Pediatric and Adult Reference Intervals for Chemistry, Immunoassay, and Hematology Markers based on the CHMS

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Outline/Objectives:

• Overview: Value of reference intervals

• Overview of CALIPER project

• CALIPER-CHMS collaboration, summary of a Canadian reference interval database
Central Role of Laboratory Medicine in Healthcare Delivery

Laboratory Medicine is part of the multi-disciplinary team at the centre of healthcare.

The quality of the Clinical Laboratory Service is critically dependent on accurate interpretation of lab results based on accurate reference intervals or decision limits.

- Identify risk factors & symptoms
- Diagnose disease
- Evaluate response
- Determine appropriate treatment

LAB
Reference intervals: **Major Gaps**

- Most available reference intervals determined on older/less accurate laboratory instruments/methodologies
- Many reference intervals incomplete or unavailable for different age groups
- Most available only for Caucasian populations
- Limited/no data for many new and emerging disease biomarkers
- Available data from samples collected from hospitalized adults and children
Development over time:

- Physiological changes over time may influence analyte levels.
- Adult reference intervals often based on narrow window of time and may not be representative of other developmental stages.

- Dramatic physiological changes take place over the course of development and aging.
Children are not small adults & Geriatrics are not old adults

- Body weight doubles by 6 months of age and triples by the first birthday
- Body length increases by 50% by 1 year
- Major organ systems grow and mature
- Accelerated growth and sexual maturation occur during puberty

- Bones decrease in density
- Muscle mass decreases in strength
- Organ function declines
- Stiffening of blood vessels and heart
- Decreased immune function
Gaps in accurate reference intervals pose a serious risk to patient care and outcomes

• **Use of inappropriate reference intervals**
  >>> risk of further blood collection, infection risk, pain and anxiety, lengthier stays, and unpleasant or invasive diagnostic procedures

• **Inadequate reference intervals**
  >>> costly and devastating, and can contribute to erroneous/delayed diagnosis of many diseases

**Reviewed in:** Critical Reviews in Clinical Laboratory Sciences (2013)
CALIPER Initiative

• To develop a comprehensive database of covariate stratified pediatric reference intervals

• To disseminate study results to pediatric healthcare community worldwide using novel knowledge translation strategies
I. Biochemical Markers (Chemistry, Proteins, Enzymes)

- Clinical Chemistry 2012

II. Immunoassays/Endocrine/Fertility

- Clinical Chemistry 2013a
- Clinical Chemistry 2013b

III. Special Chemistry/Tumor Markers

- Clinical Chemistry 2014a
- Clinical Chemistry 2014b
- Clinical Chemistry 2014c

www.caliperproject.ca

Online Database

Current: >100 Biomarkers

(Abbott Architect c8000)
The Canadian Health Measures Survey: CALIPER-CHMS Collaboration

- Expand CALIPER RI database: pediatric, adult and geriatric reference intervals established
- Observed fluctuations in analyte levels over the course of a lifetime (3-79 years)
What is the CHMS?

The Canadian Health Measures Survey (CHMS) is a Canada-wide health information survey conducted by Statistics Canada.

• Launched in 2007
  – Cycle 1: 2007-2009
  – Cycle 2: 2009-2011
  – Cycle 3: 2012-2013

• Determine health status, identify relationships between disease risk factors and health status, and explore emerging public health issues
CHMS: A Canadian Representative Sample

- 16 collection sites:
  - Atlantic (2), Quebec (4), Ontario (6), Prairies (2), British Columbia (2)

Terrace Kitimat, Edmonton, Kelowna, Regina, Thunder Bay,

St Hyacinthe, Saguenay, Fredericton, Shelburne,

Kitchener-Waterloo, Hamilton, Brockville, Toronto (2),

Montreal, Lava, Brockville, Shelburne.
CHMS: Sample Acquisition

• ~12,000 Canadians (11 age-gender groups, 500-600 per group, per cycle)
• 3-79 years old
• Collects important health information through:
  – Household interview (nutrition, smoking, alcohol, medical history)
  – Direct physical measurements (blood pressure, height, weight)
  – Blood and urine samples
CHMS: Laboratory Measures

