The CSCC Working Group on Reference Interval Harmonization (hRI):

The Latest Updates & Next Steps

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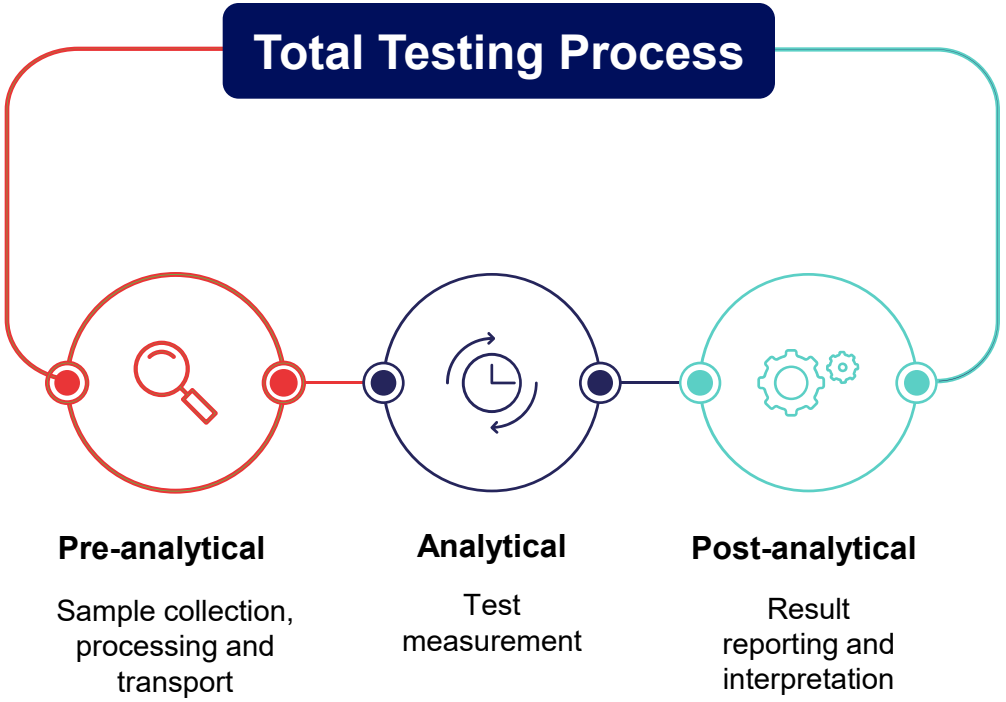
Assistant Clinical Professor, Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, AB

Harmonization in Laboratory Medicine

- Harmonization is a fundamental aspect of ensuring the analytical and clinical quality of the ***total testing process***
- Growing expectation for standardized patient care across healthcare centers
- Harmonization efforts have largely focused on the pre-analytical and analytical phase of testing, including:
    - *Standardized quality indicator goals*
    - *Increased automation*
    - *Development of commutable reference standards and improved metrological traceability*

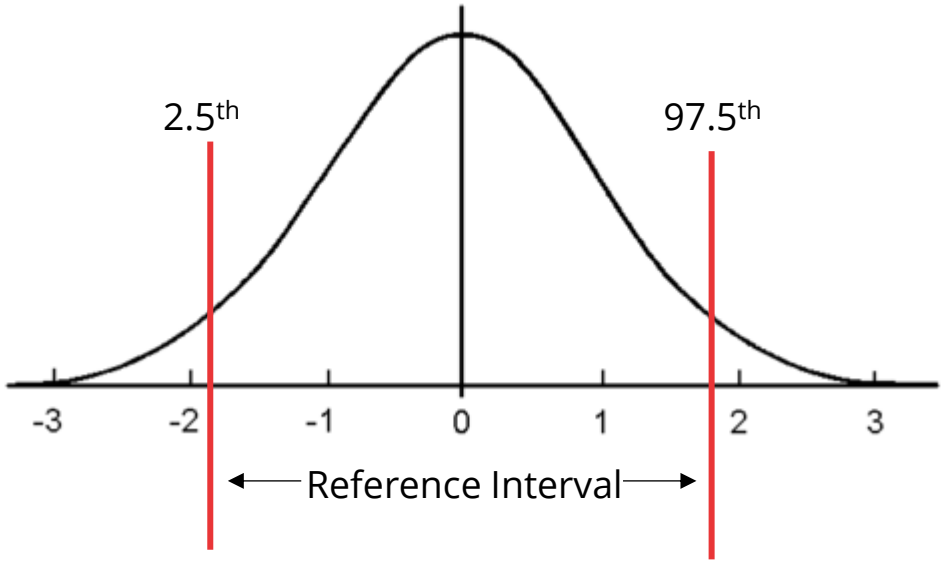


Slide Acknowledgement: Dr. Khosrow Adeli

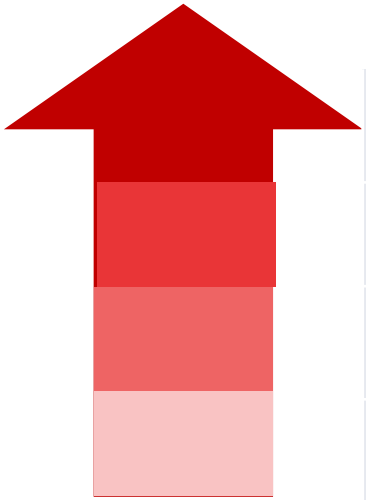
Harmonization at the *Postanalytical Phase*

Post-analytical phase: processes related to test result reporting and interpretation

Reference Interval: health associated benchmarks used to assist in clinical decision-making (central 95% of result values obtained from a reference population).



Clinical Decision Limits: threshold values that indicate significant patient risk of clinical outcome or diagnosis of a specific disease.



	HbA1c (%)
Diabetes	≥6.5
Prediabetes	6.0 – 6.4
At-Risk	5.5 – 5.9
Normal	<5.5

- Reference interval harmonization supports consistent and standardized test result interpretation, when appropriate
- Harmonized reference intervals should only be considered when significant analytical differences are NOT observed

Slide Acknowledgement: Dr. Khosrow Adeli

Driving Forces for Reference Interval Harmonization

Patients/Physicians often assume test results (and their interpretation) are **interchangeable** between laboratory

↑ **Integration** of hospital networks, **multidisciplinary care** across institutions, and **accessibility** of results to patients

Significant and unwarranted variation in RIs (same analytical methodology)

Risk of result misinterpretation

- **inadequate follow-up**
- **unnecessary investigations**
- **inappropriate resource utilization**
- **clinical confusion**

Ultimately *a major patient safety concern*

Slide Acknowledgement: Dr. Khosrow Adeli

Reference Interval Harmonization: Around the world

UK Pathology Harmony

Sampling: Consensus, adults
Sample Type: Serum
Statistical method: Consensus

NORIP

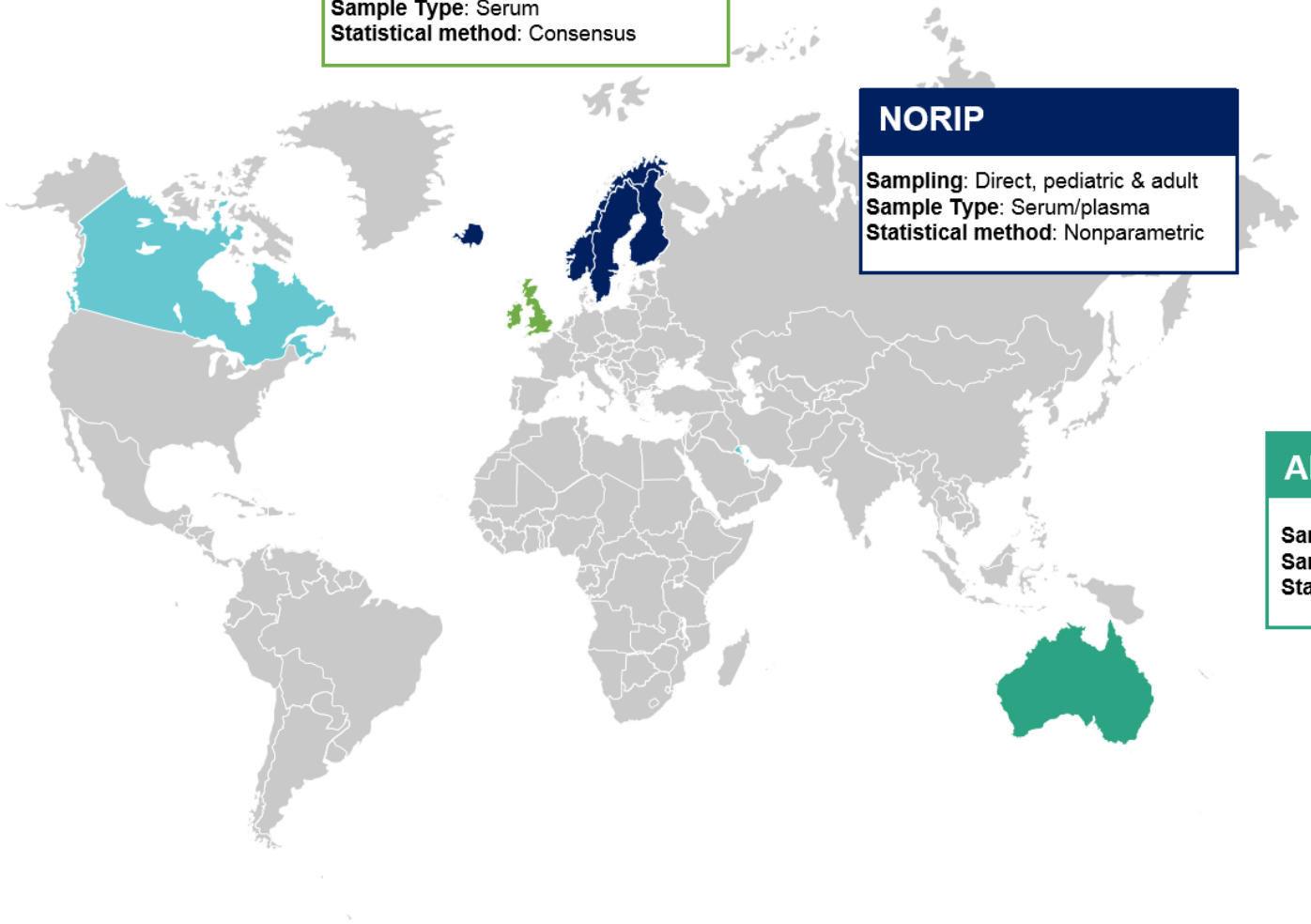
Sampling: Direct, pediatric & adult
Sample Type: Serum/plasma
Statistical method: Nonparametric

CALIPER

Sampling: Direct, pediatric
Sample Type: Serum
Statistical method: Nonparametric or robust

CSCC hRI WG

Sampling: Indirect, adult
Sample Type: Serum/plasma
Statistical method: TML method



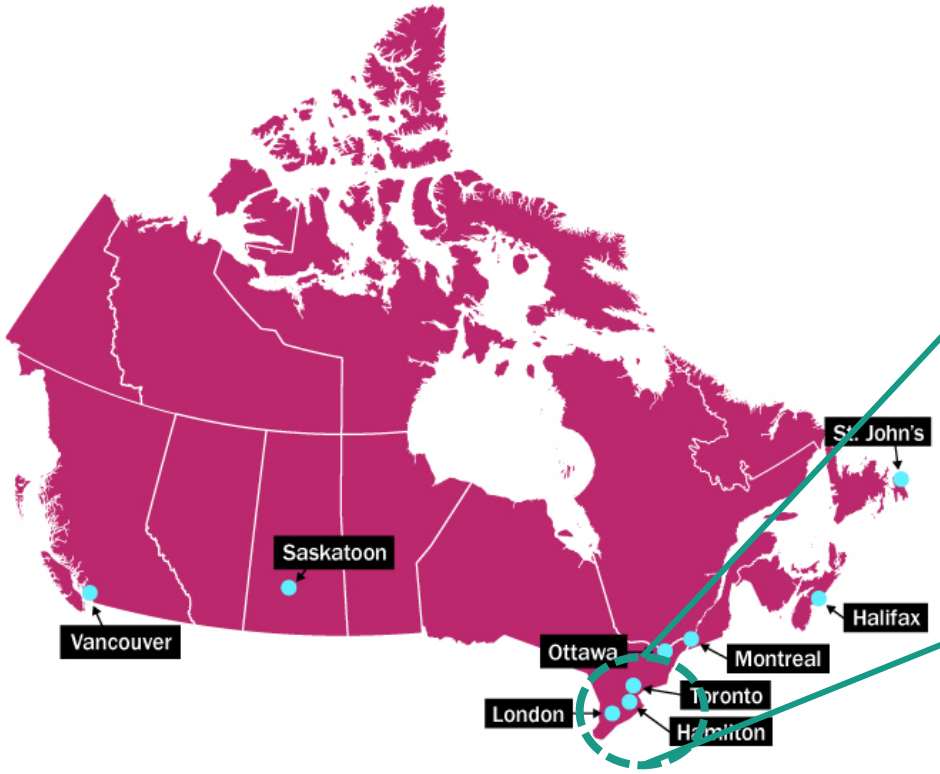
AHRIA & AHRIP

Sampling: Combination, pediatric & adult
Sample Type: Serum/plasma
Statistical method: Combination

