Reference Interval Harmonization Across Canada:

Pediatric and Adult Perspectives

Mary Kathryn Bohn, PhD Candidate
Paediatric Laboratory Medicine, The Hospital for Sick Children
Laboratory Medicine and Pathobiology, University of Toronto

Learning Objectives

1) Discuss the importance of reference interval harmonization in pediatric and adult populations and the barriers to implementation

2) Provide an overview of the **Canadian Laboratory Initiative on Pediatric Reference Intervals** (CALIPER) as well as its recent activities and contribution to harmonization

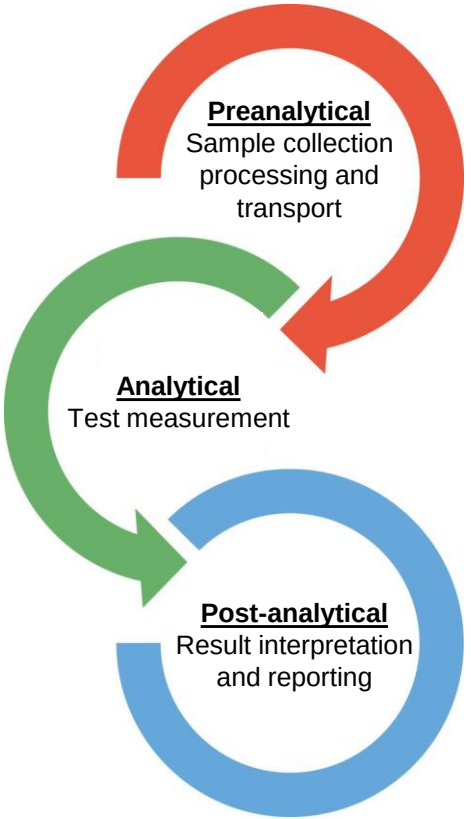
3) Provide an overview of the recent activities of the **CSCC Reference Interval Harmonization Working Group (hRI WG)**

4) Discuss planned and future work of these initiatives towards reference interval harmonization in Canada

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 driven by **integrated health networks** and **increasing access for patients** to their own medical laboratory data
- 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*

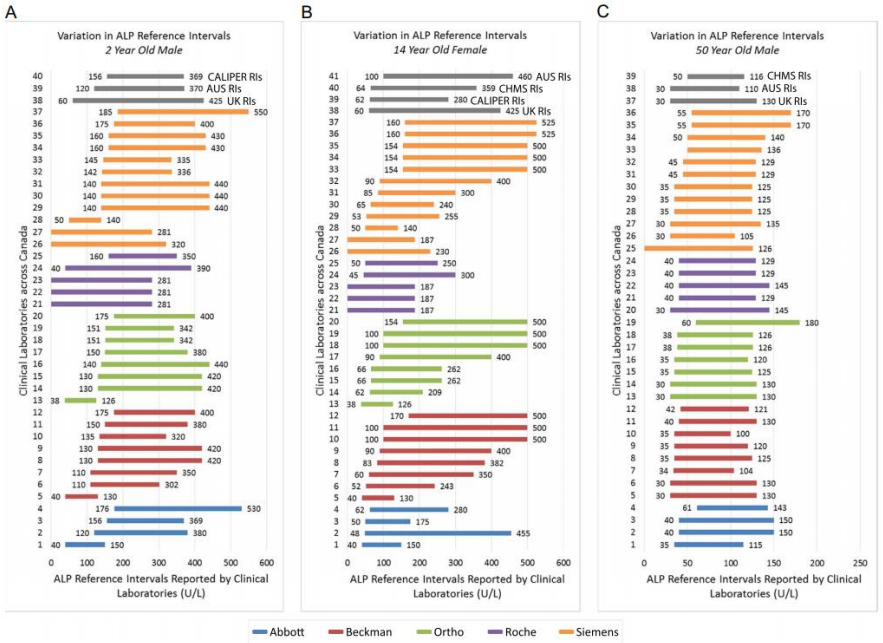
Have similar gains been made in reference interval reporting?



