Reference Interval Harmonization in Clinical Laboratories Across Ontario & Canada

CSCC Working Group on Reference Interval Harmonization (hRI)

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Dana Bailey, MSc, PhD, FCACB, DABCC
Mary Kathryn Bohn, PhD Candidate

(on behalf of the CSCC hRI)

October 26th 2020

Presentation Outline

Path to Harmonization

Speaker: Dr. Khosrow Adeli

- Outline the overall concept and approach of the CSCC hRI WG in the development of evidence-based harmonized reference intervals in the adult population
- Discuss key considerations in method development

Analyzing the Data

Speaker: Mary Kathryn Bohn

- Outline the statistical approach used to calculate harmonized reference intervals, providing a background and worked example
- Discuss rationale in data analysis measures

Path to Implementation

Speaker: Dr. Dana Bailey

- Discuss the next steps to implementing harmonized reference intervals across Ontario and Canada
- Engage with colleagues through polling questions to provide input

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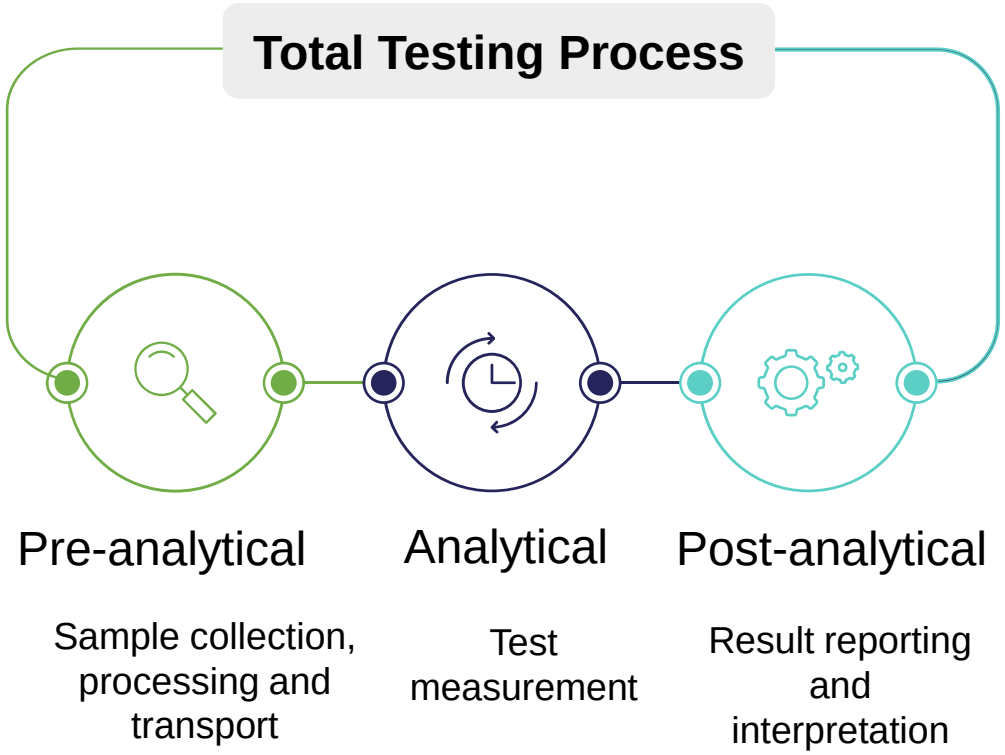
Harmonization in Laboratory Medicine

- 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*

Have similar gains been made in reference interval reporting?



Reference Interval Harmonization in Canada: *Current Gaps*

- Reference interval harmonization supports consistent and standardized test result interpretation***, when appropriate***