CALIPER Initiative: Outreach & Recruitment

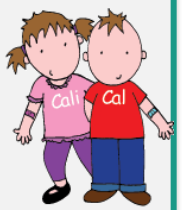
Main Objectives:

- To develop **a comprehensive database** of covariate stratified reference intervals
- To determine the **effects of key covariates (age, sex, ethnicity, BMI)** on laboratory reference intervals in healthy children and adolescents
- To **disseminate new reference data** to pediatric healthcare community worldwide via novel knowledge translation tools (WebApp & Mobile App)

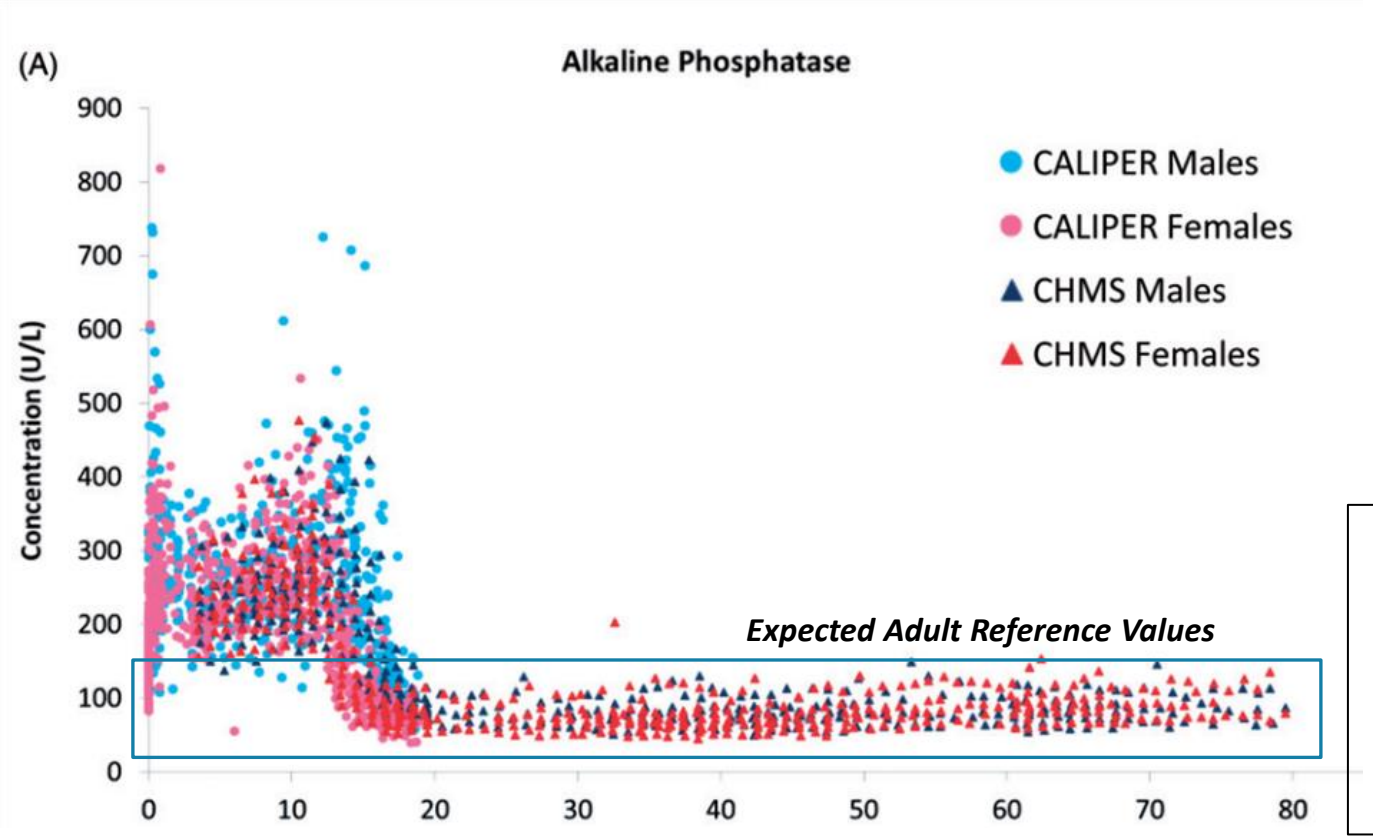


Recruitment

- *Community centers*
- *Schools*
- *Day Cares*
- *Summer Camps*



Clinical case example: *Alkaline Phosphatase*



Crit Rev Clin Lab Sci. 2017 Sep;54(6):358-413. doi: 10.1080/10408363.2017.1379945.

- Young children have significantly higher levels of ALP compared to adults
- Applying an adult reference interval would result in flagging most of the pediatric population, resulting in:
  - Unnecessary follow-up testing
  - Misinformed clinical decision making

New Data:

Roche Cobas Pro Chemistry & Immunoassays (67 assays); DiaSorin Special Chemistry; Trace Elements, Heavy Metals, Immunology, Mindray Hematology, Mass Spec Assays

Pediatric Reference Interval Harmonization in Canada

Canada-Wide Harmonization of Pediatric Reference Intervals Using the CALIPER Database:

A Comprehensive Age- and Sex-Specific Approach

www.caliperdatabase.org

www.caliperproject.ca

- ✓ Freely accessible worldwide
- ✓ Contains reference intervals for **200+ biomarkers of health and disease**
- ✓ Accessed by thousands of registered users in over **110** countries

Shaw JL et al. Crit Rev Clin Lab Sci 2013; Adeli K et al. BMJ 2018

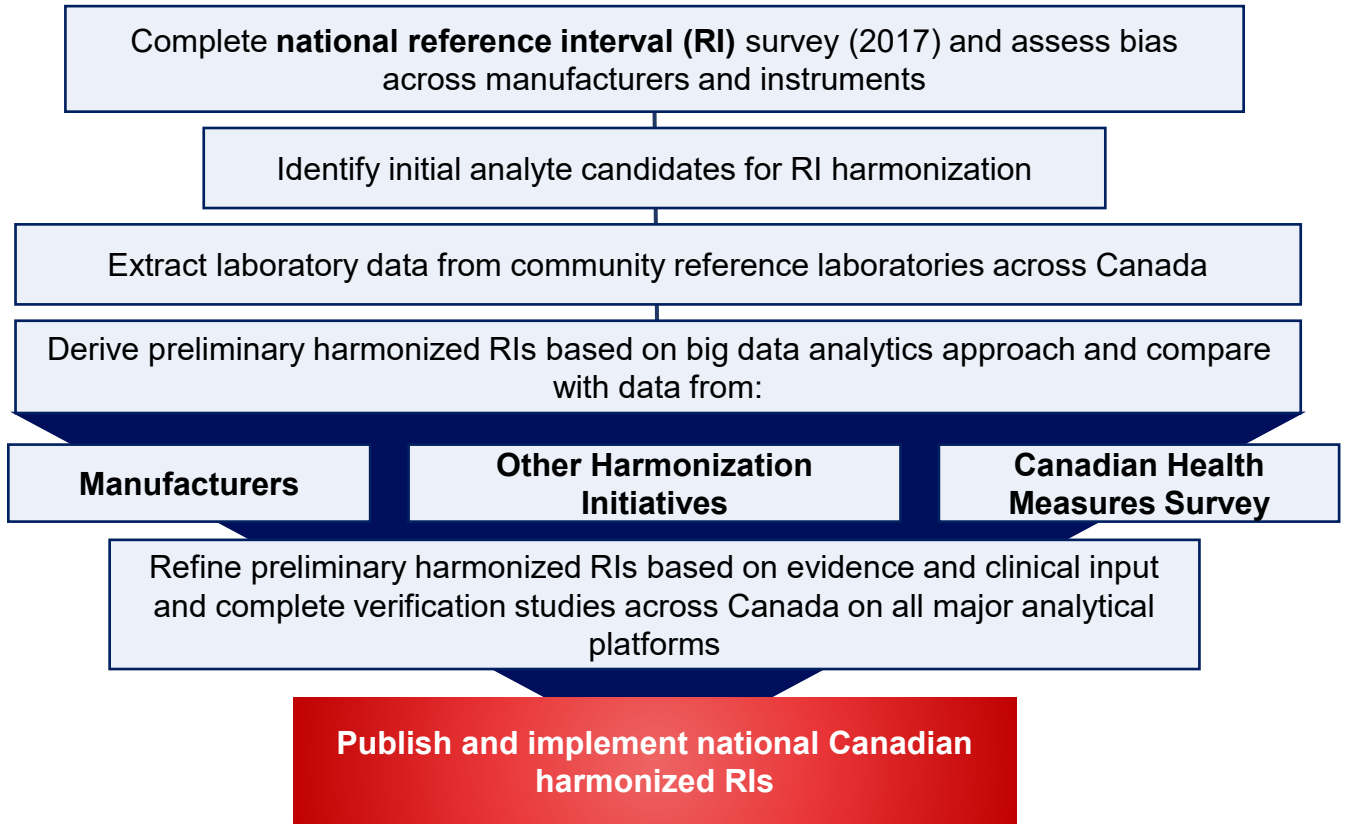
CSCC Working Group on Reference Interval Harmonization

Adult Reference Interval Harmonization in Canada

Main Objective: Establish evidence-based harmonized/common reference intervals (hRIs) and support their implementation in laboratories across Canada.

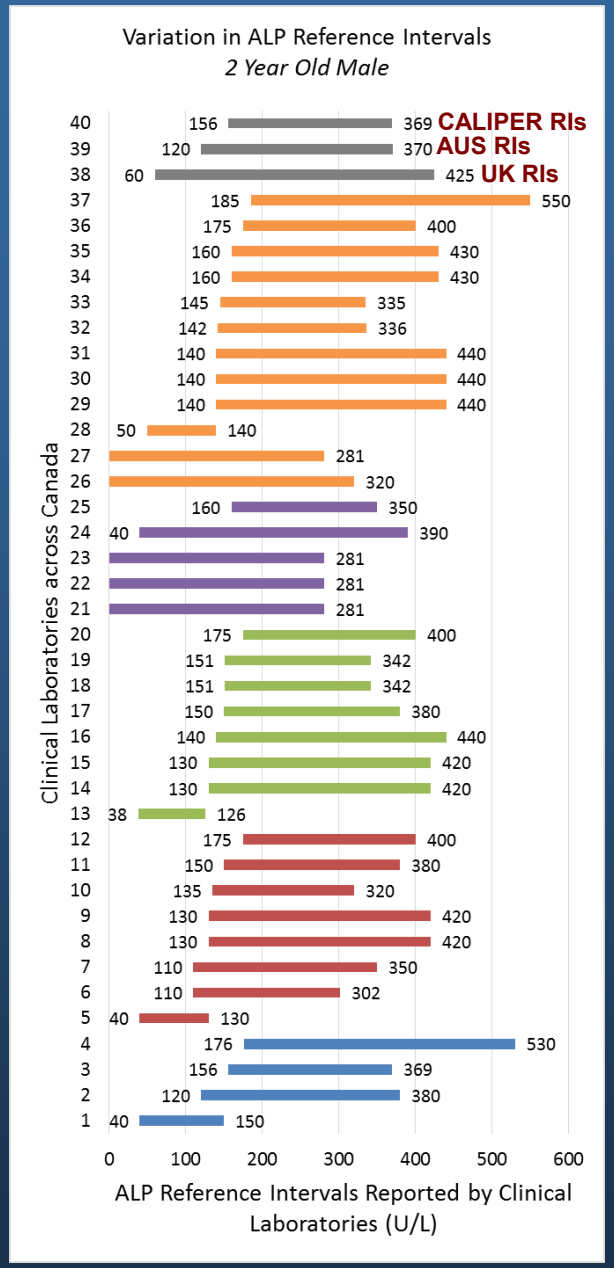
Co-Chairs
Khosrow Adeli
Christine Collier

