Reference Interval Harmonization in Canada: Evidence-Based Big Data Analytics Approach

A Report of the CSCC Working Group on Reference Interval Harmonization (hRI)

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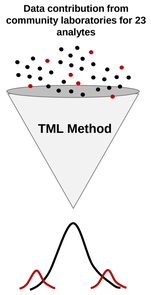
OBJECTIVES

Harmonization in laboratory medicine from specimen collection to result reporting is critical to ensure consistent and accurate clinical decision-making and to reduce unnecessary risk of error. The Canadian Society of Clinical Chemists (CSCC) Working Group (WG) on Harmonized Reference Intervals (hRIs) aims to establish hRIs for key laboratory tests and support their implementation across Canada.

Harnessing the power of big data, both direct and indirect data sources were examined, and common RIs were established and verified for 16 biochemical markers.

METHODS

INDIRECT DATA ANALYSIS



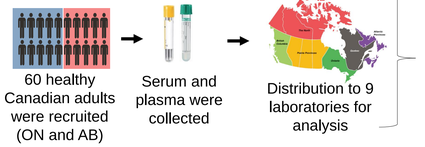
- Retrospective laboratory data was extracted for the same two-year period from four community laboratories across Canada for 23 analytes.

Siemens ADVIA	Roche cobas & Abbott Architect	Roche cobas & Abbott Architect	Roche cobas
Alberta	*British Columbia*	*Ontario*	*Ontario*

- Age-, sex-, and laboratory-specific differences for each analyte were assessed visually and via Harris and Boyd method
- Data stability over time was monitored by monthly result medians
- 16 hRIs were established using the indirect truncated maximum likelihood (TML) method
- Indirect estimates were compared to available direct data from healthy Canadians and other international harmonization initiatives
- Preliminary hRI recommendations were established upon discussion

CROSS-CANADA VERIFICATION

Aim: To verify proposed hRI recommendations for 16 assays in serum and plasma samples collected from healthy Canadian adults across different methods in Canadian laboratories.



60 healthy Canadian adults were recruited (ON and AB)

Serum and plasma were collected

Distribution to 9 laboratories for analysis

- Architect – Newfoundland
- Atellica – Quebec
- Cobas – Alberta
- Cobas – Ontario
- Cobas – Ontario
- DxC – Alberta
- Integra – Alberta
- Vitros – New Brunswick
- Vitros – Ontario

Inclusion	Exclusion
Age 19-80 years Not pregnant	History of chronic illness Acute illness within 7 days of collection Use of prescribed medication

Criteria: If ≥80% of sample test results fell within the recommended harmonized RIs across all laboratories in plasma and serum, they were considered verified across all platforms and valid for implementation in Canadian laboratories.

- ✓ **Representation from most provinces**
- ✓ **Representation from all major manufacturers**
- ✓ **Samples selected by ethnicity based on Canadian Census**
- ✓ **Percent verification calculated for each derivation**

PROPOSED RECOMMENDATIONS

Analyte	Unit	Calculated Indirect RI			Proposed Harmonized RI		Verification Range (S)	Verification Range (P)
		Partition	N	LL-UL	Partition	LL-UL		
Hepatic Markers								
ALT	U/L	**19-80y M**	3228474	11-53	**19-80y M**	<33	90-100%	85-100%
		19-80y F	3767118	8-35	**19-80y F**	<25	97-100%	93-100%
Albumin	g/L	**19-60y M**	618065	40-51	**19-80y**	40-50	65-97%	57-92%
		19-60y F	803404	39-49				
		60-80y	1014238	39-49				
ALP	U/L	**19-40y M**	460610	42-114	**19-40y M**	40-115	90-100%	89-100%
		19-40y F	621411	34-103	**19-40y F**	35-105	95-100%	84-95%
		40-80y	3776367	41-119	**40-80y**	40-120	90-95%	86-91%
LDH	U/L	**19-80y**	348310	122-237	**19-80y**	120-240	88-98%	83-97%
Total Bilirubin	umol/L	**19-80y M**	1514162	3.5-20.0	**19-80y M**	3-20	77-93%	86-90%
		19-80y F	1714743	2.8-15.8	**19-80y F**	3-16	83-90%	83-90%
Total Protein	g/L	**19-80y**	362204	61-79	**19-80y**	60-80	87-100%	82-95%
Renal Markers								
Phosphate	mmol/L	**19-60y**	234184	0.79-1.45	**19-80y**	0.8-1.45	90-97%	93-98%
		60-80y M	247183	0.77-1.43				
		60-80y F	343096	0.86-1.47				
Calcium*	mmol/L	**19-40y M**	126918	2.21-2.54	**19-80y**	2.1-2.55	90-100%	93-98%
		19-40y F	220514	2.16-2.50				
		40-80y	1498019	2.16-2.52				
Creatinine	umol/L	**19-80y M**	6367243	63-117	**19-80y M**	60-115	90-97%	90-93%
		19-80y F	7692546	48-95	**19-80y F**	50-95	93-100%	93-100%
Endocrine Markers								
Free T4	pmol/L	**19-80y**	1664797	9.7-15.5	**19-80y**	9.5-15.5	28-55%	5-96%
TSH	mIU/L	**19-80y**	8642574	0.60-4.55	**19-80y**	0.60-4.00	97-100%	95-100%
Electrolytes								
Sodium*	mmol/L	**19-80y**	7577686	138-145	**19-80y**	135-145	86-100%	80-100%
Potassium	mmol/L	**19-80y**	7792100	3.8-5.1	**19-80y**	3.8-5.1	85-97%	39-68%
Magnesium	mmol/L	**19-80y**	906400	0.73-1.00	**19-80y**	0.73-1.00	90-100%	90-100%
Total CO2	mmol/L	**19-80y**	448029	22-32	**19-80y**	22-30	55-95%	47-90%
Chloride*	mmol/L	**19-80y**	3096947	97-107	**19-80y**	97-107	87-100%	78-100%