Blood

- **General**: Complete blood count (CBC), blood chemistry panel
- **Cardiovascular health**: C-reactive protein (high sensitivity), HDL, LDL, total cholesterol, triglycerides and fatty acids
- **Diabetes**: Fasting, non-fasting and random glucose, fasting insulin and HbA1c

- **Nutritional status**: Ferritin, RBC folate, vitamin B12 and vitamin D

Urine

- **Kidney function**: Creatinine and microalbumin
- **Nutritional status**: Iodine
Exclusion Criteria:

Participants were excluded from the analysis on the basis of:

• Diagnosed serious/chronic medical illness
• Use of prescription medication within past month
• Pregnant
Statistical Analysis

Exclude Respondents based on defined exclusion criteria

Generate scatter plot and remove extreme outliers using visual inspection

Inspect Partitions using scatterplots to identify trends in age and sex

Determine Partitions by testing with the Harris & Boyd method

Check Normality using Q-Q Plot and Shapiro–Wilk test

Transform Data using Box-Cox Method

Normal Data: remove outliers using Tukey test twice

Skewed Data: remove outliers using adjusted Tukey test twice

Calculate Reference Interval using non-parametric rank method

Calculate 90% Confidence Interval and Median
**Excluded Participants:**

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Average portion of individuals excluded + outliers removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 -18 y</td>
<td>20%</td>
</tr>
<tr>
<td>19 – 59 y</td>
<td>42%</td>
</tr>
<tr>
<td>60 – 79 y</td>
<td>78%</td>
</tr>
</tbody>
</table>

**Definition of ‘health’ with aging?**
Biochemical Marker Reference Values across Pediatric, Adult, and Geriatric Ages: Establishment of Robust Pediatric and Adult Reference Intervals on the Basis of the Canadian Health Measures Survey

Khosrow Adeli, Victoria Higgins, Michelle Nieuwwesteeg, Joshua E. Raizman, Yunqi Chen, Suzy L. Wong, and David Blais

Complex Reference Values for Endocrine and Special Chemistry Biomarkers Across Pediatric, Adult, and Geriatric Ages: Establishment of Robust Pediatric and Adult Reference Intervals on the Basis of the Canadian Health Measures Survey

Khosrow Adeli, Victoria Higgins, Michelle Nieuwwesteeg, Joshua E. Raizman, Yunqi Chen, Suzy L. Wong, and David Blais

Complex Biological Profile of Hematologic Markers Across Pediatric, Adult, and Geriatric Ages: Establishment of Robust Pediatric and Adult Reference Intervals on the Basis of the Canadian Health Measures Survey

Khosrow Adeli, Joshua E. Raizman, Yunqi Chen, Victoria Higgins, Michelle Nieuwwesteeg, Mohamed Abdelhaleem, Suzy L. Wong, and David Blais
CALIPER-CHMS Collaboration

Potassium

Concentration (mmol/L)

Age (years)

Female
Male

Clinical Chemistry 2015a
Creatinine, Serum

Urea

Uric Acid

Clinical Chemistry 2015a
Clinical Chemistry 2015b
• Chemistry biomarkers: 24 markers
  alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALKP), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), calcium (total), chloride, cholesterol (total), creatinine (serum), creatinine (urine), glutamyltransferase (GGT), glucose, HDL cholesterol, lactate dehydrogenase (LDH), LDL cholesterol, phosphate, potassium, protein (total), sodium, triglycerides, urea, uric acid, urine iodine

• Immunoassay/special chemistry: 13 markers
  apoA1, apoB, ferritin, glycohemoglobin (Hb A1c), high-sensitivity C-reactive protein (hsCRP), homocysteine, insulin, parathyroid hormone (PTH), red blood cell (RBC) folate, serum folate, urine albumin, vitamin B12, 25-OH vitamin D

• Hematology: 16 markers
  hemoglobin, hematocrit, red blood cell (RBC) count, RBC distribution width (RDW), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet count, mean platelet volume (MPV), total white blood cell (WBC) count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, fibrinogen
CALIPER-CHMS Collaboration

I. Establishment of reference interval database:
   - Establish pediatric, adult and geriatric reference intervals for analytes tested by CHMS
     *based on large and representative sample of the Canadian population

II. Graphs show population distributions for each analyte
   - Fluctuations in analyte levels that occur over the course of a lifetime (3-79 yrs)
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