Reference Interval Harmonization

- Appropriate and consistent test interpretation relies on reference intervals (RIs)
- **Harmonized RIs should only be considered when significant analytical differences are NOT observed**
  - *Inappropriate harmonization can negatively impact clinical decision-making*
- Several surveys globally have reported wide variation in RIs across laboratories, even in those using the same analytical platform *(CSCC, Clin Biochem;50(16-17))*

There is a *high risk of inappropriate test result interpretation when RIs are not appropriately harmonized, potentially leading to unnecessary and even invasive interventions as well as erroneous or missed diagnosis*.



- **37 laboratories reported RIs for 7 analytes**
- **High variation in reported RIs even between laboratories using the same instrumentation**
- **Most RI variation was greater than test result variation**

Clinical Biochemistry. 2017 Nov 1;50(16-17):925-35.

Barriers to Reference Interval Harmonization

Development:

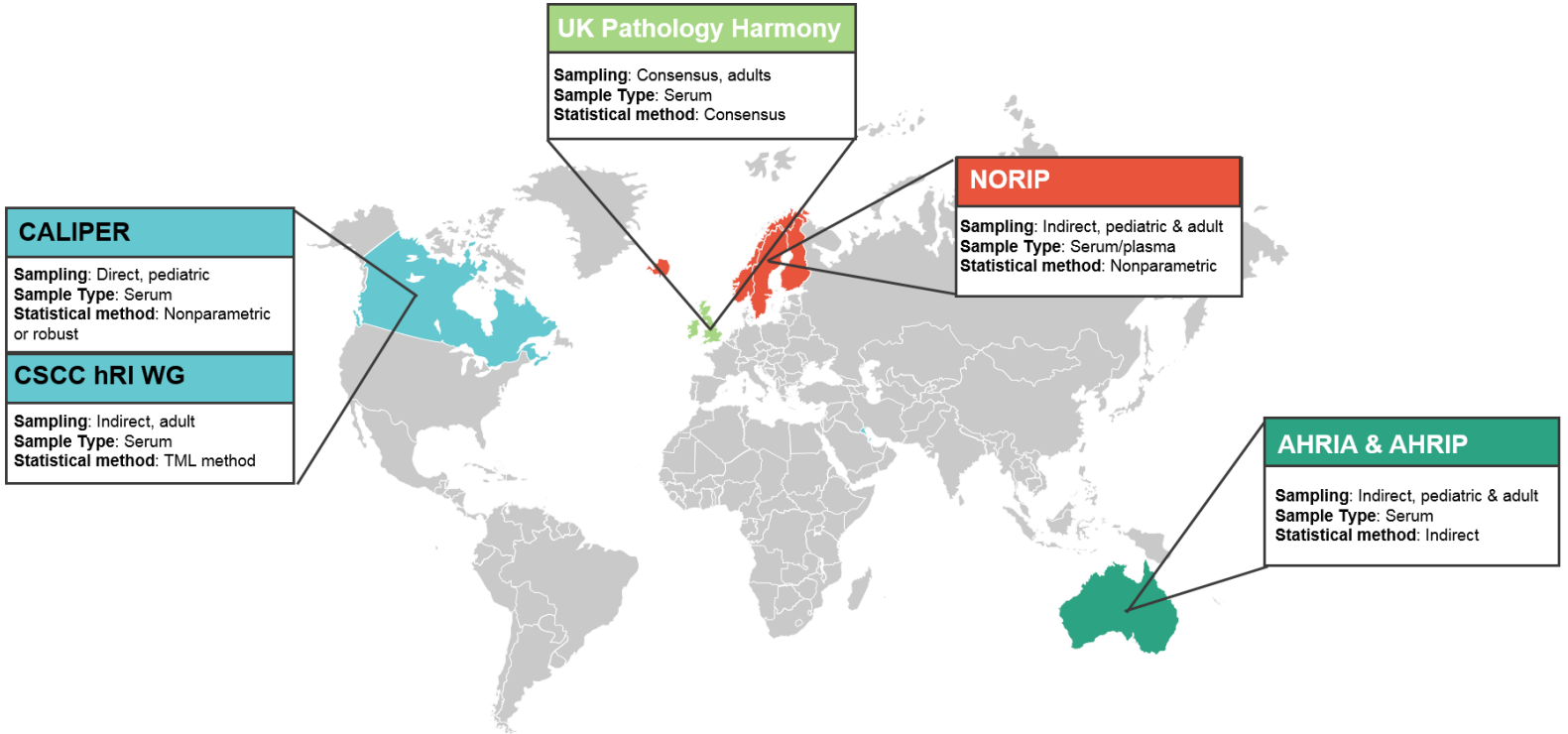
- Need to ensure analyte of interest is sufficiently standardized across relevant analytical platforms
- Need to ensure RIs are representative of the population for which they will serve
    - ***Requires very high sample size to make meaningful determinations***

