“Normal” vs. “Clinically Relevant Abnormal”
Laboratory Test Results

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Use and Misuse of Metal Chelation Therapy
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Environmental Health Laboratory *
National Center for Environmental Health

- At the forefront of efforts to assess people’s exposure to environmental chemicals by using advanced laboratory science and innovative techniques.
- Measuring chemicals directly in people’s blood or urine is a process known as BIOMONITORING.
- Biomonitoring measurements --- most health-relevant assessments of exposure; measure the total amount of the chemical that actually gets into people from all environmental sources (e.g., air, soil, water, dust, or food).

*Division of Laboratory Sciences
### Outline

- What are reference values and interval?
- Why are reference values important?
- What type of reference values are available?
- What factors to consider when developing reference values and intervals?
- What factors to consider when interpreting laboratory values?

### What are reference values and interval?

- Reference values and interval are to provide comparison data for the interpretation of a person’s laboratory results.
- Reference values and interval have replaced “normal” values and interval because the latter term is ambiguous.
- Conventional reference values and interval
Conventional reference values and interval

Why are reference values important?

- Reference values can be used in medicine and epidemiology to assist in the diagnosis and prevention of disease.
What types of reference values are available?

- Population-based reference values
- Locally agreed upon clinical action levels
- Expert panel determinations
- Values based on health outcomes and risks
- Multiples of the upper reference limit
- Prior values from the same individual

What factors should be considered when developing reference values?

- Pre-analytical
- Analytical
- Post-analytical
- Biological variation
National Report on Human Exposure to Environmental Chemicals

Metals
- Antimony, arsenic
- Barium, beryllium
- Cadmium, cesium, cobalt
- Lead
- Mercury, molybdenum
- Platinum
- Thallium, tungsten
- Uranium

Pesticides
- Carbamate insecticides
- Fungicides, herbicides
- Organochlorine pesticides
- Organophosphorus insecticides
- Pyrethroid pesticides

Acrylamide, Cotinine / NNAL, DEET
Disinfectant by-products
Environmental phenols
PCBs/PCDDs/PCDFs/PBDEs
Perchlorate, perfluorochemicals
Phthalates, polycyclic aromatic hydrocarbons
Volatile organic compounds
National Report on Biochemical Indicators of Diet and Nutrition

Water-soluble vitamins & metabolites
• Folate, vitamin B12
• Homocysteine, methylmalonic acid

Iron-status indicators

Trace elements
• Iodine, selenium

Fat-soluble vitamins & nutrients
• Vitamin A, vitamin E, carotenoids
• Vitamin D

Phytoestrogens
U.S. National Health and Nutrition Examination Surveys

NHANES (National Health and Nutrition Examination Surveys)

NHANES
Only nationally representative survey that collects biological samples

- Conducted by the National Center for Health Statistics, CDC
- Designed to collect information about the health status, health-related behavior, and nutrition of the U.S. population
- Unique in that it combines a home interview with health tests that are done in a Mobile Examination Center
NHANES (National Health and Nutrition Examination Surveys)

NHANES
Cross-sectional nationally representative survey

Stage 1
Counties

Stage 2
Segments

Stage 3
Households

Stage 4
SPs

- Civilian, non-institutionalized population of the United States
- Ages 2 months and older for selected analytes
- Residents of all 50 states and DC
- 5,000 persons examined each year at 15 locations
- Survey design determines which populations are over-sampled

NHANES (National Health and Nutrition Examination Surveys)

NHANES
Information available

- Demographic: Age, sex, race/ethnicity
- Socio-economic: Education, income, profession
- Life-style: Smoking, exercise, supplement use
- Dietary: 24-h recall, food frequency questionnaire
- Health condition: Diseases (e.g., diabetes, CAD, cancer)
- Anthropometric: Height, weight, BMI, skin fold
- Laboratory: Hematology, clinical chemistry, nutritional indices, environmental chemicals, infectious disease markers
- Physical examination: BP, hearing/eye/dental, bone densitometry, muscle strength, balance, skin disease, cognitive testing, cardio-respiratory fitness, peripheral vascular disease, peripheral neuropathy

NHANES (National Health and Nutrition Examination Surveys)
Continuous NHANES survey started in 1999

- Survey is run continuously in two-year survey cycles
- Each cycle (2 years) is a representative sample of the U.S. population
- No more “breaks” between surveys to develop and implement new analytical methods, survey components, or to conduct data analyses
- Over 200 environmental and nutritional analytes reported by several environmental health laboratories at CDC
- Banking of biological samples (e.g., serum, plasma, urine, WBCs) for future research

NHANES (National Health and Nutrition Examination Surveys)
What factors should be considered when interpreting laboratory values?