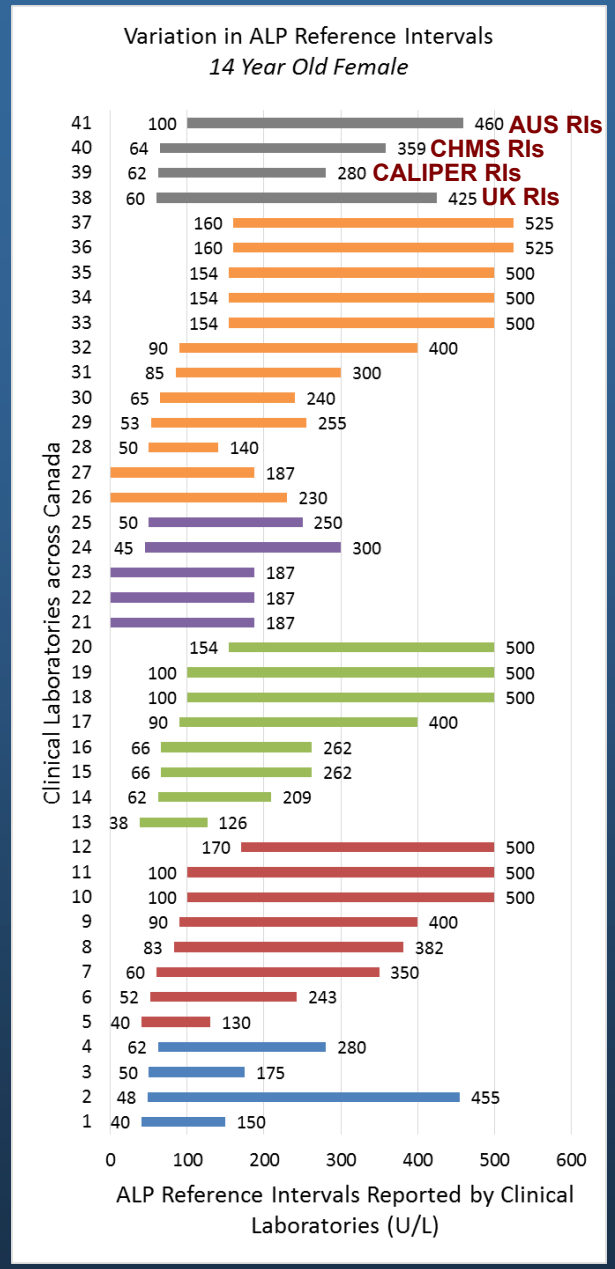
Current WG Members
Cynthia Balion
Mary Kathryn Bohn
George Cembrowski
Victoria Higgins
Benjamin Jung
Zahraa Mohammed Ali
Dana Nyholt
Atoosa Rezvanpour
Karina Rodriguez-Capote
David Seccombe
Jennifer Taher
Albert Tsui
Allison Venner
Nicole White-Al Habeeb

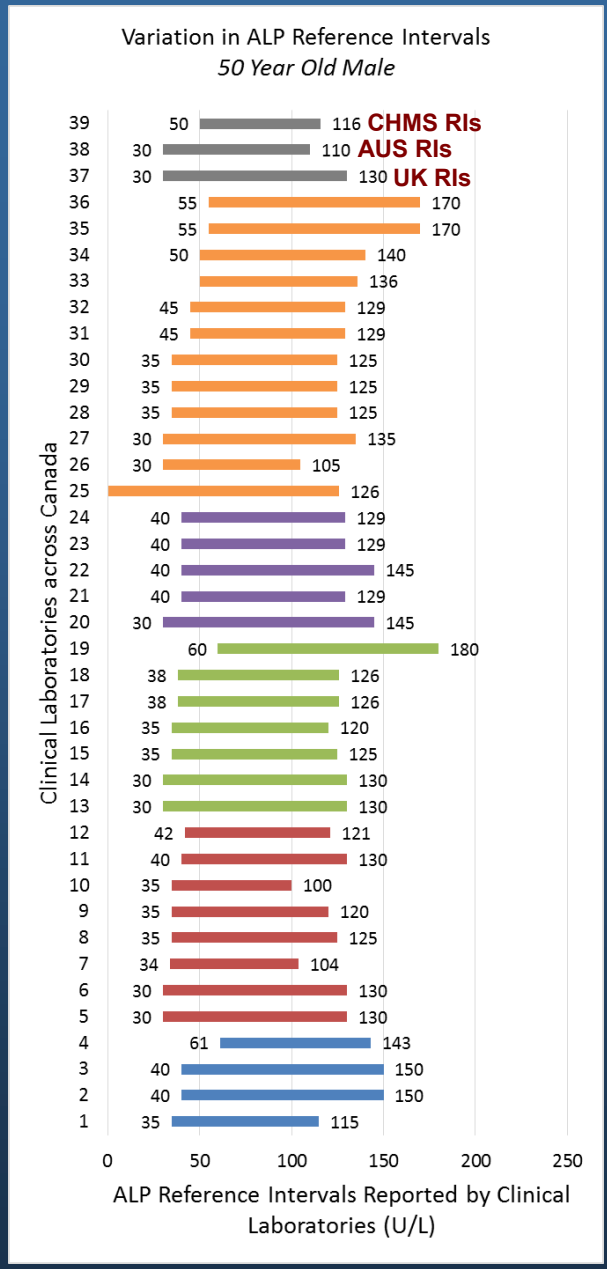


National Survey

Observed variation in reference intervals across instruments cannot be explained by the bias between results obtained on instruments by different manufacturers.







Abbott Beckman Ortho Roche Siemens

Clinical Biochemistry (2017)

Slide Acknowledgement: Dr. Khosrow Adeli

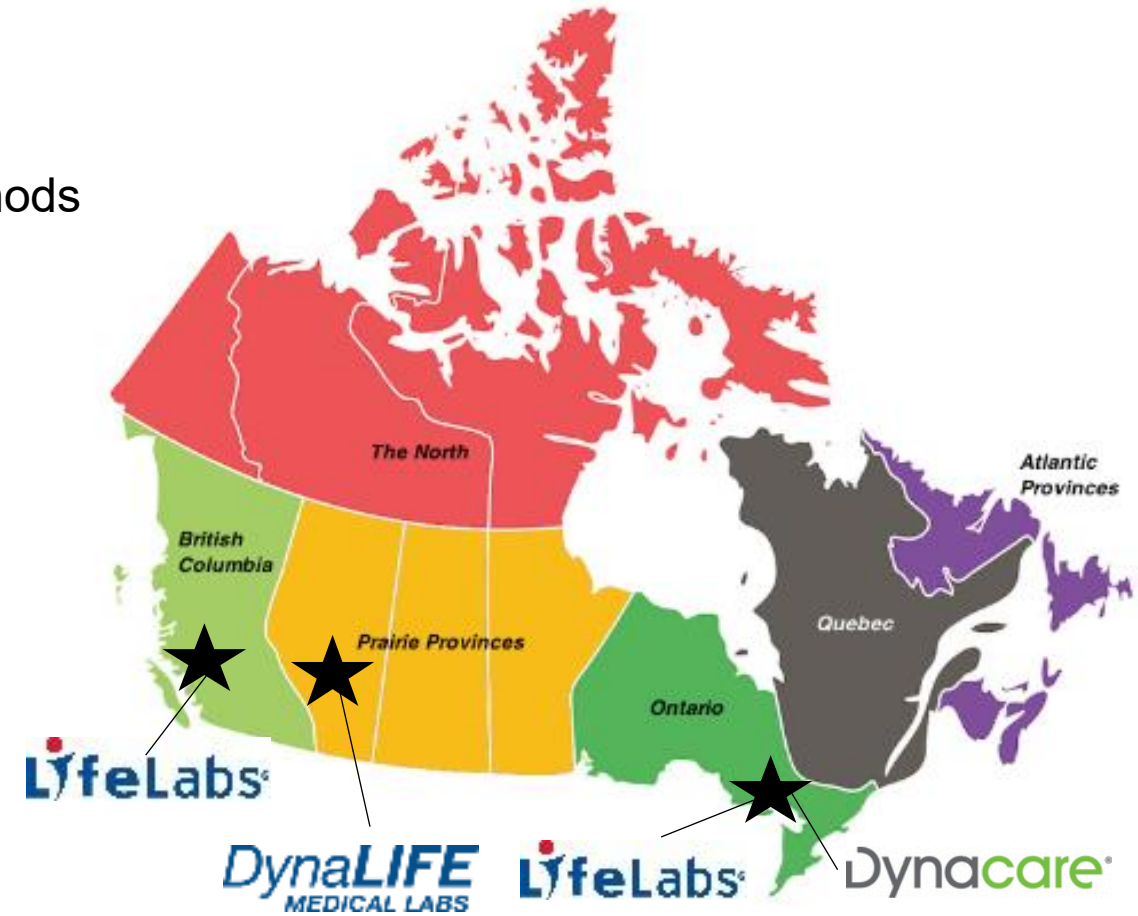
Approach: Obtaining data for RI calculations and harmonization

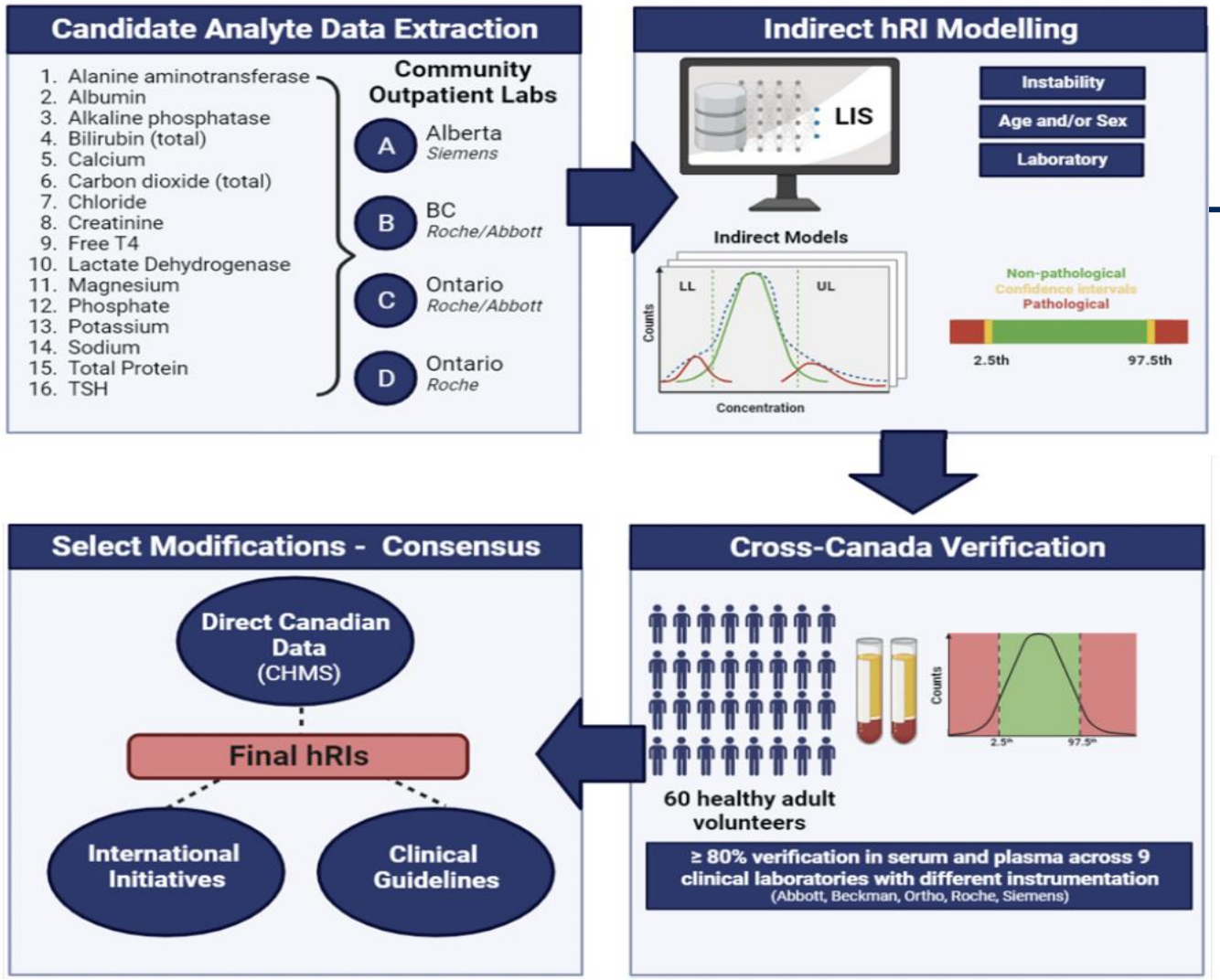
- Appropriate selection of data contributing centres is essential to optimize the performance of indirect methods

Criteria for data centre contribution:

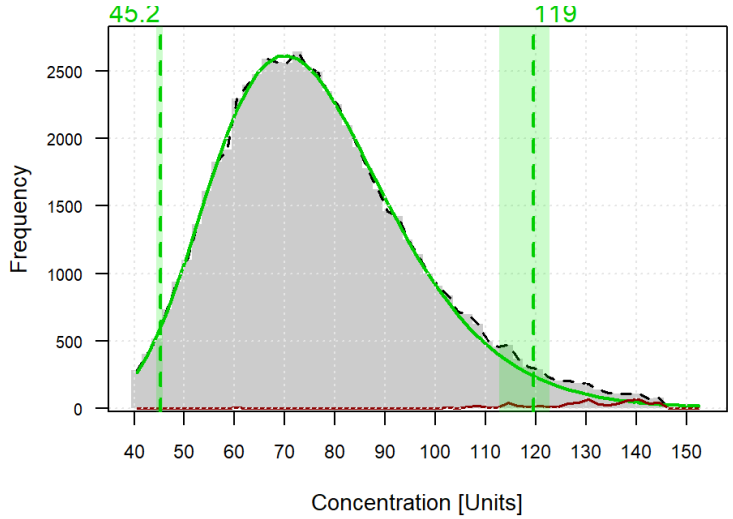
- *Large **outpatient** population*
- *Representative of Canadian population*
- *Representative of different analytical platforms*
- *Consistent results over time*