Implementation:

- Requires laboratory efforts to verify proposed harmonized RIs in accordance with CLSI guidelines
- Requires significant IT time to implement into LIS systems

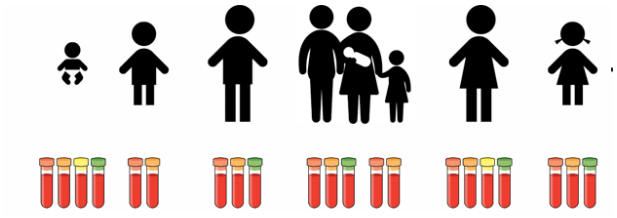
Reference Interval Harmonization Globally

Several countries have undertaken large harmonization initiatives to both develop and implement harmonized reference intervals into clinical practice.



Direct vs Indirect Reference Interval Approaches

Direct Approach



\+
- Recommended by CLSI
- Better representation of a true healthy population
- Minimal pre-analytical variation

\-
- Extensive resource requirements
- Large sample size required
- Updating recommendations as new analytical platforms develop is challenged

Indirect Approach

Laboratory information systems

\+
- Less resources required
- Data can easily be representative for many regions & platforms
- Pre-analytical processes reflect routine laboratory practice

\-
- Requires in-depth statistical analysis and consideration
- Determination of healthy population/distribution relies on statistical methods
- Typically no clinical information provided

Reference Interval Harmonization in Canada

Pediatrics
(birth to <19 years)

Adults
(19 to <80 years)

CALIPER
'ARM' us with the knowledge to help others

CSCC | CANADIAN SOCIETY OF CLINICAL CHEMISTS

CALIPER Project: *An Overview*

Main Objectives:

1. To determine the effects of **key covariates** on reference intervals for biochemical parameters in healthy children and adolescents

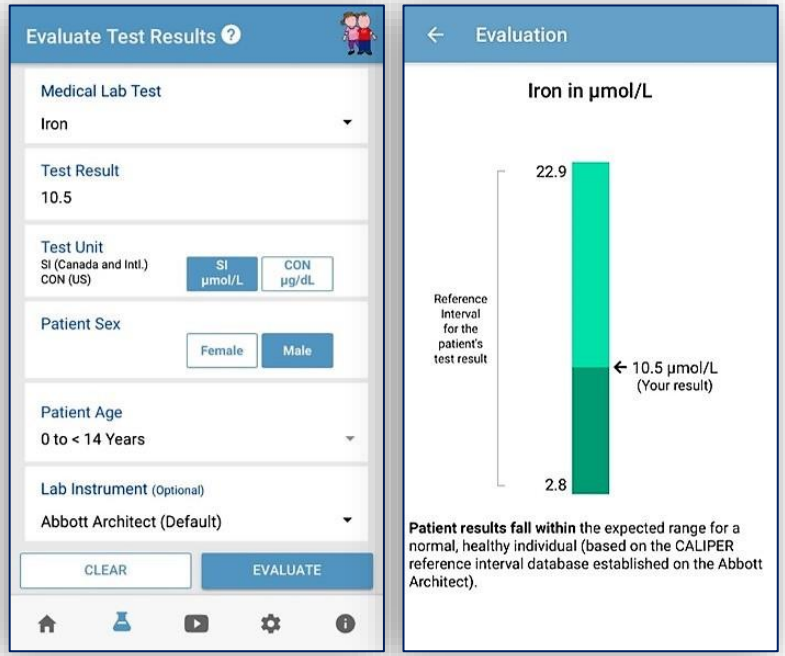
2. To develop a comprehensive **database of covariate stratified reference intervals** on multiple analytical platforms

3. To disseminate study results to pediatric healthcare community worldwide (www.caliperdatabase.org)

Progress to Date:

- Recruited over **12,000 healthy children and adolescents** from the Greater Toronto Area and Hamilton regions

- Established robust reference intervals for over **185 biomarkers** on multiple analytical platforms

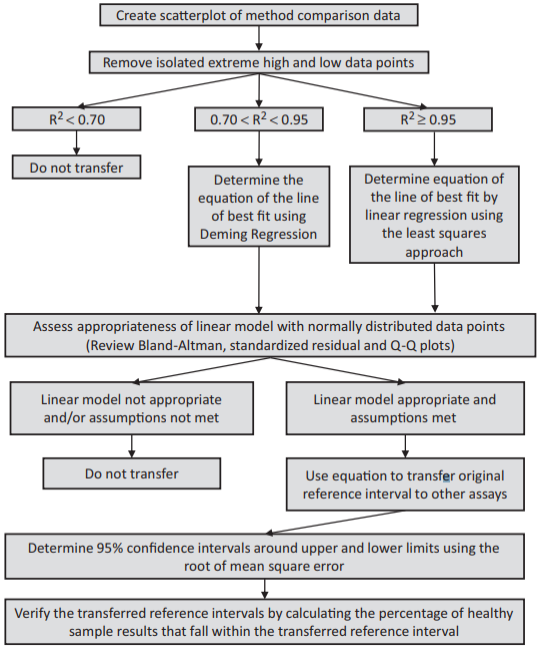


CALIPER

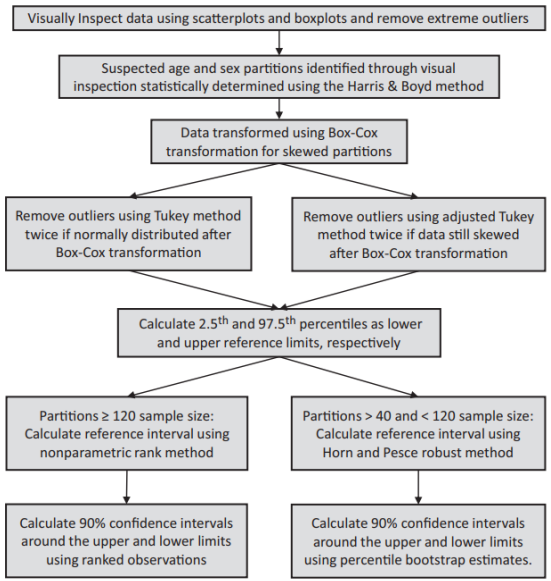
'ARM' us with the knowledge to help others

CALIPER: Approach and Contribution to Harmonization

Clinical Chemistry Assays



Immunoassays and Specialized Parameters



Abbott

Ortho Clinical Diagnostics

SIEMENS

BECKMAN COULTER

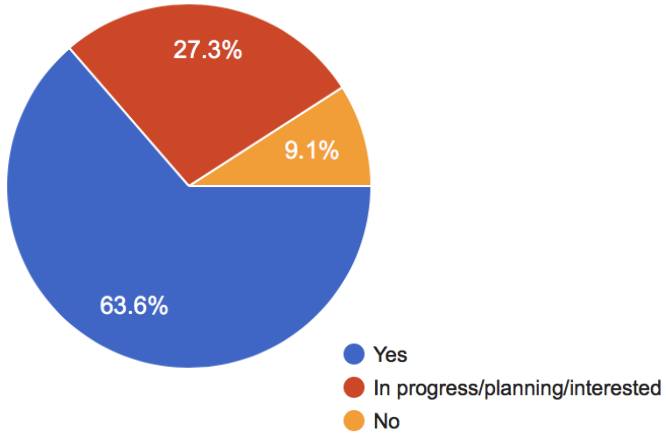
Roche

Critical reviews in clinical laboratory sciences. 2017 Aug 18;54(6):358-413.