- **Endogenous**
  - Age, sex, genetics (inherent to the individual)

- **Exogenous**
  - Diet, exercise, smoking, alcohol, medications

- **Laboratory**
  - Analytical method, storage and transport of sample, collection of sample

- **Mathematical method used to report results**
Conventional reference values and intervals

Healthy population

Conventional reference values and intervals

Diseased population

Individuality and reference values

- Intra-individual and inter-individual variations can significantly differ for certain laboratory results.

- Individuality can affect the use of reference values for laboratory tests and the interpretation of laboratory results.

Figure. Mean and range values for serum creatinine in healthy subjects.

Females (open circles) and males (filled circles).

The dotted lines mark the upper limits of the population–based reference interval of creatinine for females (90 umol/L) and for males (105 umol/L).

Individuality

Figure. Means and non-parametric ranges for serum creatinine.

Table. Means and non-parametric ranges for serum creatinine from healthy volunteers.

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>Mean</th>
<th>CV i (%)</th>
<th>CV g (%)</th>
<th>Index of individuality *</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (15)</td>
<td>77.9</td>
<td>4.1</td>
<td>14.1</td>
<td>0.29</td>
</tr>
<tr>
<td>Women (8)</td>
<td>71.4</td>
<td>4.9</td>
<td>11.8</td>
<td>0.41</td>
</tr>
<tr>
<td>Men (7)</td>
<td>83.9</td>
<td>3.4</td>
<td>6.8</td>
<td>0.54</td>
</tr>
</tbody>
</table>

- Index of individuality = CV_i / CV_g
- CV = (Σ d² / 2n)¹/²

**Index of Individuality**

- **Index of individuality (II)**
  - \( = \left(\frac{CV_a^2 + CV_i^2}{2}\right)^{1/2} / CV_g\)
  - where \(CV_a\), \(CV_i\), and \(CV_g\) are analytical, within-subject, and between-subject coefficients of variations, respectively

- **Index of Individuality**

Individuality and reference values

- **Index of Individuality (II) = \( CV_i / CV_g \)**
- **Low II (<0.6) = marked individuality**
- **High II (>1.4) = little individuality**
  - Useful for conventional reference values
- **Thus, consider the individual variability of the laboratory test when using reference values**


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### Individuality and reference values

#### Stratification

**Urine creatinine (mmol/day)**

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>Mean</th>
<th>CV i (%)</th>
<th>CV g (%)</th>
<th>Index of individuality *</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (15)</td>
<td>10.7</td>
<td>13.0</td>
<td>28.2</td>
<td>0.46</td>
</tr>
<tr>
<td>Women (8)</td>
<td>8.0</td>
<td>15.7</td>
<td>11.0</td>
<td>1.42</td>
</tr>
<tr>
<td>Men (7)</td>
<td>13.9</td>
<td>11.0</td>
<td>6.0</td>
<td>1.83</td>
</tr>
</tbody>
</table>

- **Index of individuality = \( CV_i / CV_g \)**
- **CV = \( (\Sigma d^2 / 2n)^{1/2} \)**

Table. Means and coefficient variations for urine creatinine from healthy volunteers.

Monitoring changes in serial results for an individual

- **Compare with clinical fixed criteria or cutoffs**
  - Locally agreed upon clinical action levels
  - Expert panel determinations
  - Values based on health outcomes and risks
  - Multiples of the upper reference limit

- **Reference change values (RCV)**
  \[ RCV = 1.414 \times Z \times \left( CV_a^2 + CV_i^2 \right)^{\frac{1}{2}} \]


“Normal” vs. “Clinically Relevant Abnormal” Laboratory Test Results

**Conclusions**

- Reference value and interval are preferred terminology to “normal”

- Laboratory values are affected by pre-analytical, analytical, and post-analytical factors

- Biological variations can affect the applicability of reference values and intervals to individual results
Thank you!

For more information please contact Agency for Toxic Substances and Disease Registry or the Centers for Disease Control and Prevention

ATSRR:
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E-mail: cdcinfo@cdc.gov Web: http://www.atsdr.cdc.gov

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the Agency for Toxic Substances and Disease Registry

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