Formed collaborations with community laboratories to support this initiative





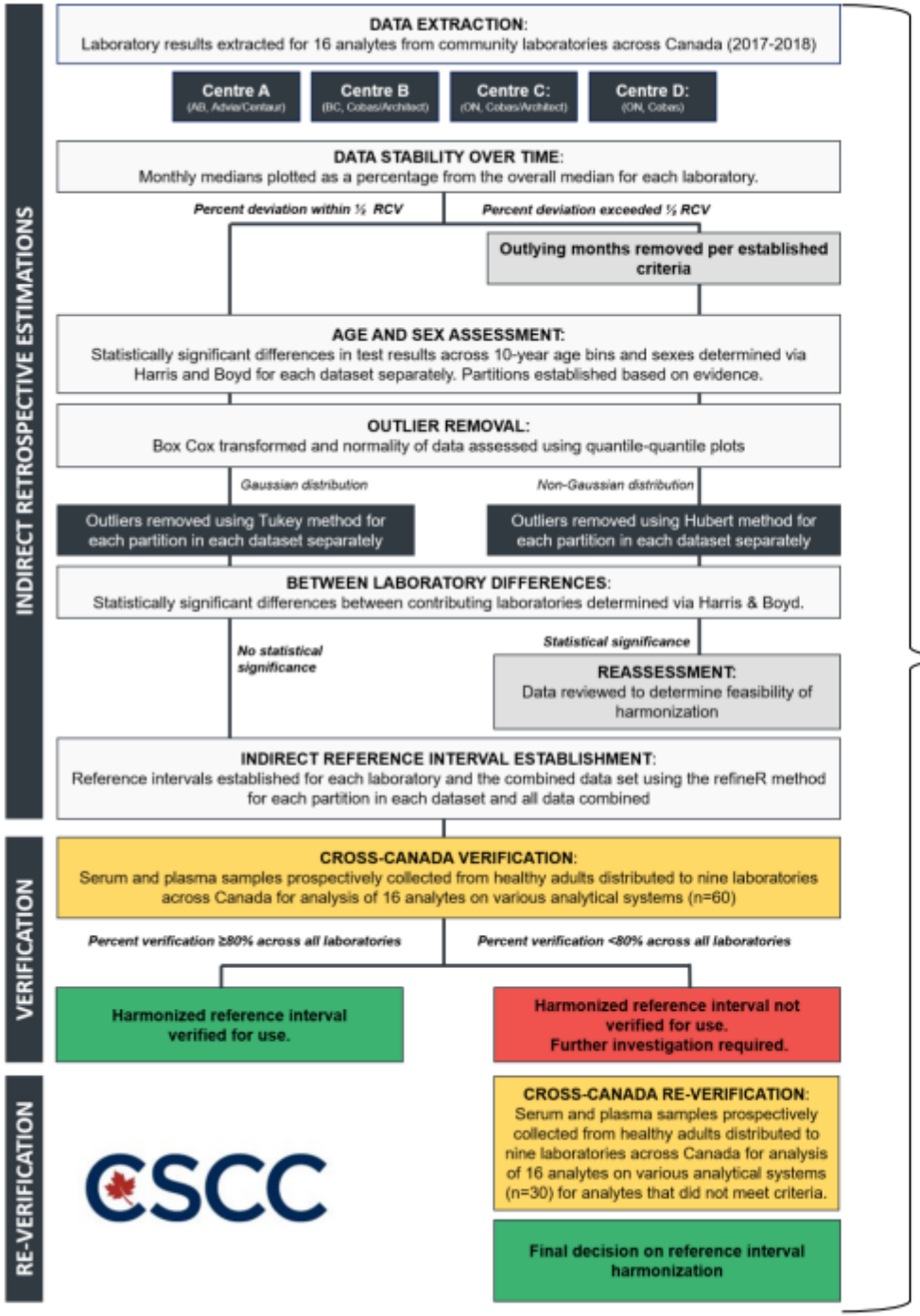
RefineR

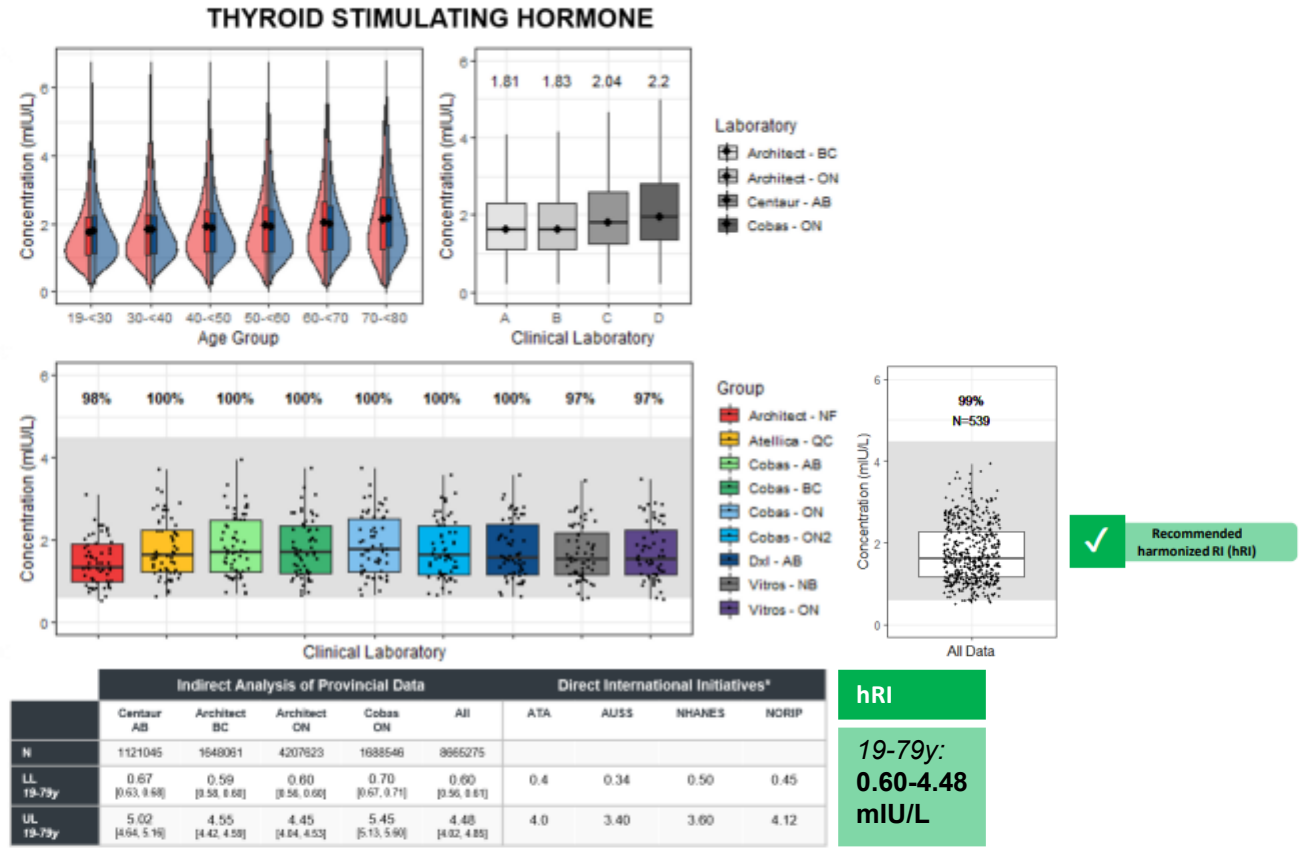


- Estimates reference interval from real-world data consisting of a mixed distribution of non-pathological and pathological test results
- Estimates parameters of a 1- or 2-parameter Box-Cox transformed normal distribution using regularized maximum likelihood optimization

Figure 1. Summary of multi-step data-driven approach for reference interval harmonization in Canada. *CHMS: Canadian Health Measures Survey, hRIs: harmonized reference intervals, LIS: laboratory information system, LL: lower limit, T4, thyroxine, TSH: thyroid-stimulating hormone, UL: upper limit*

Bohn MK, et al. Best Practice Guidelines on Reference Interval Harmonization in Canada. Submitted to Clinical Biochemistry





	Indirect Analysis of Provincial Data					Direct International Initiatives*			
	Centaur AB	Architect BC	Architect ON	Cobas ON	All	ATA	AUSS	NHANES	NORIP
N	1121045	1648061	4207823	1688546	8665275				
LL 19-79y	0.67 [0.63, 0.68]	0.59 [0.58, 0.60]	0.60 [0.58, 0.60]	0.70 [0.67, 0.71]	0.60 [0.56, 0.61]	0.4	0.34	0.50	0.45
UL 19-79y	5.02 [4.64, 5.16]	4.55 [4.42, 4.58]	4.45 [4.04, 4.53]	5.45 [5.13, 5.90]	4.48 [4.02, 4.85]	4.0	3.40	3.60	4.12

hRI

19-79y:
0.60-4.48 mIU/L

Result Summary:

- **~ 9 million results** evaluated
- No age/sex-specific differences observed
- Recommended hRI verified in all 9 Canadian laboratories participating in cross-Canada verification program (*serum and plasma*)
- Results suggest excellent concordance between laboratories, allowing RI harmonization for TSH

Adult Reference Interval Harmonization in Canada

Clinical Chemistry 69:9
991–1008 (2023)

Informatics and Statistics

Reference Interval Harmonization: Harnessing the Power of Big Data Analytics to Derive Common Reference Intervals across Populations and Testing Platforms

Mary Kathryn Bohn,[a,b] Dana Bailey,[c] Cynthia Balion,[d] George Cembrowski,[e] Christine Collier,[f] Vincent De Guire,[g] Victoria Higgins,[h] Benjamin Jung,[a,b] Zahraa Mohammed Ali,[i] David Seccombe,[j] Jennifer Taher,[b,k] Albert K.Y. Tsui,[e,l] Allison Venner,[l,m] and Khosrow Adeli[a,b,*]

Harmonized RIs recommended for 11 analytes + 2 with special considerations

Analyte	Calculated Harmonized Reference Interval		Recommended Harmonized Reference Interval	Number of Canadian Labs Achieving >90% Verification*	Matrices	Available Clinical Decision Limits or Direct Data in Healthy Canadians
Alkaline Phosphatase	19 to 39 years M	42-113 U/L	42-113 U/L	100% (9/9 labs)	Serum/Plasma	None
	19 to 39 years F	35-100 U/L	35-100 U/L			
	40 to 79 years	41-250 U/L	41-250 U/L			
Alanine Aminotransferase	19 to 79 years M	<47 U/L	<47 U/L	100% (9/9 labs)	Serum/Plasma	<33 U/L (ref 16)
	19 to 79 years F	<29 U/L	<29 U/L			<25 U/L (ref 16)
Calcium[a]	19 to 39 years M	2.20-2.55 mmol/L	All: 2.15 to 2.55 mmol/L	88% (7/8 labs)	Serum/Plasma	None
	19 to 39 years F	2.16-2.50 mmol/L				
	40 to 79 years	2.15-2.51 mmol/L				
Carbon dioxide, total	19 to 79 years	22-31 mmol/L	22-31 mmol/L	11% (1/9 labs)	Serum/Plasma	None
Chloride	19 to 79 years	97-107 mmol/L	97-107 mmol/L	88% (7/8 labs)	Serum/Plasma	None
Creatinine	19 to 79 years M	62-112 µmol/L	62-112 µmol/L	100% (9/9 labs)	Serum/Plasma	None
	19 to 79 years F	47-87 µmol/L	47-87 µmol/L			
Lactate Dehydrogenase	19 to 79 years	122-235 U/L	122-235 U/L	89% (8/9 labs)	Serum/Plasma	None
Magnesium	19 to 79 years	0.73-1.00 mmol/L	0.73-1.00 mmol/L	100% (9/9 labs)	Serum/Plasma	None
Phosphate	19 to 49 years	0.79-1.49 mmol/L	All: 0.80–1.50 mmol/L	100% (9/9 labs)	Serum/Plasma	None
	50 to 79 years M	0.74-1.44 mmol/L				
	50 to 79 years F	0.88-1.53 mmol/L				
Thyroid Stimulating Hormone	19 to 79 years	0.60-4.48 mIU/L	0.60-4.48 mIU/L	100% (9/9 labs)	Serum/Plasma	0.40–4.00 mIU/L (ref 14)
Total Protein	19 to 79 years	62-79 g/L	62-79 g/L	78% (7/9 labs)	Serum/Plasma	None
Special Considerations						
Albumin (BCG only)	19 to 59 years M	42-50 g/L	All: 40-50 g/L	83% (5/6 labs)	Serum/Plasma	None
	19 to 59 years F	39-49 g/L				
	60-79 years	38-48 g/L				
Potassium	19 to 79 years	3.9-4.9 mmol/L	3.9-4.9 mmol/L	44% (4/9 labs)	Serum	None

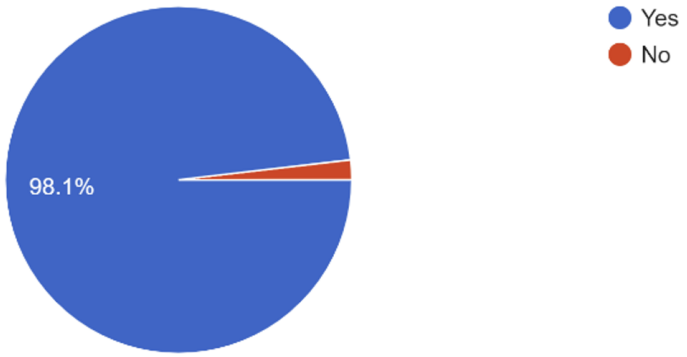
Adult Reference Interval Guidelines

Canada-Wide Feedback Survey

>100 Lab Directors/Professionals Contacted

(54 survey responses and 15 email responses)

Do you support this initiative?