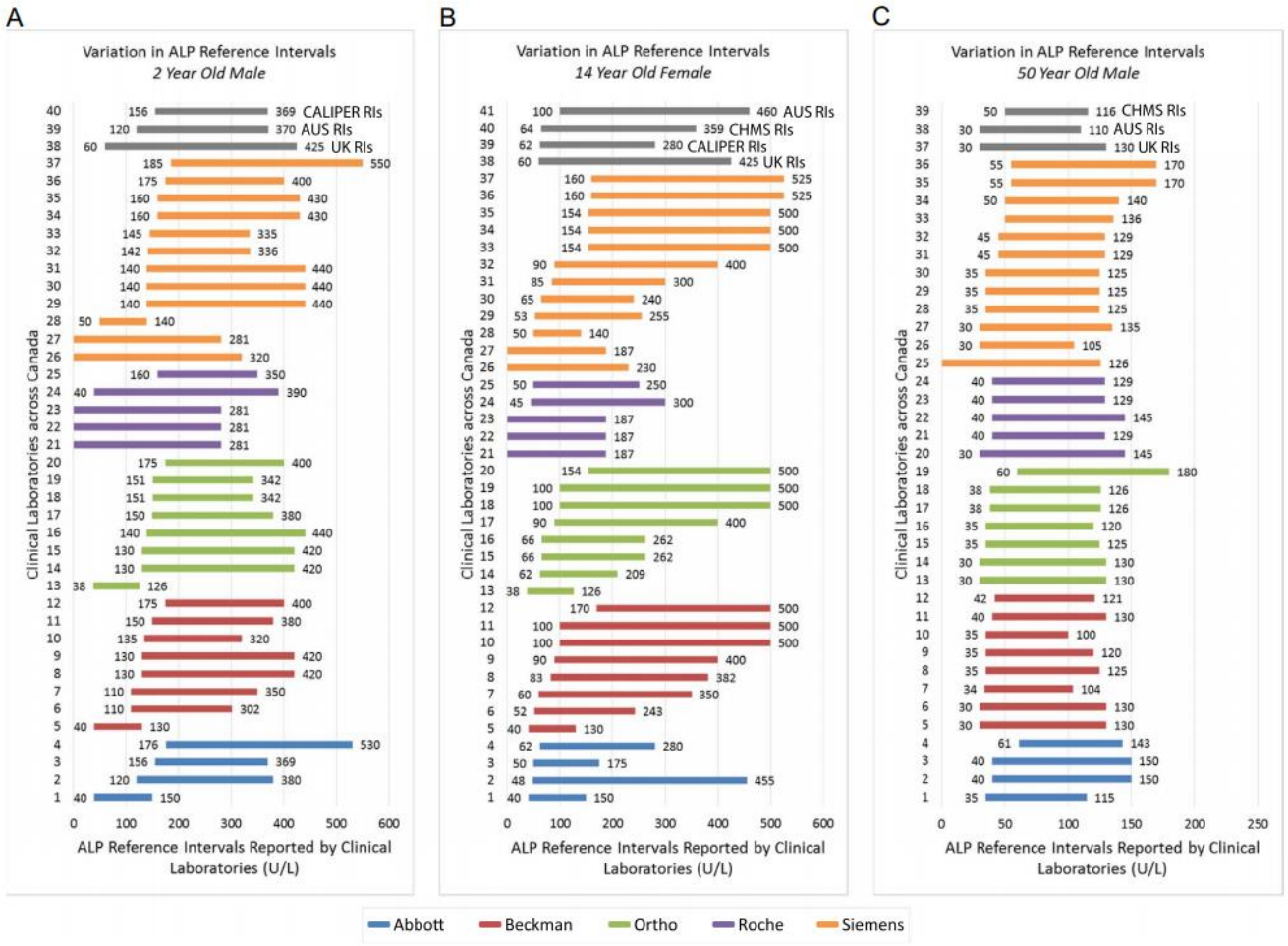
CSCC 2017 National Survey on Reference Intervals:

Design:

- 37 laboratories, 7 analytes: RIs for ALT, ALP, calcium, creatinine, fT4, hemoglobin, sodium
- 40 laboratories measured 6 analytes in reference samples (hemoglobin excluded)

Key Findings:

- Variability in RIs even between laboratories using the same instrumentation
- RI variability exceed test result variability



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

Reference Interval Harmonization in Canada: *CSCC hRI WG*

CSCC Working Group on Reference Interval Harmonization

Main Objective: Establish evidence-based harmonized and/or common reference intervals (where possible) and support their implementation in clinical laboratories across Canada

Co-Chairs
Khosrow Adeli
Christine Collier

Data Analysis Team
Shervin Asgari
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Angela Fung
Josko Ivika
Felix Leung
Michelle Parker
Omair Sarfaraz
Julie Shaw
Janet Simons
Uvaraj Uddayasankar
Dorothy Truong

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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