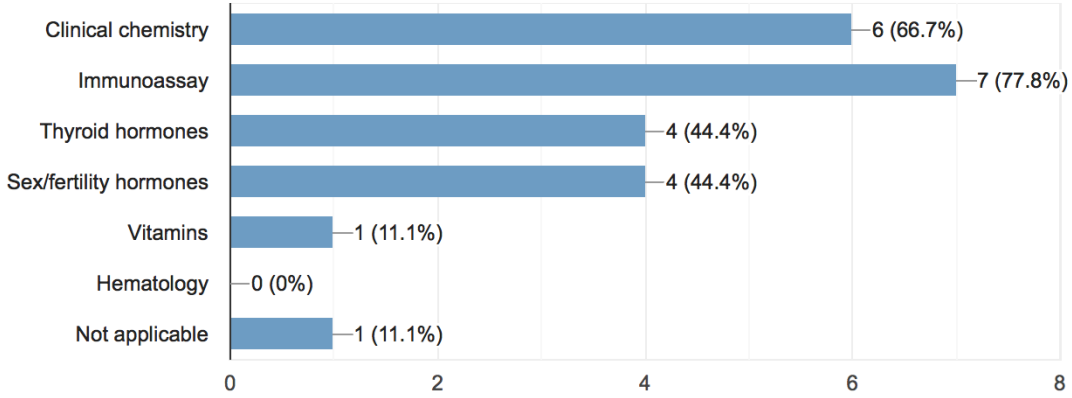
CALIPER: Implementation Across Canada

- CALIPER reference intervals have been implemented in many laboratories across Canada and worldwide
    - ***Contributed to RI harmonization in the pediatric population in Canada***
- Preliminary anonymous survey circulated via CSCC list serve to gage implementation and provide opportunity to feedback (***11 laboratories, location anonymous***):

Has your laboratory implemented CALIPER RIs?



For what laboratory tests?



CSCC hRI WG: Approach Overview - Adults

I. *Initial literature review, national survey and critical gap identification*

Completion of **extensive literature review** on reference standards for metabolic, nutritional, and endocrine markers

Completion of national reference standard survey with response from 36 laboratories across Canada

Identification of **clear need** for *reference standard harmonization*

Wide consultation through in-person workshops with hRI CSCC members, clinical experts, and statisticians to establish our evidence-based approach

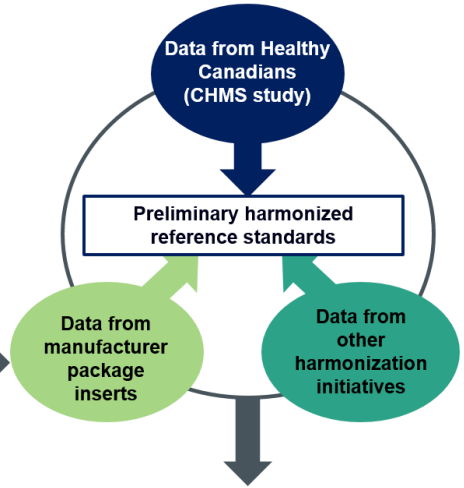
II. *Establishment of preliminary harmonized reference standards using a big data analytics approach*

Big Data Analytics: Outpatient data extraction from inter-provincial community reference laboratories

Laboratory tests: chloride, magnesium, potassium, sodium, total CO2, calcium, creatinine, and phosphate, ALP, albumin, ALT, total protein, total bilirubin, LDH, FT3, FT4, TSH
Date of collection: 01/01/2017-12/31/2018
Manufacturers: Abbott, Roche, & Siemens

Establishment of preliminary harmonized reference standards <u>based solely</u> on interprovincial outpatient data (n=14M+) and the TML method

III. *Comparison to data from healthy Canadians, other harmonization groups, and manufacturers*

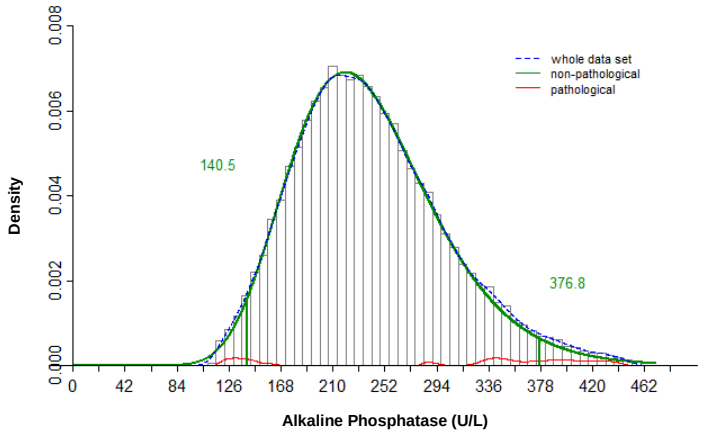


*Based on the comparison of **preliminary harmonized reference standards** established by big data mining to sources listed above, final recommendations were decided on by CSCC hRI WG members at a workshop in January 2020*