Reference Interval Harmonization (hRI) Guidelines

Best Practice Guidelines on Reference Interval Harmonization in Canada

Evidence-based recommendations from the CSCC Working Group on Reference Interval Harmonization (CSCC WG-hRI)

Mary Kathryn Bohn,[a,b] Dana Nyholt,[c] Cynthia Balion,[d] George Cembrowski,[e] Christine Collier,[f] Vincent De Guire,[g] Victoria Higgins,[c,h] Benjamin Jung,[a,b] Olivia Landon[a], Zahraa Mohammed-Ali,[i] David Seccombe, [f] Jennifer Taher,[b,j] Albert K.Y. Tsui,[c,h] Allison A. Venner,[h,k] Nicole White Al-Habeeb[l], and Khosrow Adeli[a,b,*]

1. Clinical laboratories should adopt harmonized reference intervals for 13 analytes (albumin (BCG method only), alkaline phosphatase, alanine aminotransferase, creatinine, calcium, carbon dioxide, chloride, creatinine, lactate dehydrogenase, magnesium, phosphate, total protein, and thyroid stimulating hormone)
2. Clinical laboratories should adopt separate reference intervals for potassium for serum and plasma.
3. Clinical laboratories should adopt separate reference intervals for albumin measured by bromocresol green and bromocresol purple method.
4. Harmonized reference intervals for free thyroxine, total bilirubin, and sodium are not recommended at this time.
5. Clinical laboratories should consider verifying proposed harmonized reference intervals on their local analytical platform and population prior to implementation.

Accepted pending minor revisions (Clinical Biochemistry)

Lipid Subcommittee Updates

Previous Work

Canadian Journal of Cardiology 37 (2021) 933–937

Training/Practice
Health Policy and Promotion

A Snapshot of Lipid-Reporting Practices in Canadian Clinical Laboratories: An Urgent Need for Harmonisation

Victoria Higgins, PhD,[a,‡] Nicole White-Al Habeeb, PhD, FCACB,[b,‡] Allison A. Venner, PhD, FCACB,[c] Dana Bailey, PhD, FCACB, DABCC,[d] Christine Collier, PhD, FCACB,[e] and Khosrow Adeli, PhD, FCACB, FAACC, DABCC;[a,f] on behalf of the Canadian Society of Clinical Chemists Working Group on Reference Interval Harmonisation

Canadian Journal of Cardiology 38 (2022) 1180–1188

Guidelines

Canadian Society of Clinical Chemists Harmonized Clinical Laboratory Lipid Reporting Recommendations on the Basis of the 2021 Canadian Cardiovascular Society Lipid Guidelines

Nicole M.A. White-Al Habeeb, PhD,[a,‡] Victoria Higgins, PhD,[b,c,‡] Allison A. Venner, PhD,[d] Dana Bailey, PhD,[a] Daniel R. Beriault, PhD,[e,f] Christine Collier, PhD,[g] and Khosrow Adeli, PhD;[e,h] on behalf of the Canadian Society of Clinical Chemists Working Group on Reference Interval Harmonization

- **Chairs:** Victoria Higgins, Nicole White-Al Habeeb
- **Members:**
  - Khosrow Adeli
  - Daniel Beriault
  - Christine Collier
  - Dana Nyholt
  - Allison Venner

Canadian Journal of Cardiology 40 (2024) 1183–1197

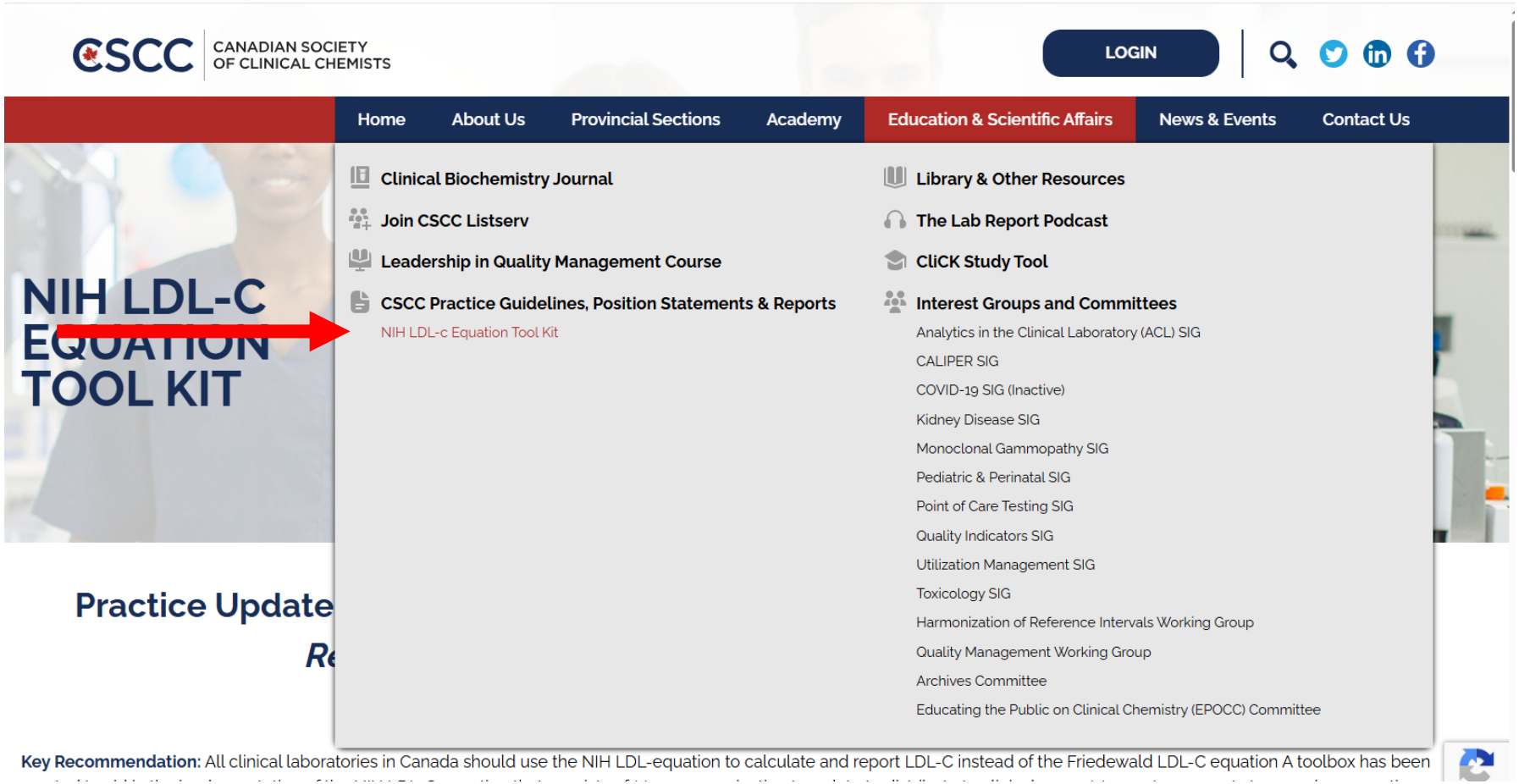
Guidelines

Canadian Society of Clinical Chemists Harmonized Pediatric Lipid Reporting Recommendations for Clinical Laboratories

Victoria Higgins, PhD,[a,b,‡] Nicole M.A. White-Al Habeeb, PhD,[c,‡] Dana Bailey, PhD,[c] Daniel R. Beriault, PhD,[d,e] Ivan M. Blasutig, PhD,[f,g,h] Christine P. Collier, PhD,[i,j] Allison A. Venner, PhD,[k,l] and Khosrow Adeli, PhD;[d,m] on behalf of the Canadian Society of Clinical Chemists Working Group on Reference Interval Harmonization

Practice Update: Recommendations on LDL-C Calculation & Reporting

- Communication template
- Transition reporting comments
- Key verification conditions and template to verify correct calculation by NIH LDL-C equation



Lipid Subcommittee Next Steps

- Guideline/Implementation document
  - Provide detailed implementation guidance
    - LIS-specific challenges
    - LIS-specific templates
- Survey of Canadian clinical labs
  - Ideally include respondents from the previous survey in addition to others
  - Determine how many labs implemented each recommendation
  - Outline challenges prevented implementation
    - Concerns from clinicians
    - LIS limitations
    - Resource constraints

Harmonization of CSF Analysis for Investigation of Multiple Sclerosis (hCAMI) Subcommittee Updates

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Variation in processes and reporting of cerebrospinal fluid oligoclonal banding and associated tests and calculated indices across Canadian clinical laboratories

V. Higgins [a,b,*], D. Beriault [c,d,e], A. Mostafa [b], M.P. Estey [a,b], T. Agbor [a,b,f], O.Z. Ismail [a,b], M.L. Parker [a,b,*]

- Published April 2023
- 39 questions sent to clinical chemists at all 13 clinical laboratories in Canada performing CSF OCB analysis (100% response rate)
- BC (3), Alberta (2), Ontario (4), Quebec (3), New Brunswick (1)
- Variation in practice observed in several areas:
  - Quality assurance
  - Paired sample acceptability criteria
  - Interpretation
  - Reporting

hCAMI Committee Established Spring 2023

Aim:

Establish recommendations for laboratory processes and reporting of CSF OCB and associated tests supporting MS diagnosis

Membership

*co-chairs

Clinical Chemists

- *Victoria Higgins
- *Daniel Beriault
- *Michelle Parker
- Basma Ahmed
- Vipin Bhayana
- Ronald Booth
- Yu Chen
- Christine Collier
- Myriam Gagne
- Jessica Gifford
- Ola Ismail
- Joseph Macri
- Ashley Newbigging
- Lily Olayinka
- Karina Rodriguez-Capote
- Liju Yang

Neurologists

- Mark Freedman
- Craig Moore
- Ilia Poliakov
- Raphael Schneider
- Simon Thebault

hCAMI Subcommittee Workflow

1. Quality assurance practices
2. Plasma acceptability and time interval requirements for paired CSF and blood
3. If and how to report CSF-specific band counts
4. Interpretation and follow-up for mirror patterns (i.e., inflammatory response, monoclonal gammopathy)
5. Interpretation of matched bands with differing intensity between CSF and serum
6. Panel components and reference intervals/decision limits

hCAMI Subcommittee Workflow

1

CRITICAL REVIEWS IN CLINICAL LABORATORY SCIENCES
https://doi.org/10.1080/10408363.2025.2490166
Taylor & Francis
Taylor & Francis Group
Check for updates
INVITED REVIEW

A review of laboratory practices for CSF oligoclonal banding and associated tests

Victoria Higgins[a,b], Yu Chen[c,d,e], Mark S. Freedman[f], Karina Rodriguez-Capote[g,h] and Daniel R. Beriault[i,j]

2

Contents lists available at ScienceDirect
Clinical Biochemistry
journal homepage: www.elsevier.com/locate/clinbiochem
ELSEVIER

A survey of Canadian neurologists' perspectives and preferences for laboratory reporting of CSF oligoclonal banding

Victoria Higgins[a,b,*], Michelle L. Parker[a,b], Daniel R. Beriault[c,d,e], Ahmed Mostafa[a,b], Mathew P. Estey[a,b], Terence Agbor[f], Ola Z. Ismail[a,b]