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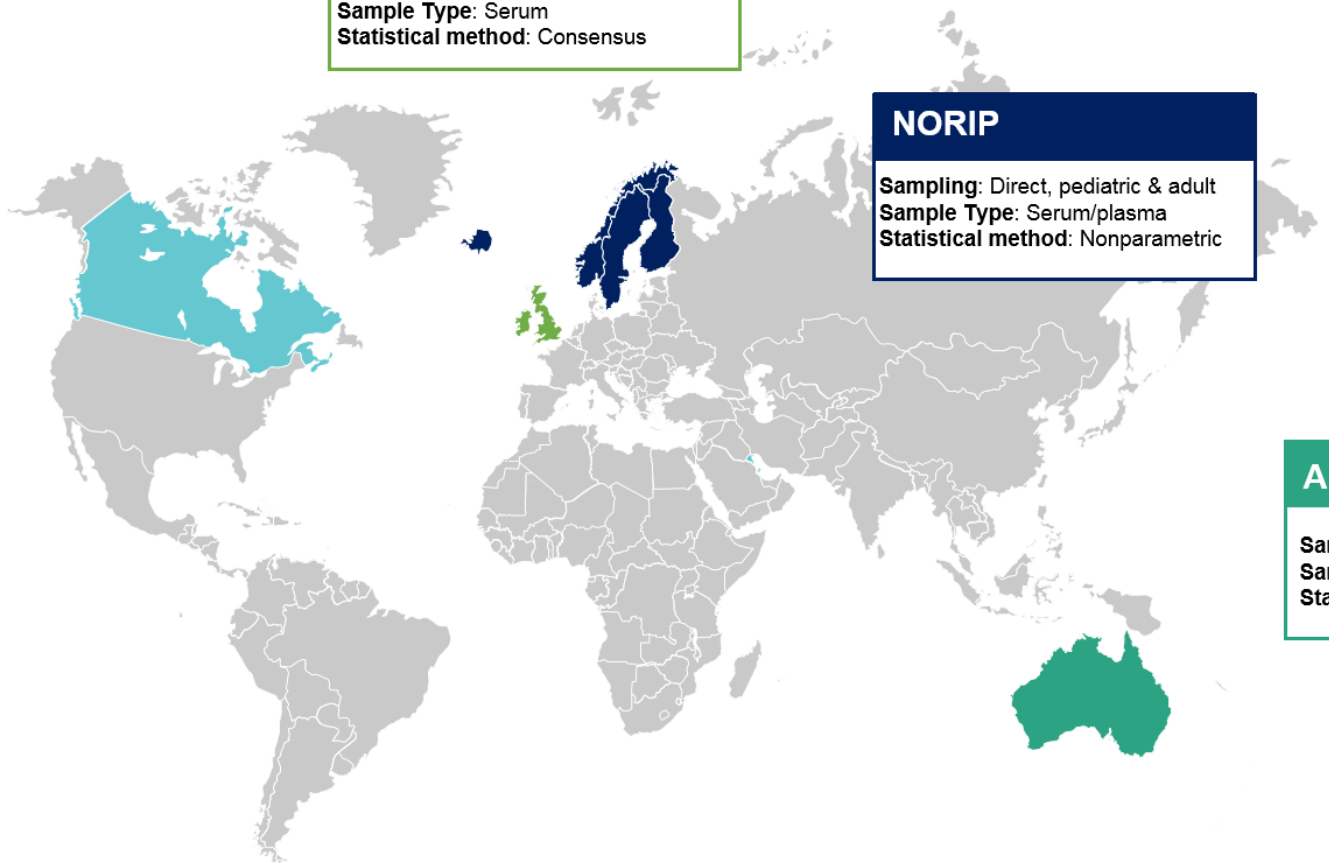
Sampling: Indirect, adult
Sample Type: Serum/plasma
Statistical method: TML method



AHRIA & AHRIP

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

How did we select our approach?

