Acidosis Pref
High Osmolar Gap Pref
Methanol poisoning Pref
Sugg. blood ETOH levels Pref
Suggest ABG Pref
Urgent management required Pref

Post analysis in EQA

Evaluation of test results:

- Interpretative comments
- Appropriate calculation
- Reference intervals & decision limits
- Reporting units
- Critical values
- Turnaround time
Post analysis in EQA

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Incongruence in reference-intervals
Analytes

ALAT
ASAT
CK
GGT
LD
Amyl
AF
Ca
Cl
Gluc
K
Kreat
Mg
Na
TE

Harmonisation ref intervals:

not Standardized

Standardized
Analytes

- ferritine
- Albumin
- ACE
- Lp(a)
- Ammonia
- PCT
- Fosfaat
- Fe
- Urea
- lipase
Harmonisation reference intervals:

**Standardized: sodium**

**Not Standardized:** ALB, Ferr

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>100 % ?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td>? %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td>? %</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td></td>
<td></td>
<td></td>
<td>100 %</td>
</tr>
</tbody>
</table>

Estimated agreement in interpretation:

- A (100 % ?)
- B (? %)
- C (? %)
- D (100 %)
Goal post analysis EQA

- Create insight into differences in ref interval
- Impact on interpretation of result
- Compare individual laboratory interpretation with ‘harmonized’ interpretation
Methods

1. Questionnaire for reference intervals of 8 analytes (n=55 laboratories)
   1. 55yr old woman
2. Visualize LL and UL
3. Calculate interpretation ‘low’, ‘normal’, ‘hi’ with EQA results compared to ‘target decision’ with:
   a) Own reference intervals
   b) Harmonized reference intervals
4. Calculate disagreement of decision between a & b)
Sample 1a ‘Target’ decision
Ref value vs harmonized LL & UL

Target decision

Laboratory-based reference-intervals

Harmonized reference-intervals

% agreement:

- 80%
- 95%
Reference interval ferritin

Ferritin LRL

Method

Abbott Alinity
Beckman Coulter Access/Dxl
Roche Cobas
Siemens Atellica
Siemens Dimension Vista

number of laboratories

0.0 2.5 5.0 7.5 10.0
10 15 20 25 30
Lower Reference Limit of Ferritin (µg/L)

Ferritin URL

Method

Abbott Alinity
Beckman Coulter Access/Dxl
Roche Cobas
Siemens Advia/Centaur
Siemens Atellica
Siemens Dimension Vista

number of laboratories

0 5 10 15
150 200 250 300 350 400
Upper Reference Limit of Ferritin (µg/L)

Radboudumc
Agreement in interpretation?

2021.5A sample result

Reported Ferritin Concentration (µg/L)
Reference interval: Albumin

**Standardized**

agreement in interpretation

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**Albumin LRL**

**Albumin URL**
Agreement in interpretation: Albumin

Albumin 2021.1B sample result (g/L)

Albumin laboratory LRL
Visualise LL and UL: standardised tests
The agreement for interpretation of sodium 147 mmol/l is

A. Less than 80%
B. Between 80-90%
C. Between 90-95%
D. Higher than 95%

The agreement in interpretation:

- A: 0-58%
- B: ?%
- C: 32-86%
- D: 100%

Standardized: Agreement in interpretation?
LL and agreement in interpretation: Sodium

Sodium 2021.1F sample result (mmol/L)
UL and agreement in interpretation: Sodium

Sodium 2021.4C sample result (mmol/L)

Reported Sodium Concentration (mmol/L)
Take home

- Discrepancies in ref intervals still exists for standardized analytes
- Use of ‘harmonized’ ref intervals lead to ‘harmonized interpretation’
- EQA program for harmonization of ref intervals can aid
- Pilot: SKML rondzending ‘interpretation harmonization’

<table>
<thead>
<tr>
<th>not Standardized</th>
<th>Standardized</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 0-58 %</td>
<td>B 80-85%</td>
</tr>
<tr>
<td>C 32-86 %</td>
<td>D &gt; 95%</td>
</tr>
</tbody>
</table>

agreement in interpretation
Special thanks to

Marith van Schrojenstein-Lantman
Marc Thelen
EQA general clinical chemistry members