3

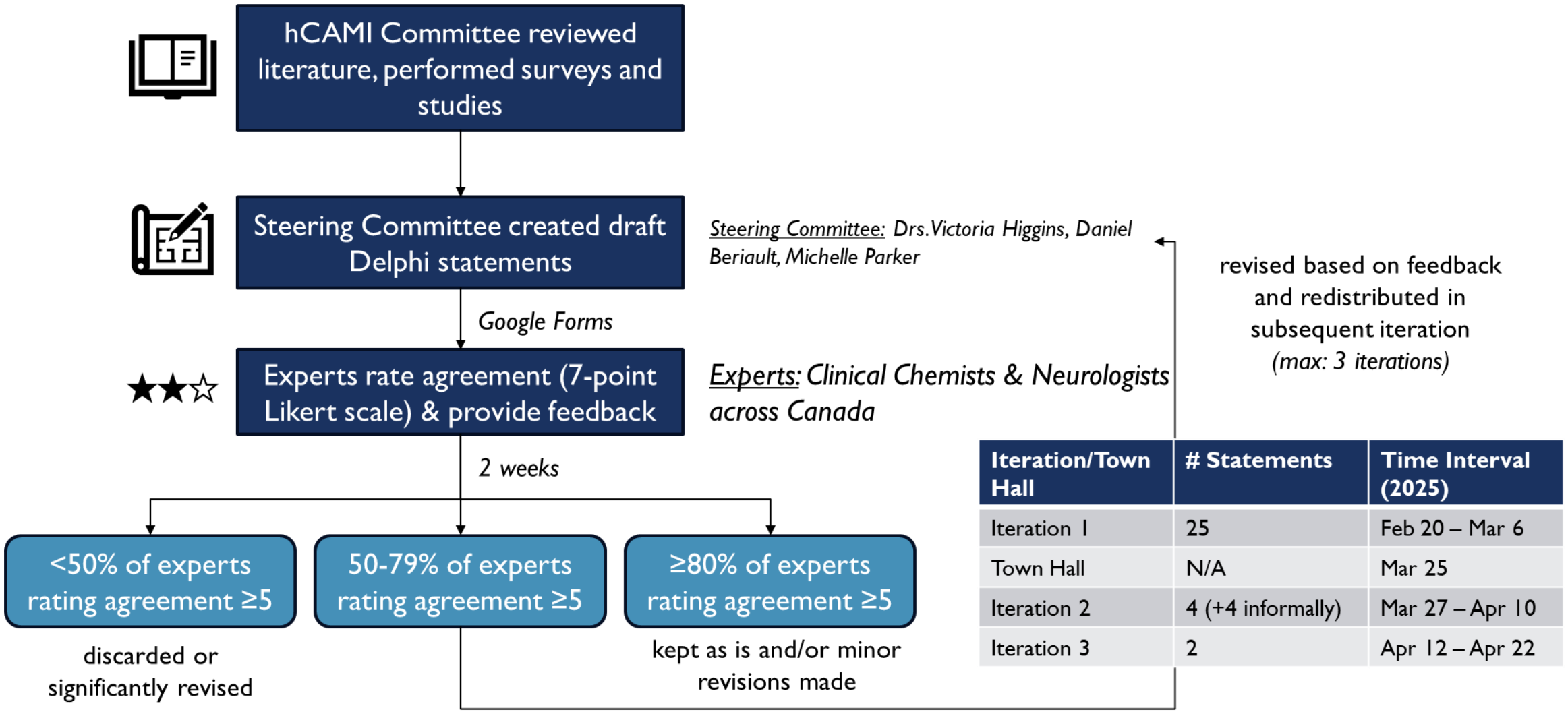
DE GRUYTER
Clin Chem Lab Med 2025; aop

Letter to the Editor

Lily Olayinka, Yu Chen, Karina Rodriguez-Capote, Jessica L. Gifford, Caitlin Buch, Spencer Weber, Michelle L. Parker, Natalia Volodko, Mathew P. Estey, Dustin Proctor, Ashley Newbigging, Pierre Bordeleau, Maggie Powell, Daniel R. Beriault, Joseph Macri and Victoria Higgins*

Oligoclonal banding analysis: assessing plasma use and time interval requirements for paired CSF and blood

hCAMI Subcommittee Delphi Process & Consensus Criteria



Iteration/Town Hall	# Statements	Time Interval (2025)
Iteration 1	25	Feb 20 – Mar 6
Town Hall	N/A	Mar 25
Iteration 2	4 (+4 informally)	Mar 27 – Apr 10
Iteration 3	2	Apr 12 – Apr 22

hCAMI Subcommittee Delphi Conclusions & Next Steps

- Conclusions
  - 21/25 statements met consensus in Iteration #1
  - 23/25 statements met consensus by Iteration #2
  - 24/25 statements met consensus by Iteration #3
  - 1 statement did not meet consensus – “Delphi Statement #13: CSF OCB reports should include the observed CSF-specific band counts.”
- Draft of recommendations paper sent to subcommittee, currently being revised/updated
- Recommendations to be sent to CSCC for endorsement, then published by the end of this year

Poster at ADLM/CSCC 2025 in Chicago, IL

- Wednesday July 30, 2025, 9:30 AM – 5:00 PM Central Time (Presentation: 1:30 PM – 2:30 PM)
- Poster Board Number: B-102
- Poster Title: Harmonizing cerebrospinal fluid analysis for multiple sclerosis investigation: An update from the hCAMI subcommittee of the Canadian Society of Clinical Chemists (CSCC)

New CSCC hRI Working Group Webpage!

Implementation	Publications	Presentations
Lipid Subcommittee	hCAMI Subcommittee	Resources
hRI Guidelines		

Introduction

The CSCC Working Group on Reference Interval Harmonization (hRI) aims to develop and implement evidence-based recommendations for pediatric, adult, and geriatric biochemical hRIs and test reporting across Canada. Since 2015, the CSCC hRI WG has applied evidence-based statistical analysis to determine indirect hRIs from ~300,000 – 13,000,000 datapoints per analyte obtained from community and hospital laboratories. Additionally, the CSCC hRI WG has provided key recommendations on the reporting of national clinical guidelines, including dyslipidemia reporting. The adoption of hRIs nationally is critical for improving and standardizing the interpretation of laboratory test results and for fostering cohesion between test providers.

New CSCC hRI Working Group Webpage!

Key objectives of The CSCC hRI WG include:

- **Standardize Reference Intervals** – Develop and align reference intervals for common clinical laboratory tests.
- **Promote Evidence-Based Practices** – Use robust methodologies and population-based data.
- **Enhance Quality & Patient Safety** – Reduce variability in test interpretation.
- **Collaborate with Stakeholders** – Engage health agencies, professional societies, and laboratory networks.
- **Advance Research & Knowledge Translation** – Establish evidence-based reference intervals and create practical guidelines.
- **Advocate for Global Harmonization** – Contribute to international efforts and share best practices.
- **Facilitate Education & Training** – Provide resources to laboratory professionals and raise awareness among clinicians.

These efforts aim to enhance laboratory result reliability and improve healthcare outcomes in Canada.
Please contact us with any questions, suggestions, feedback, or speaking requests!

- Khosrow Adeli (khosrow.adeli@sickkids.ca)
- Christine Collier (christinecollier064@gmail.com)

Mission Statement
Establish evidence-based harmonized/common reference intervals (hRIs) and support their implementation in laboratories across Canada.

Expand All + | Hide All –

UPCOMING PRESENTATIONS +

TIMELINE OF KEY DELIVERABLES +

ONGOING PROJECTS +

MEMBERSHIP +

CSCC Reference Interval Harmonization Working Group Workshop – July 28, 2025

Agenda

1. Welcome and Introduction (*Dr. Benjamin Jung*)
2. The CSCC hRI Initiative: History, Mission, and Achievements (*Dr. Victoria Higgins*)
    a. Lipid Subcommittee Updates
    b. Harmonization of CSF Analysis for Investigation of Multiple Sclerosis (hCAMI) Subcommittee Updates
3. Next Steps for the CSCC hRI Working Group (*Dr. Benjamin Jung*)
    a. Promotional Campaign for Canada-wide adoption of published recommendations
    b. Ontario activities
    c. Phase 2 tests for harmonization evaluation

CSCC Working Group on Reference Interval Harmonization

Adult Reference Interval Harmonization in Canada

Main Objective: Establish evidence-based harmonized/common reference intervals (hRIs) and support their implementation in laboratories across Canada.

Done

Complete **national reference interval (RI)** survey (2017) 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 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

In Progress

Publish and implement national Canadian harmonized RIs

Clinical Chemistry 69:9
991–1008 (2023)

Informatics and Statistics

Reference Interval Harmonization: Harnessing the Power of Big Data Analytics to Derive Common Reference Intervals across Populations and Testing Platforms

Mary Kathryn Bohn,[a,b] Dana Bailey,[c] Cynthia Balion,[d] George Cembrowski,[e] Christine Collier,[f] Vincent De Guire,[g] Victoria Higgins,[h] Benjamin Jung,[a,b] Zahraa Mohammed Ali,[i] David Seccombe,[j] Jennifer Taher,[b,k] Albert K.Y. Tsui,[e,l] Allison Venner,[l,m] and Khosrow Adeli[a,b,*]

National hRI Implementation

- ✓hRI Research Article – Published in Clinical Chemistry
- ✓Best Practice Guidelines on Reference Interval Harmonization in Canada – Accepted pending minor revision in Clinical Biochemistry
  - ✓Reviewed and approved by CSCC

1. Clinical laboratories should adopt harmonized reference intervals for the following 13 analytes:

Albumin (BCG)	**Calcium**	**LDH**	**Total Protein**
ALK	**Chloride**	**Mg**	**TSH**
ALT	**CO2**	**Phosphate**	
	Creatinine	**Potassium (serum)**	

Promotional Campaign of Canada Wide Adoption

✓Strategies developed at regular meetings throughout year (biweekly)
✓Presented at recent in-person hRI meeting (July 11)

<u>Key Implementation Strategies</u>

1. Dissemination of Guidelines
2. Town Halls
3. Virtual Resources
4. Meetings and Presentations
5. Education and Training Programs
6. Stakeholder Engagement and Feedback

Need your support!

1. Dissemination of Guidelines

- **Initial Publication:**
    - Promote the initial publication of the hRI guidelines through a peer-reviewed article in *Clinical Biochemistry* to reach a wide audience in the clinical laboratory community.
- **Website Promotion:**
    - Highlight the publication and its key takeaways on the CSCC website for easy access and visibility. Ensure the guidelines are easily downloadable for laboratory professionals.
- **Distribution to Stakeholders:**
    - Actively distribute the manuscript to interested individuals within the laboratory medicine field, including lab directors, medical technologists, pathologists, and clinical scientists.

2. Town Halls

- **CSCC-Supported Funding:**
    - Host a series of town halls supported by CSCC funding to engage with laboratory leaders across Canada. These can be held virtually or in hybrid formats, with regional teams based on geographic locations (Western Canada, Ontario, Eastern Canada, etc.).
- **Regional Engagement:**
    - Organize a team comprising both junior and senior members of the Working Group (WG) to lead each regional town hall. Assign point people in each large region to coordinate and promote these events.
- **Direct Engagement with Lab Directors:**
    - Invite lab directors, especially from community labs such as LifeLabs and DynaCare, to attend the town halls. Provide opportunities for them to voice their concerns and ask questions.
- **On-Site Visits:**
    - Teams can also visit key large centers in each region to present on the importance of harmonization and provide guidance on the implementation process.
- **Standardized Presentations:**
    - Develop a standard set of 15-20 slides for the town halls, which can be shared and finalized before the events. This ensures consistency across the different regional teams.

3. Virtual Resources

- **Podcasts/Interviews:**
    - Create podcasts and video interviews with subject-matter experts discussing the importance of hRI and the harmonization process. Share these resources on the CSCC website to further educate lab professionals and stakeholders.
- **User Testimonials:**
    - Feature video testimonials from laboratories that have already implemented hRIs, focusing on their challenges, successes, and insights. These testimonials will serve as case studies to inspire others.
- **Regular Updates:**
    - Publish regular articles in CSCC News, featuring updates on the hRI project, key milestones, and success stories. Request a dedicated half-page to one-page section in each issue to highlight the benefits of harmonization. This could also be done in other organizations' newsletters.
- **Website Updates:**
    - Continually update the CSCC website with news and developments related to the hRI project. This can include the publication of new resources, success stories, or guidance documents.
- **CSCC Roundtable:**
    - Organize a presentation during the CSCC Roundtable meetings, once the guidelines are published, to encourage further engagement and support.

4. Meetings and Presentations

- **ADLM/CSCC Annual Meeting:**
    - Host a 2-hour session at the ADLM/CSCC annual meeting in Chicago to present the hRI guidelines and engage stakeholders who may not yet be familiar with the initiative.
- **Presentations to Governing/Collaborating Bodies:**
    - Approach other relevant organizations such as the Canadian Society for Medical Laboratory Science (CSMLS) and the Canadian Association of Medical Biochemists (CAMB) to request a presentation on the harmonization effort at their annual meetings.
- **Partnerships and Networking:**
    - Build relationships with influential governing bodies and laboratory organizations to ensure widespread adoption of the hRI guidelines across Canada.

5. Education and Training Programs

- **Workshops and Webinars:**
    - Organize workshops and webinars to train laboratory professionals on how to implement hRIs into their laboratory practices. These sessions could cover topics such as the technical aspects of harmonization, overcoming common challenges, and how harmonized reference intervals improve patient care.
- **Lab Accreditation and Certification:**
    - Work with accrediting bodies to ensure that laboratories are encouraged or required to adopt harmonized reference intervals as part of their accreditation process.
- **Certification for Implementation:**
    - Develop a certification program for laboratories that successfully implement hRIs, providing recognition for their commitment to improving laboratory testing practices and patient outcomes.