M: male, F: female, RI: reference interval, S: serum, P: serum, ALT: alanine aminotransferase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, T4: free thyroxine, TSH: thyroid stimulating hormone, CO2: carbon dioxide, *one laboratory excluded from verification analyses due to pre-analytical issues

CONCLUSIONS

- The comprehensive approach to RI harmonization was undertaken: (1) analysis of big-data from community laboratories across Canada; (2) statistical evaluation of age-, sex, and laboratory-specific differences; (3) derivation of hRIs using the TML method; and (4) hRI verification across nine laboratories with different instrumentation..
- Indirect analysis revealed few statistical differences between laboratory centers/provinces using different analytical platforms, supporting the feasibility of RI harmonization.
- Sex-specific hRIs were established for: alanine aminotransferase, alkaline phosphatase, creatinine, and total bilirubin.
- Age-specific hRIs were only needed for alkaline phosphatase.
- hRIs were verified across nine Canadian laboratories with different instrumentation with 12 and 11 meeting the proposed hRI 80% criterion for serum and plasma specimens, respectively.

Future work will focus on developing support tools towards the implementation of these recommendations as well as investigation of analytes that did not pass selected criteria.

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RESULTS

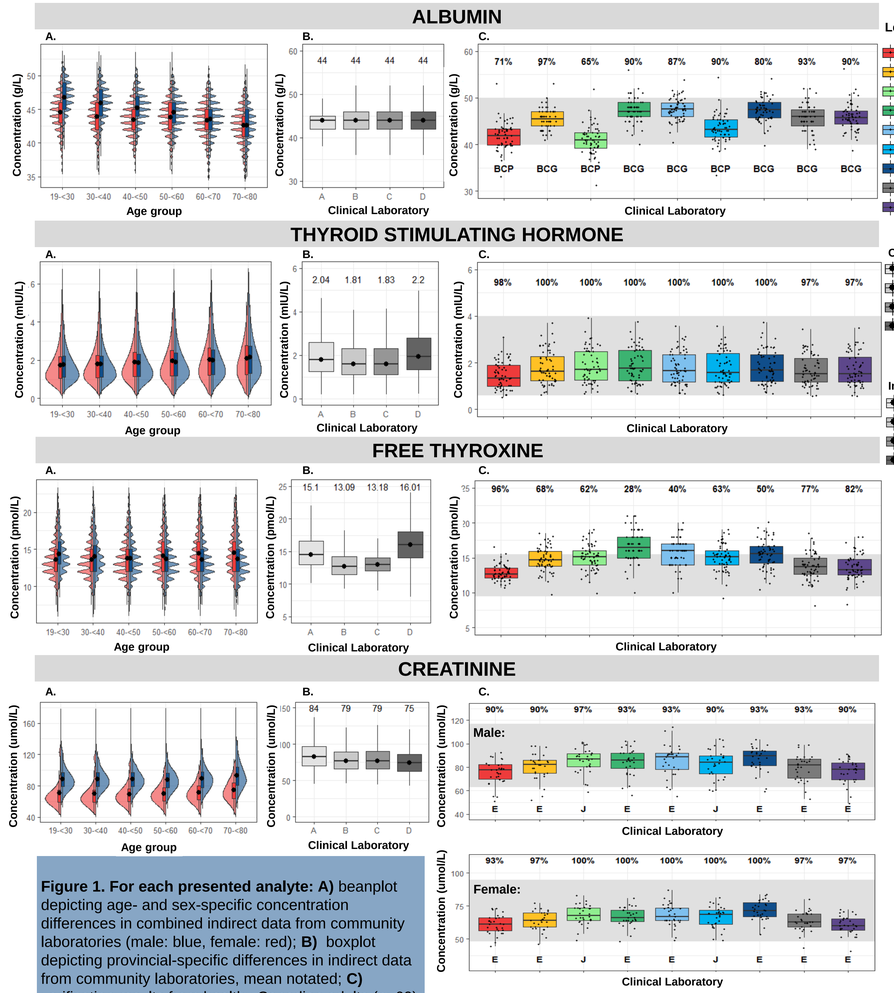

Figure 1. For each presented analyte: A) beanplot depicting age- and sex-specific concentration differences in combined indirect data from community laboratories (male: blue, female: red); **B)** boxplot depicting provincial-specific differences in indirect data from community laboratories, mean notated; **C)** verification results from healthy Canadian adults (n=60) by laboratory instrument and province, shaded grey area indicates proposed hRI and notation indicates percentage falling within hRI. Black lines indicate median. E: enzymatic, J: Jaffe, BCP: bromocresol purple, BCG: bromocresol green.

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TML method: doi.org/10.1515/CCLM.2007.250
Review: doi.org/10.1515/labmed-2020-0133

Email us to learn more or any additional questions