Evidence-Based Harmonization of Adult Reference Intervals Across Canada using Big Data Analytics: A Report of the CSCC Working Group on Reference Interval Harmonization (hRI)

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INTRODUCTION

- Marked variation in reported reference intervals for many well-standardized laboratory tests continues to exist across clinical laboratories, increasing the risk of inaccurate and inconsistent test result interpretation.
- The **Canadian Society of Clinical Chemists (CSCC) Working Group (WG) on Reference Interval Harmonization (hRI)** aims to establish harmonized reference intervals for key laboratory tests and support their implementation across Canada.
- Harnessing the power of a novel big data analytics approach, both direct (healthy adult population data) and indirect (outpatient lab data) were examined from across Canada.
- Common reference intervals were found to be feasible with the initial evaluations for 17 of the 23 initial routine biochemical markers that were assessed.

OBJECTIVE

To develop, verify, and support the implementation of harmonized reference intervals for key biomarkers of health and disease across Canadian laboratories.

METHODS

Complete **national reference interval (RI)** survey (2016) and assess bias across manufacturers and instruments

Identify initial analyte candidates for RI harmonization

Extract laboratory data from community reference laboratories across Canada

Derive preliminary harmonized RIs based on big data analytics approach (TML) and compare with data from:

Manufacturers | **Other Harmonization Initiatives** | **Canadian Health Measures Survey**

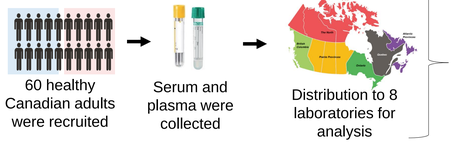
Refine preliminary harmonized RIs based on evidence and clinical input and complete verification studies across Canada on all major analytical platforms

Publish and implement national Canadian harmonized RIs

Indirect Data Extraction: Anonymized data were collected by LifeLabs (ON and BC), DynaLIFE (AB), and Dynacare (ON) from **January 2017** to **December 2019** for 17 analytes using instrumentation from Roche, Abbott, and Siemens.

***Indirect Data Analysis*:** Anonymized data assessed through the Truncated Maximum Likelihood method (TML) developed by Arzideh et al (1,2). Additional data review included assessment of: **1)** monthly instability, **2)** center-specific differences, **3)** age- and sex-specific differences. All calculations were compared to direct data from international initiatives/manufacturers and preliminary recommendations were derived.

Direct Verification Study:



60 healthy Canadian adults were recruited

Serum and plasma were collected

Distribution to 8 laboratories for analysis

- ✓ Representation from all provinces
- ✓ Representation from all major manufacturers
- ✓ Percent verification calculated for each derivation