6. Stakeholder Engagement and Feedback

- **Regular Stakeholder Surveys:**
    - Implement surveys and feedback mechanisms to gather input from laboratory directors and staff on their experiences with the implementation process. Use this data to adjust strategies and address barriers.
- **Incentives for Early Adopters:**
    - Offer incentives for early adopters of the hRI guidelines, such as discounts on future training or recognition through CSCC's communications channels, to motivate laboratories to lead the way in harmonization.

Ontario Activities

- Champion: Khosrow Adeli
- Department of Laboratory Medicine and Pathobiology, University of Toronto
- Ontario Laboratory Medicine Program (OLMP) - Biochemistry

Reference Interval Harmonization in Ontario:

Proposal to OLMP (Biochemistry)

Updates:

- *GTA Wide Reference Interval Survey and Results of a Verification Study (7 hospitals)*
- *Proposal for an Ontario-Wide Reference Interval Survey and Reference Interval Verification Study*

1. Survey: Greater Toronto Area Reference Intervals

- **An anonymous survey was collaboratively designed to assess variation in reference intervals for 16 key chemistry analytes across Toronto hospitals and community laboratories**

- **Information collected for each analyte included:**
  - Manufacturer
  - Method
  - Reference Interval
  - Matrices

- **Invitations to participate in the survey were sent to nine laboratories (2023/02/01, 100% completion)**
  - **2/9** – community laboratories
  - **7/9** – hospital laboratories

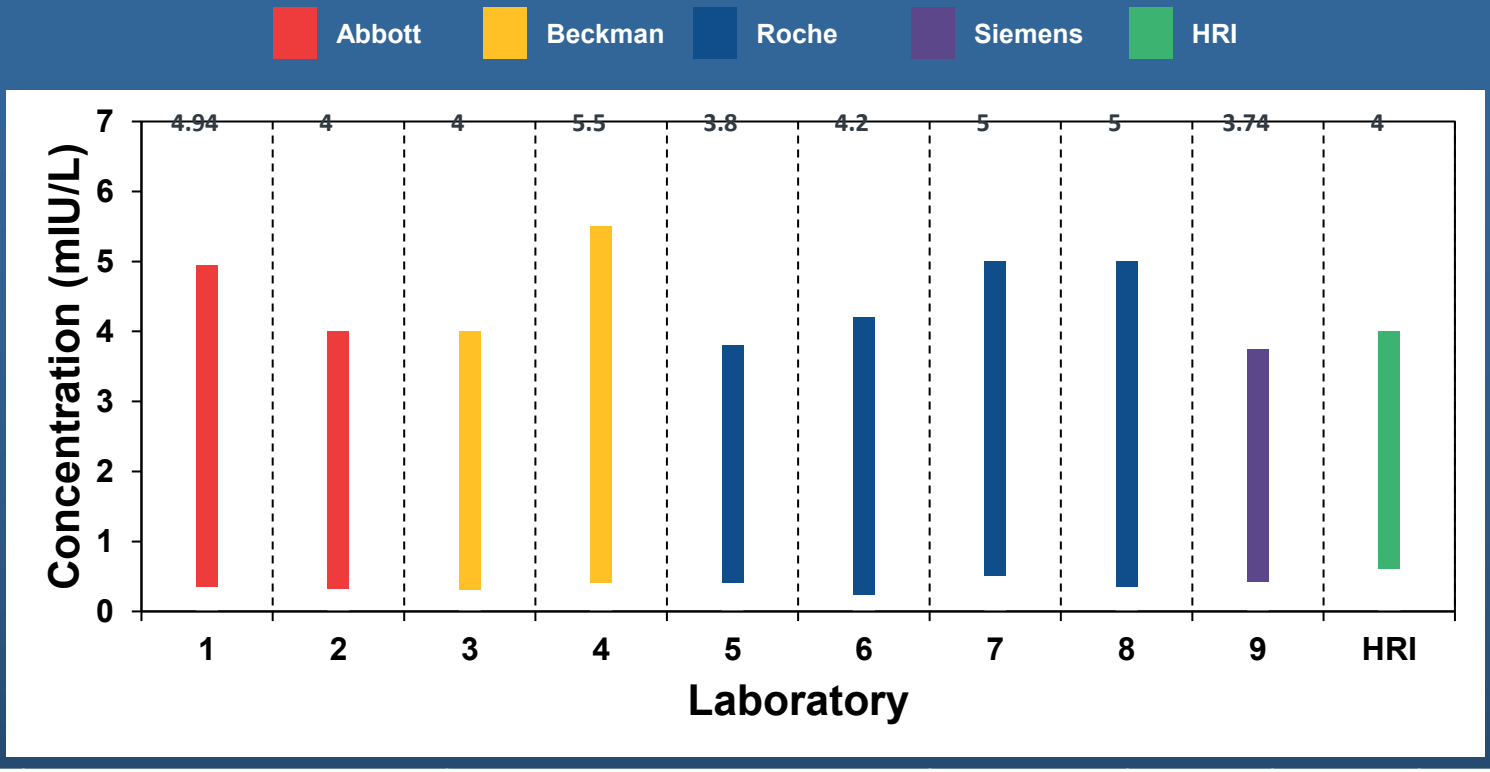
- **Survey results (2023/03/01) per analyte are summarized throughout this presentation**

Analytes
Albumin
ALT
ALP
Bilirubin (total)
Calcium
Carbon dioxide (total)
Chloride
Creatinine
Free T4
LDH
Magnesium
Phosphate
Potassium
Sodium
Total Protein
TSH

TSH

Reference Intervals in use across Greater Toronto Area:

9 Major Clinical Laboratories surveyed



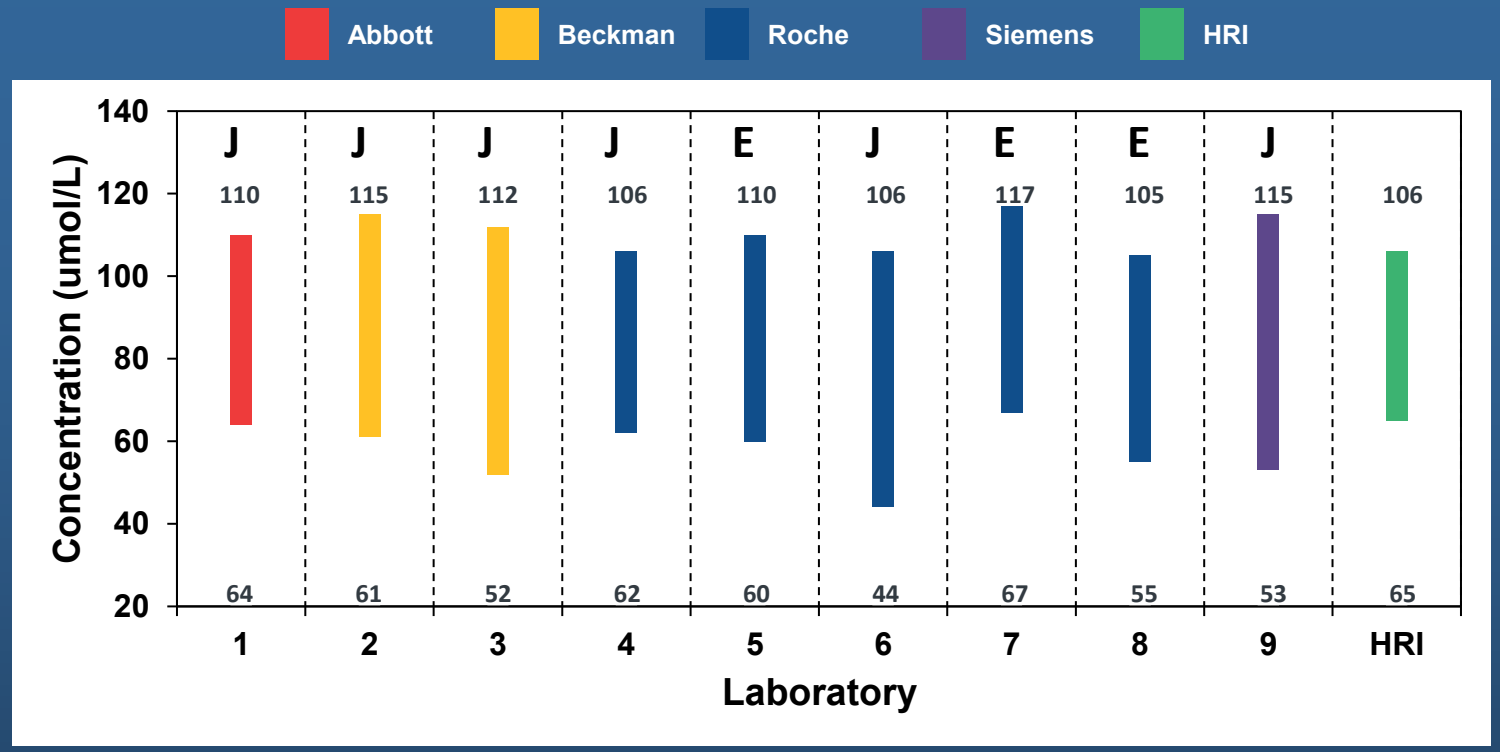
#	Platform	Method	Specimen	Unit	LL	UL
1	Abbott Alinity i	CMIA	Plasma	mIU/L	0.35	4.94
2	Abbott Alinity i	CMIA	Serum	mIU/L	0.32	4
3	Beckman DXI Access	paramagnetic particle chemiluminescent immunoassay	Plasma	mIU/L	0.3	4
4	Beckman DXI600	Access TSH (3rd IS) immunoassay	Serum	mIU/L	0.4	5.5
5	Roche cobas e602	Noncompetitive immunoassay	Both	mIU/L	0.4	3.8
6	Roche e601	Sandwich immunoassay	Plasma	mIU/L	0.24	4.2
7	Roche e602	Sandwich immunoassay	Both	mIU/L	0.5	5
8	Roche e801	Electrochemiluminescence immunoassay (ECLIA)	Serum	mIU/L	0.35	5
9	Siemens Atellica	Sandwich Immunoassay	Plasma	mIU/L	0.42	3.74
HRI	**All**	**All**	**Both**	mIU/L	**0.6**	**4**

Creatinine (Male)

GTA Survey

Reference Intervals in use across Greater Toronto Area:

9 Major Clinical Laboratories surveyed



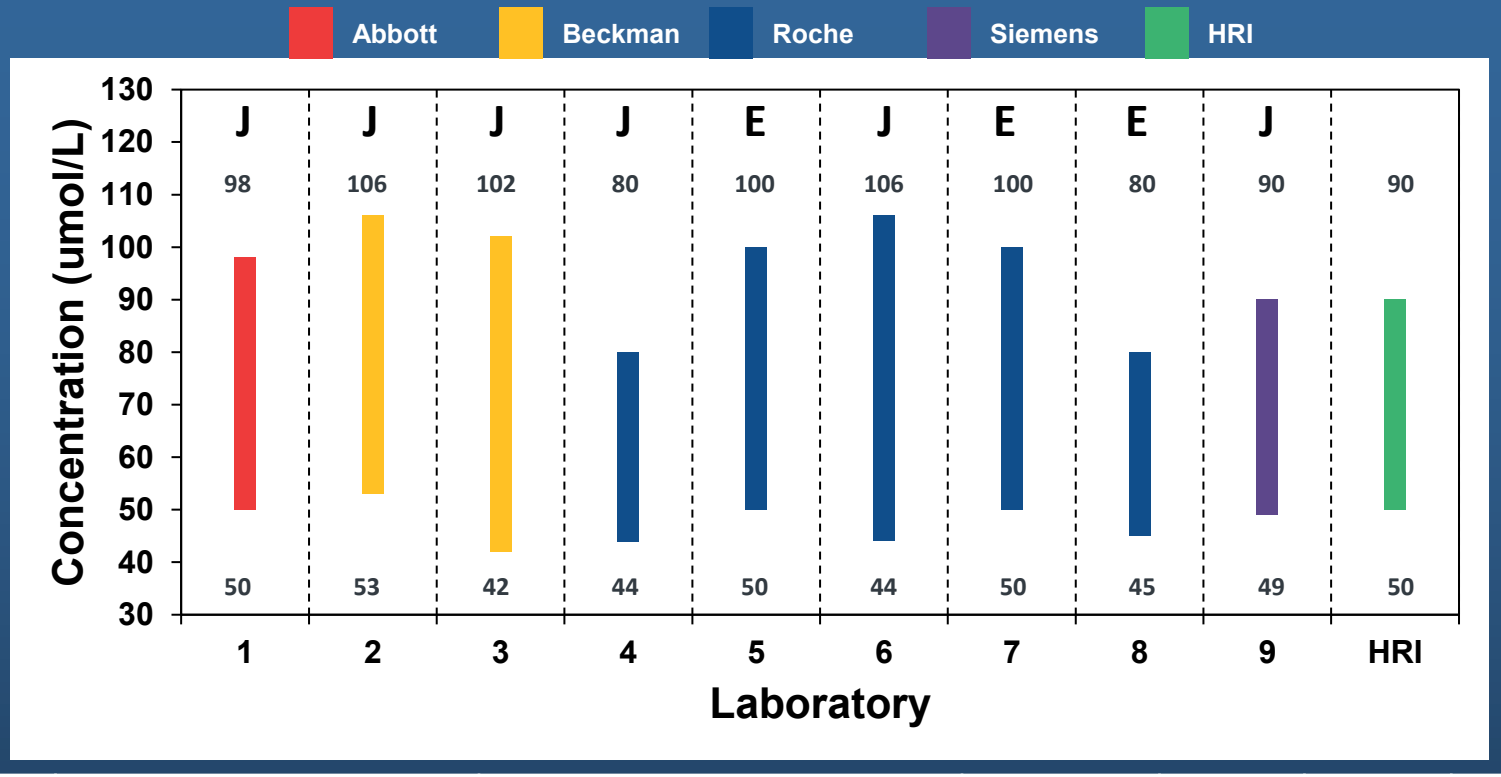
J: Jaffe
E: Enzymatic

#	Platform	Method	Specimen	Unit	LL	UL
1	Abbott Alinity c	Kinetic Alkaline Picrate	Plasma	umol/L	64	110
2	Beckman DxC 700 AU	Jaffe reaction	Plasma	umol/L	61	115
3	Beckman AU680	kinetic Jaffe	Serum	umol/L	52	112
4	Roche c501	Rate-blanking Jaffe method	Plasma	umol/L	62	106
5	Roche c701	enzymatic	Serum	umol/L	60	110
6	Roche c702	Rate-blanking Jaffe method	Both	umol/L	44	106
7	Roche Cobas C701	enzymatic method	Serum	umol/L	67	117
8	Roche cobas c702	Spectrophotometric enzymatic	Both	umol/L	55	105
9	Siemens Atellica	Kinetic alkaline picrate	Plasma	umol/L	53	115
HRI	**All**	**All**	**Both**	umol/L	65	106