CSCC hRI WG: Selected Statistical Method

Truncated Maximum Likelihood Method:

- Described in 2007 by Arzideh and colleagues (CCLM, 2007;45(8))
- **Overall methodology:** Use maximum likelihood estimation techniques to determine the central component of a mixed population dataset
- **Main Assumptions:**
    1. The central part of the distribution curve contains the great majority of results for no-diseased subjects and contamination with data from disease subjects can be neglected
    2. The isolated results of the non-diseased subgroup are approximately normally distribution after or before Box-Cox transformation
    3. Analytical drift effects do not occur during the data collection period



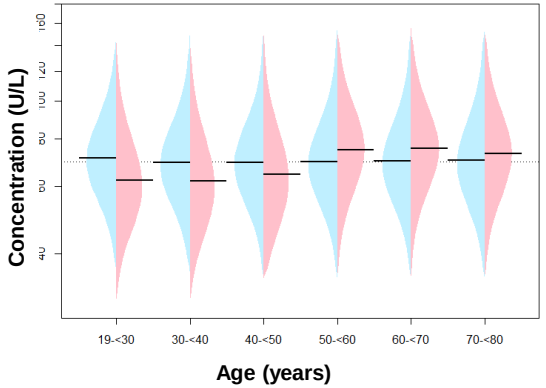
Estimated distributions for non-pathological values (green curve), pathological values (red) and whole data (blue). Green lines (and given numers) indicate 2.5 and 97.5 percentiles of the estimated distribution for non-pathological values (RL).

Clinical Chemical Laboratory Medicine. 2007 Aug 1;45(8):1043-57.

CSCC hRI WG: Statistical Considerations

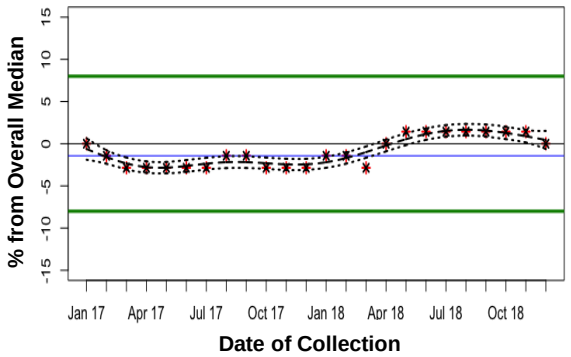
Alkaline Phosphatase – An Example

I. Age & Sex-Specific Differences



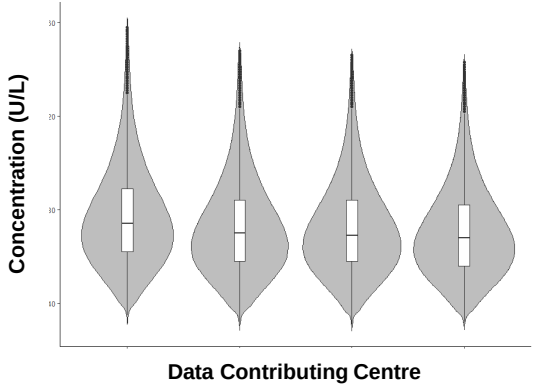
Statistical evaluation: Visual assessment using beanplots and scatterplots, statistical assessment using Harris & Boyd

II. Analytical Stability



Statistical evaluation: Percent deviation of monthly medians from annual medians does not exceed reference change value (RCV)