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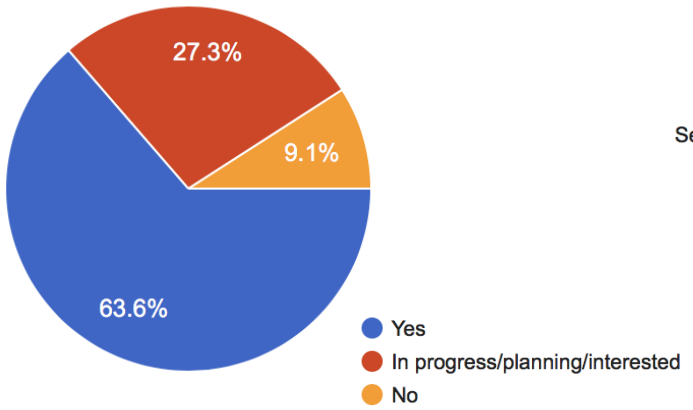
Reference Interval Harmonization: *Adult vs Pediatrics*

- CALIPER reference intervals have been implemented in many laboratories across Canada, USA and worldwide
  - ***Almost all children hospitals across Canada and US have implemented CALIPER Reference Ranges***
  - ***Contributed to RI harmonization in the pediatric population in Canada***

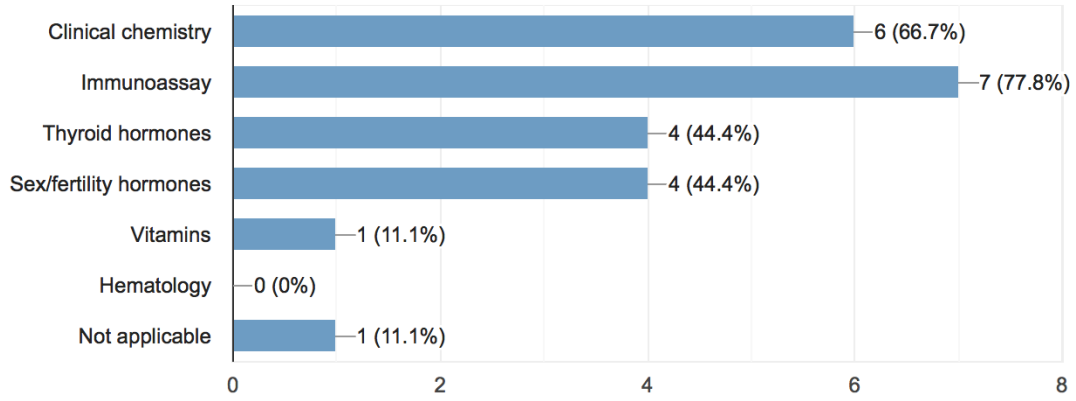
CALIPER
'ARM' us with the knowledge to help others

Preliminary anonymous survey circulated via CSCC listserve

Has your laboratory implemented CALIPER RIs?



For what laboratory tests?



CSCC hRI WG decided to focus on adults

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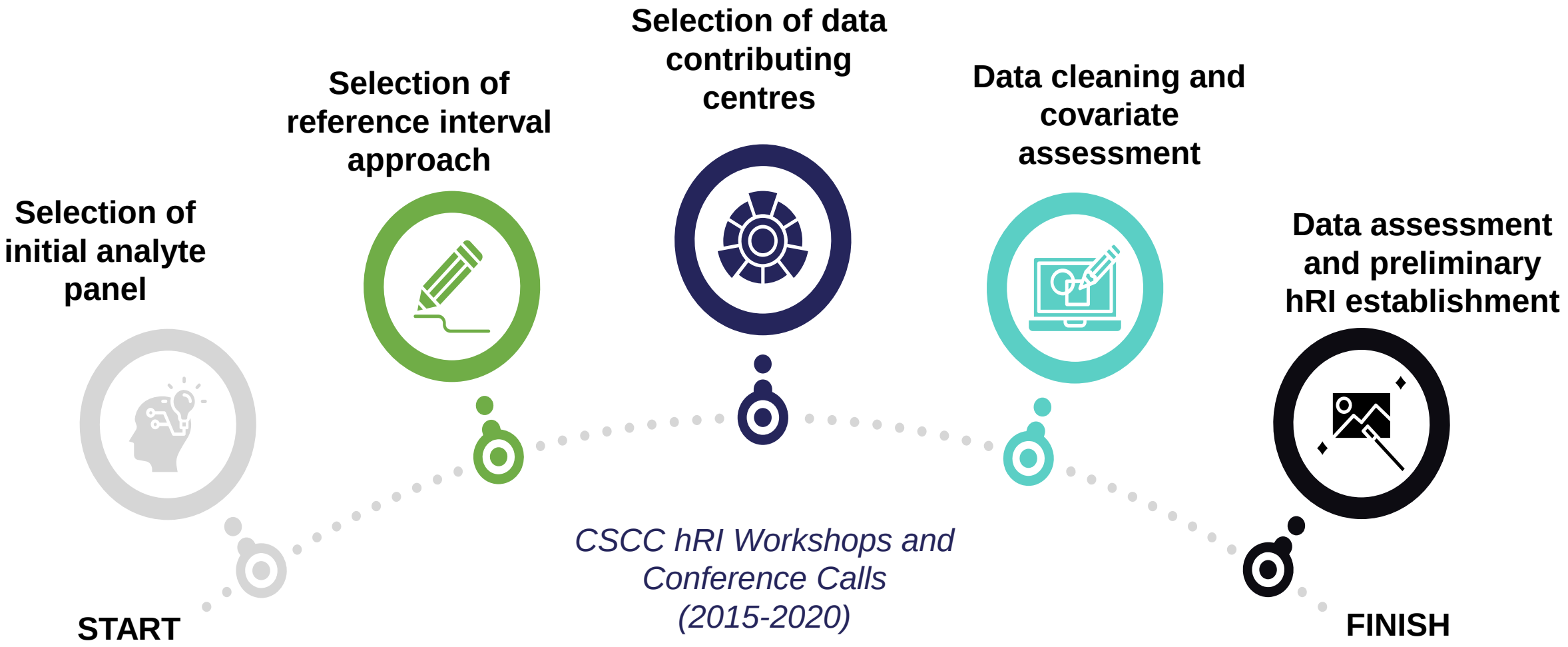
CSCC hRI WG: Path to Reference Interval Harmonization in Adults