Creatinine (Female)

Reference Intervals in use across Greater Toronto Area:

9 Major Clinical Laboratories surveyed



J: *Jaffe*
E: *Enzymatic*

#	Platform	Method	Specimen	Unit	LL	UL
1	Abbott Alinity c	Kinetic Alkaline Picrate	Plasma	umol/L	50	98
2	Beckman DxC 700 AU	Jaffe reaction	Plasma	umol/L	53	106
3	Beckman AU680	kinetic Jaffe	Both	umol/L	42	102
4	Roche c501	Rate-blanking Jaffe method	Plasma	umol/L	44	80
5	Roche c701	enzymatic	Serum	umol/L	50	100
6	Roche c702	Rate-blanking Jaffe method	Both	umol/L	44	106
7	Roche Cobas C701	enzymatic method	Serum	umol/L	50	100
8	Roche cobas c702	Spectrophotometric enzymatic	Both	umol/L	45	80
9	Siemens Atellica	Kinetic alkaline picrate	Plasma	umol/L	49	90
HRI	**All**	**All**	**Both**	**umol/L**	50	90

2. Direct analysis of 30 Healthy Adult Samples at 7 GTA Hospitals employing Different Assays/Platforms

Analyte	Matrix	Lab 1	Lab 2	Lab 3	Lab 4	Lab 5	Lab 6	Lab 7	Total Verification	Verification >80%
Albumin (BCG)	Serum	96.67% (G) (29/30)	86.67% (G) (26/30)		86.67% (G) (26/30)	86.67% (G) (26/30)	96.67% (G) (29/30)		90.60% (136/150)	100% 5/5 labs
ALP	Serum	86.67% (26/30)	86.67% (26/30)	90% (27/30)	90% (27/30)	83% (25/30)	90% (27/30)	83.33% (25/30)	87.14% (183/210)	100% 7/7 labs
ALT	Serum	86.67% (26/30)	96.67% (29/30)	96.67% (29/30)	93.33% (28/30)	100% (30/30)	83.33% (25/30)	90% (30/30)	93.81% (197/210)	100% 7/7 labs
Calcium	Serum	96.67% (29/30)	96.67% (29/30)	86.67% (26/30)	93.33% (28/30)	96.67% (29/30)	100% (30/30)	96.67% (29/30)	95.24% (200/210)	100% 7/7 labs
Chloride	Serum	96.67% (29/30)	93.33% (28/30)	96.67% (29/30)	96.67% (29/30)	96.67% (29/30)	100% (30/30)	96.67% (29/30)	96.67% (203/210)	100% 7/7 labs
Creatinine	Serum	93.33% (28/30)	93.33% (28/30)	96.67% (29/30)	93.33% (28/30)	93.33% (28/30)	93.33% (28/30)	96.67% (29/30)	94.29% (198/210)	100% 7/7 labs
FT4	Serum	23.33% (7/30)	96.67% (29/30)	20% (6/30)	26.67% (8/30)	89.66% (26/29)	30% (9/30)	76.67% (23/30)	51.67% (108/209)	28.57% 2/7 labs
LDH	Serum	96.67% (29/30)	93.33% (28/30)	93.33% (28/30)	86.67% (26/30)	93.33% (28/30)	90% (27/30)	86.67% (26/30)	91.43% (192/210)	100% 7/7 labs
Magnesium	Serum	100% (30/30)	100% (30/30)	96.67% (29/30)	96.67% (29/30)	100% (30/30)	93.33% (28/30)	96.67% (29/30)	97.62% (205/210)	100% 7/7 labs
Phosphate	Serum	100% (30/30)	100% (30/30)	96.67% (29/30)	100% (30/30)	100% (30/30)	96.67% (29/30)	96.67% (29/30)	98.57% (207/210)	100% 7/7 labs
Potassium	Serum	63.33% (19/30)	67% (20/30)	63.33% (19/30)	20.00% (6/30)	60.00% (18/30)	26.67% (8/30)	66.67% (20/30)	52.86% (111/210)	0% 0/7 labs
Sodium	Serum	43% (13/30)	96.67% (29/30)	96.67% (29/30)	96.67% (29/30)	90% (27/30)	100% (30/30)	100% (30/30)	89.05% (187/210)	86% 6/7 labs
Total Bilirubin	Serum	100% (30/30)	96.67% (29/30)	96.67% (29/30)	100% (30/30)	96.67% (29/30)	96.67% (29/30)	96.67% (29/30)	97.62% (205/210)	100% 7/7 labs
Total CO2	Serum	66.67% (20/30)	86.87% (26/30)	76.67% (23/30)	60% (18/30)	100% (30/30)	43.33% (13/30)	36.67% (11/29)	67.14% (141/210)	28.57% 2/7 labs
Total Protein	Serum	100.00% (30/30)	86.67% (26/30)	66.67% (20/30)	73.33% (22/30)	90.00% (27/30)	66.67% (20/30)	93.33% (28/30)	82.38% (173/210)	57.14% 4/7 labs
TSH	Serum	93.33% (28/30)	86.67% (26/30)	93.33% (28/30)	93.33% (28/30)	93.10% (27/29)	93.33% (28/30)	93.33% (28/30)	92.34% (193/209)	100% 7/7 labs

*Preliminary data, not reviewed

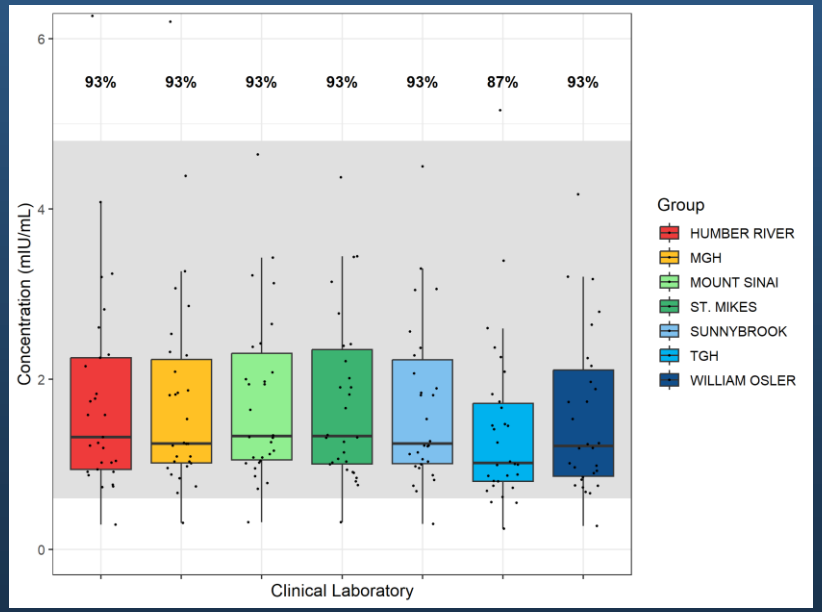
GTA-Wide Reference Interval Verification : Toronto Hospitals (June-July 2025)

TSH: 30 healthy adult samples analyzed by 7 GTA hospitals

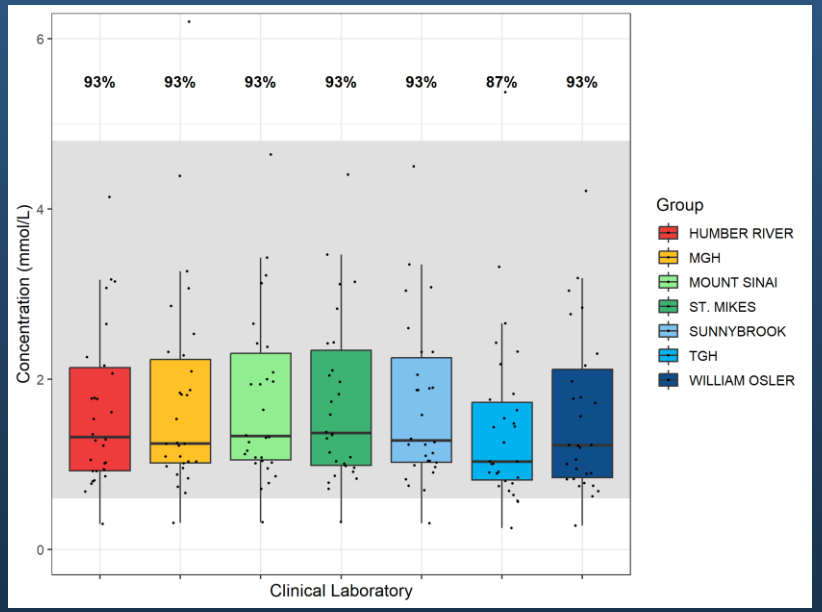
Proposed Harmonized Reference Interval (0.6-4.4)

All results well below the upper limit of 4.4

Plasma



Serum



*Preliminary data, not reviewed

1. Ontario-Wide Adult and Pediatric
Reference Interval Verification

Healthy Pediatric and Adult Serum/Plasma Samples (20-40)

Cross-Ontario Verification Study

(10 Key Laboratories)

Hamilton, London, Kingston, Ottawa, Toronto

Data Analysis
(CSCC Working Group on Reference Interval Harmonization)

2. Ontario-Wide
Lab Survey (250 Labs)

Phase 2 Tests for Harmonization Evaluation

Category	Analytes
Chemistry	AST, GGT, amylase, lipase, IgG, IgA, IgM, C-reactive protein, magnesium, phosphate, uric acid, urea, iron, transferrin, TIBC, plasma potassium, direct bilirubin, creatine kinase
Immunoassays	FT4, TT3, FT3, total testosterone, free testosterone, SHBG, estradiol, cortisol, progesterone, LH, FSH, ferritin, Vitamin D
Hematology	WBC, RBC, hemoglobin, hematocrit, MCV, MCH, MCHC, RDW, platelets, MPV, neutrophils (#, %), lymphocytes (#, %), monocytes (#, %), eosinophils (#, %), basophils (#, %)

Other Activities/Directions

- Method-specific RI harmonization
  - E.g. Common RIs for free T4 did not verify across platforms but comparable values observed in direct sample analysis

- Reporting recommendations for reference intervals and clinical decision limits

Acknowledgments

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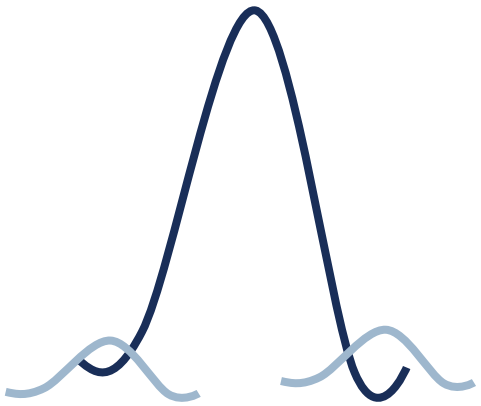

Discussion

- Have you implemented (or started implementing) harmonized RIs or lipid recommendations?
- What challenges were met or are anticipated?
- What ideas do you have for the hRI WG to promote implementation?
- What resources/support would you like the hRI WG to provide?
- What analytes would you like to see in Phase II?
- What other subcommittees would you like to see for harmonization initiatives (e.g., lipids and CSF OCB)?
- What would you like to see on the CSCC Website?