Whose test is right: yours or mine?

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What is a reference interval

- 2 sd = 68%
- 2 sd = 95%
- 3 sd = >99%
What is normal?

- Gaussian
- Percentile
- Culturally desirable
- Risk factor
- Diagnostic
- Therapeutic

- Normal means “typical”
- Normal means not requiring further follow-up or intervention
- Normal means healthy ie absence of disease
What is normal: haemoglobin in WAAF

![Graph showing haemoglobin levels over time in WAAF](image-url)
Why do Docs do too many tests?

- To be complete
- “They say”
- We’ll get in trouble if we don’t
- If I don’t do it know it will be forgotten
- Since the patient is here, we might as well
- We are in an academic unit
- Malpractice
- Protocol
- If it were my relative
- How do I know he doesn’t have ... (the heroic search)
- The fishing expedition
- I would want to know if my tests were abnormal

NEJM 1979;300:1983
Why does primary care do blood tests?

- Specific diagnosis 23%
- Screening 10%
- Monitoring diseases and treatments 38%
- Patient reassurance 16%
- Doctor reassurance 11%
- Uncertainty 14%

Eur J GP 2001;7:138
What is a reference interval

1. What is the analyte?
2. What is the interval?
3. What is the confidence?
4. What is the population?
5. What is the decision limit?
6. What is the clinical risk?
Uncertainty

Ferritin (µgL)

Inadequate stores

Adequate stores

Zone of uncertainty

10 ~50
How much physiology do we know?

- Sex
- Age
- Ethnicity
- Obesity
- Time (day/season)
- Diet
- Within person variation
Alanine aminotransferase (NHANES III) - white females
Alanine aminotransferase (NHANES III) - white females
Effect of season

<table>
<thead>
<tr>
<th></th>
<th>Winter</th>
<th>Summer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers</td>
<td>15.6 ± 1.2</td>
<td>15.6 ± 1.0</td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>15.4 ± 1.1</td>
<td>14.8 ± 0.9</td>
</tr>
</tbody>
</table>

Clin Lab Haem 1997;19:177-81
Time of day

![Graph showing hemoglobin levels over time]

- Hemoglobin, mmol/L
- Time, h

8 AM 2 PM 8 PM 2 AM 8 AM

DOI 10.1515/cclm-2016-0716
Within person variation

mmol/L * 16.1 = g/L

RCV = 7.6%
Reference limits or Decision limits

Cholesterol
Diabetes
PSA
CA125
eGFR
Haemoglobin
Variation in thyroid function within reference range and adverse outcomes

- **TSH > 2.0 mU/L**: Increased 20 year risk of hypothyroidism
- **TSH > 2.0 mU/L**: Increased frequency of thyroid autoantibodies
- **TSH 2.0-4.0 mU/L**: Cholesterol values respond to thyroxine replacement
- **TSH > 4.0 mU/L**: Increased risk of heart disease
- **TSH 0.2-5.5 mU/L**: Decreased psychological wellbeing in patients on thyroid hormone compared with controls
- **TSH in normal range**: Impaired psychomotor development of infant if occurs in first trimester

*Lancet* 2002;360:353-4
Decision limits

Mean HbA$_1c$ = 11%

Retinopathy progression, rate

Length of follow-up, years

Diabetes 1995;44:968
What is a normal cholesterol?
The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration?

Ernest Beutler and Jill Waalen

Blood 2006;107:1747
• Sexual dimorphism in humans only
• Iron deficiency is common in women worldwide except Bantu, Ethiopia and Australia Aborigines
• 25-30% US women have absent iron stores or low transferrin saturation
• Therapeutic iron raises Hb in women close to values in men
• Systematic review (1994)
  - ferritin 50 mg/L = 50% chance of absent marrow iron stores
WHO definition of anaemia and mortality

16334 apparently healthy subjects
Annual health checks
71200 examinations
11511 males
4823 females

WHO anaemia
Males <130 g/L
Females <120 g/L

Low fitness 29% M; 28% F
Anaemia & mortality in the elderly

Prospective
65-84 years
Blood tests 7536
Full data 4501

Anaemia defined as:
M 100-129
F 100-119

Age adjusted nadir for death is at
Males  Hb 150 g/L
Females Hb 140 g/L
Threshold Haemoglobin Levels and the Prognosis of Stable Coronary Disease: Two New Cohorts and a Systematic Review and Meta-Analysis

20,131 new D stable IHD

14,171 first MI survival >7 days
Challenges

- What is normal
- Accept kit inserts or determine local RI
- Who are appropriate reference individuals
- Are RI related to method bias
- How many variables are considered
- Tests with no reference data
- Assays with different standardisation
- What are RIs for analytes with decision limits
- Narrative reports
- Can we continue the current pretence in the era of EPR
Who will be using laboratory reports?

- Patients
- Pharmacists
- Physicians assistants
- Nurses
- Physicians
- Other AHP
- National disease registries
- Managers & commissioners
- Insurance companies

How will each of them use the information?

What information do each of them want?
**What do patients and doctors want?**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Doctors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• All possible helpful information</td>
<td>• <em>Help!</em></td>
</tr>
<tr>
<td>• Available as soon as technically possible</td>
<td>• Fast and accurate results</td>
</tr>
<tr>
<td>• To make the best informed decision possible</td>
<td>• Understandable and useful information</td>
</tr>
<tr>
<td>• In order to reduce the risk of...</td>
<td>• Direction on therapy</td>
</tr>
<tr>
<td>...morbidity, mortality, misdiagnosis, complications, depression, treatment failure, etc etc</td>
<td>• Low costs - but this may not be important</td>
</tr>
</tbody>
</table>
100 apparently healthy males
Normal MCV

Median Ferritin (µg/L)
Beckman 79
Centaur 110
Roche 127
What method? - Vitamin B12

100 apparently healthy females
Normal MCV

Median B12 (ng/L)
Beckman  261
Centaur  389
Roche    451
RI for Bayer Vitamin B12 cited by clinical laboratories

Vitamin B12 (ng/L)

Individual laboratories

ACB mailbase Geoff Holder Dec 2004
What are we doing to help?

- What test do I order?
- What tube do I use?
- What sample do I take?
- When do I take it?
- When will I get the result?
- What does the result mean?
Reference interval errors

• Errors in Laboratory reference limits as shown in a collaborative quality-assurance program
  - Clin Chem 1986;32:845
• ... IMEP-17 survey in Australia showed no relationship between method bias and reference limits ...
• Survey of reference ranges and clinical measurements for psychoactive drugs in serum
  - Ther Drug Monit 2003;25:243
• A survey of endocrine function testing by clinical biochemistry laboratories in the UK