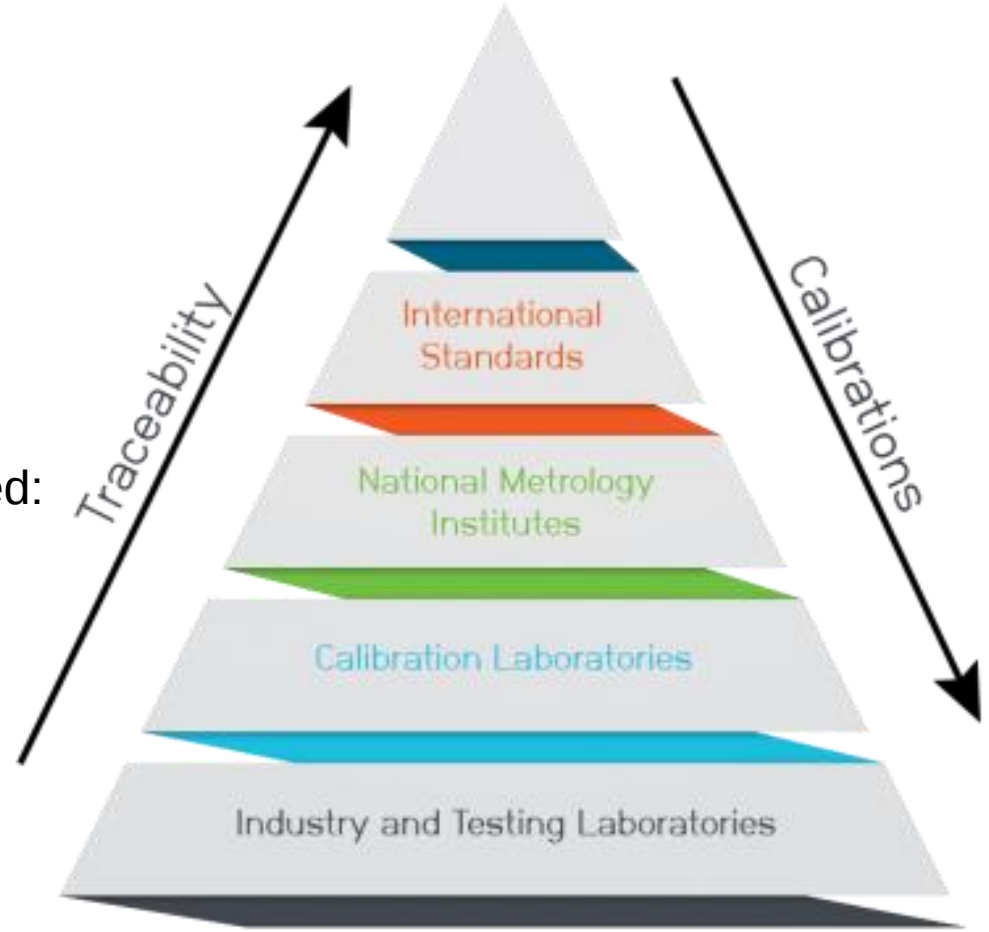


CSCC hRI WG: Path to Reference Interval Harmonization

Selection of Initial Analyte Panel

- Candidate analytes for harmonization must demonstrate minimal analytical bias across the platforms to be harmonized