RESULTS

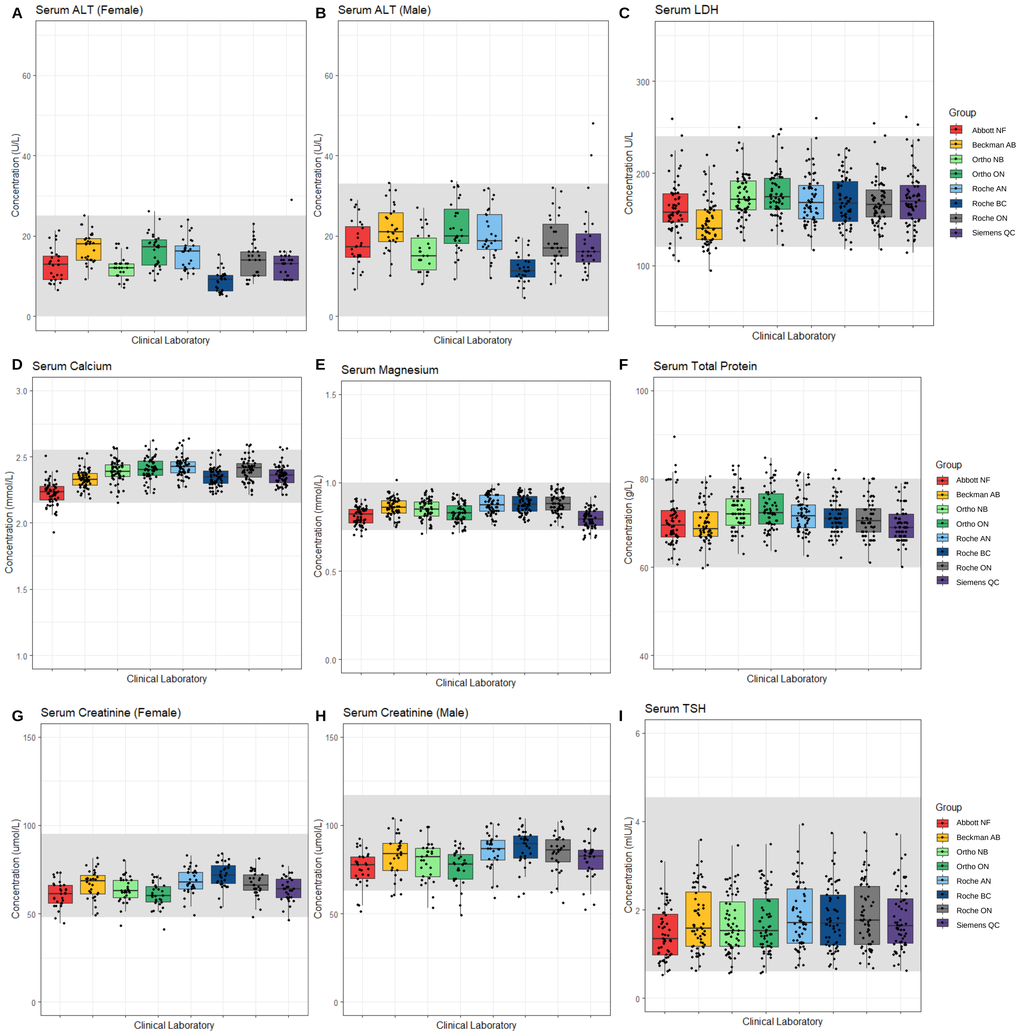


Figure 1. Box plots of participant sample results across Canadian laboratories for select analytes as part of the verification study: **A)** ALT (female); **B)** ALT (male); **C)** LDH; **D)** calcium; **E)** magnesium; **F)** total protein; **G)** creatinine (female); **H)** creatinine (male); **I)** TSH. Grey shaded area indicates preliminary harmonized reference intervals.
NF, Newfoundland, AB, Alberta, NB, New Brunswick, ON, Ontario, QC, Quebec. BC, British Columbia.

RESULTS

Table 1. Calculated reference intervals using the TML method, preliminary recommendations and range of percent verification across laboratories.

Analyte	Calculated Indirect RI		Preliminary Harmonized RI		Verification Range (Serum)	Verification Range (Plasma)
Hepatic Markers						
ALT (U/L)	19-80y M	11-53	19-80y M	<33	96-100%	85-100%
	19-80y F	8-35	19-80y F	<25	97-100%	93-100%
Albumin BCG (g/L)	19-60y M	40-51	19-80y	40-50	65-97%	63-92%
	19-60y F	39-49				
	60-80y	39-49				
ALP (U/L)	19-40y M	42-114	19-40y M	40-115	95-100%	95-100%
	19-40y F	34-103	19-40y F	35-105	80-100%	80-95%
	40-80y	41-119	40-80y	40-120	90-95%	85-95%
LDH (U/L)	19-80y	122-237	19-80y	120-240	88-98%	83-97%
Total Bilirubin (umol/L)	19-80y M	3.5-20.0	19-80y M	3-20	79-93%	80-93%
	19-80y F	2.8-15.8	19-80y F	3-16	82-90%	82-90%
Total Protein (g/L)	19-80y	61-79	19-80y	60-80	87-100%	80-90%
Renal Markers						
Phosphate (mmol/L)	19-60y	0.79-1.45	19-80y	0.8-1.45	90-97%	93-98%
	60-80y M	0.77-1.43				
	6-80 y F	0.86-1.47				
Calcium (mmol/L) [A]	19-40y M	2.21-2.54	19-80y	2.1-2.55	81-100%	85-97%
	19-40y F	2.16-2.50				
	40-80y	2.16-2.52				
Creatinine (umol/L)	19-80y M	63-117	19-80y M	63-117	90-97%	90-93%
	19-80y F	48-95	19-80y F	48-95	93-100%	93-100%
Endocrine Markers						
FT3 (pmol/L)	19-80y	3.01-5.68	19-80y	3.0-5.7	59-97%	58-97%
FT4 (pmol/L)	19-80y	9.7-15.5	19-80y	9.5-15.5	28-96%	28-96%
TSH (mIU/L)	19-80y	0.60-4.55	19-80y	0.60-4.55	97-100%	95-100%
Electrolytes						
Sodium (mmol/L) [A]	19-80y	138-145	19-80y	137-145	83-100%	61-100%
Potassium (mmol/L) [A]	19-80y	3.8-5.1	19-80y	3.8-5.1	85-98%	39-67%
Magnesium (mmol/L)	19-80y	0.73-1.00	19-80y	0.73-1.00	90-100%	81-100%
Total CO2 (mmol/L)	19-80y	22-32	19-80y	22-30	55-78%	47-90%
Chloride (mmol/L) [A]	19-80y	97-107	19-80y	97-107	87-100%	80-100%

[A] One laboratory removed due to analytical performance issues. Green indicates >80% verification.

CONCLUSIONS & NEXT STEPS

- There were no clinically significant differences in the indirect or direct analyses across Canadian laboratories with different analytical platforms for most analytes, verifying hRIs as per defined criteria.
- Analytes that did not meet the criteria for verification included: albumin, free T3, free T4, total CO2 in both serum and plasma. Plasma sodium and potassium also did not meet verification criteria. These data could be explained by analytical factors (e.g. lack of assay standardization and multiple albumin methods) and/or pre-analytical factors (e.g. loss of CO2).
- Further assessment, including EQA evaluation, measurement uncertainty assessment, and additional verification sample analysis is needed to finalize recommendations for analytes that did not meet the criteria
- These data support the feasibility of RI harmonization for most assays, and the robustness of preliminary recommendations derived using a big data analytics method.
- Future work will focus on assisting implementation in Canadian laboratories for these initial 17 analytes, including the development of educational resources and consultation with clinicians, industry, and chemistry colleagues.

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