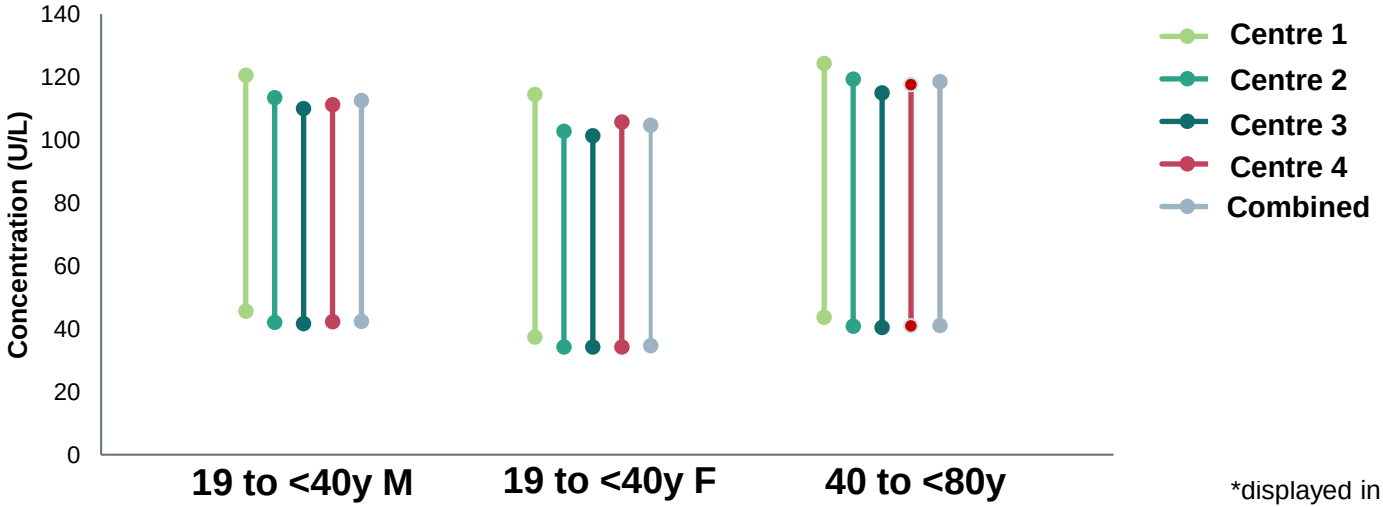
III. Center-Specific Differences



Statistical evaluation: Visual assessment using boxplots and statistical assessment using Harris & Boyd

CSCC hRI WG: Reference Interval Establishment

Alkaline Phosphatase – An Example



*displayed in U/L

Partition	n	Centre 1 *Siemens*	n	Centre 2 *Roche*	n	Centre 3 *Roche*	n	Centre 4 *Roche*	n	Canada-Wide
19 to <40y M	59449	**46-121**	70533	**42-114**	104587	**42-110**	226041	**42-111**	460610	**42-113**
19 to <40y F	80633	**37-115**	89813	**34-103**	141920	**34-101**	309045	**34-106**	621411	**35-105**
40 to <80y	348444	**44-124**	594315	**41-119**	787251	**41-115**	2046357	**41-118**	3776367	**41-119**

CSCC hRI WG: Progress to Date

Electrolytes

- ✓ Sodium
- ✓ Potassium
- ✓ Magnesium
- ✓ Chloride
- ✓ CO2

Hepatic

- ✓ ALT
- ✓ ALP
- ✓ Total Protein
- ✓ Total Bilirubin
- ✓ Albumin
- ✓ LDH

Renal

- ✓ Creatinine
- ✓ Calcium
- ✓ Phosphate

Endocrine

- ✓ FT3
- ✓ FT4
- ✓ TSH

Development of preliminary harmonized reference intervals

Where do we go from here?

Pediatrics
(birth to <19 years)

- **Keeping up to date**: Continue to update CALIPER database as new assays and analytical platforms become available
- Consider new studies to assess which analytes may be amenable to RI harmonization in paediatrics

Adults
(19 to <80 years)

- **RI Verification Program:** To verify proposed harmonized RIs in Canadian laboratories across difference analytical platform
- Circulation of **proposed harmonized practice guidelines** to target groups for input:

Clinical Leaders | **Industry Representatives** | **Laboratory Professionals**

- ✓ *Discuss proposed harmonized practice guidelines*
- ✓ *Suggest potential items for improvement and/or modification*
- ✓ *Discuss expected challenges and concerns associated with recruitment*
- ✓ *Address any questions or concern regarding proposed guidelines*

Questions?

Interested in participating in CSCC hRI verification program?

Please contact us!
Khosrow Adeli, Khosrow.adeli@sickkids.ca
Christine Collier, christine.collier@fraserhealth.ca

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