- For the analytical platforms used in Canada, we evaluated:
  - ***Method***
  - ***Manufacturer***
  - ***Calibration traceability***
  - ***Reference method***



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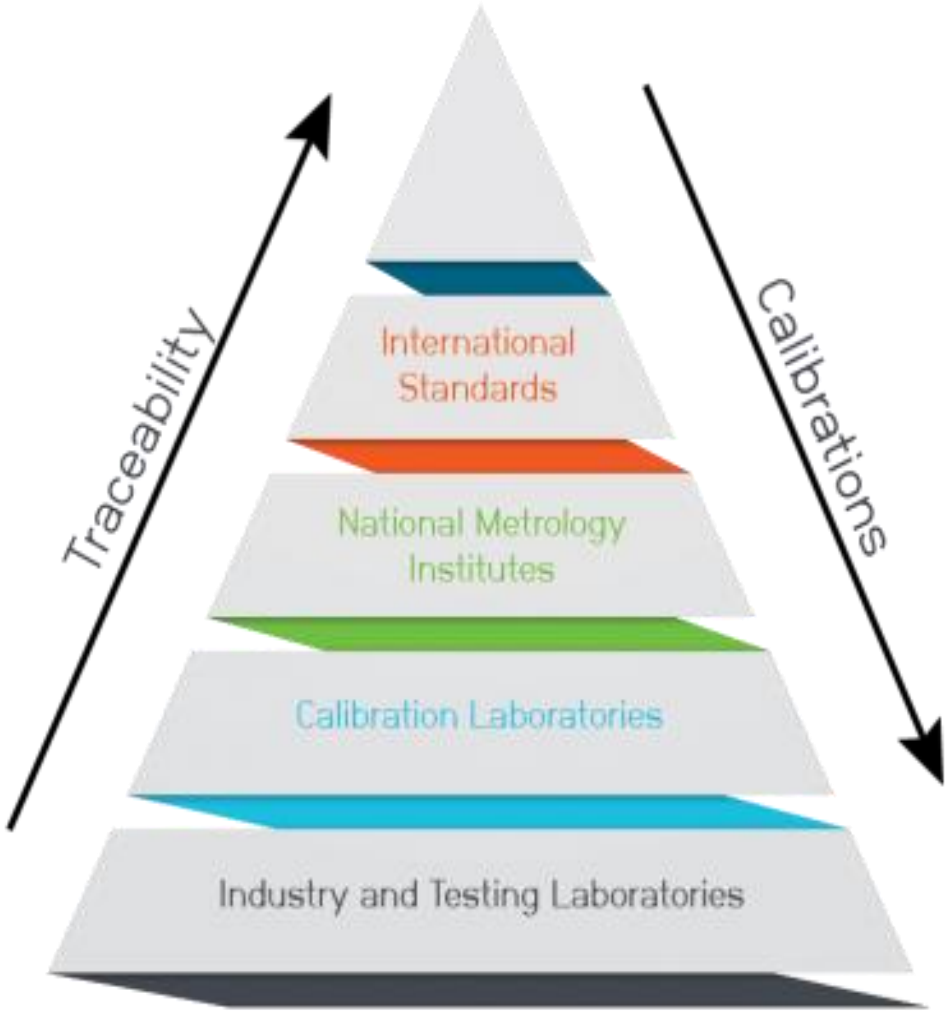
Selection of Initial Analyte Panel

ALP – An Example

Method	Manufacturer	Model	Reference Method
Colorimetric (p-nitrophenyl phosphate)	Roche	cobas	IFCC
	Abbott	Architect	IFCC
	Beckman	Synchron	IFCC
	Siemens	ADVIA	IFCC
	Siemens	Dimension EXL	IFCC
	Siemens	Dimension Vista	IFCC
	Ortho	Vitros	IFCC



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Selection of Initial Analyte Panel

An initial panel of 17 analytes were selected as candidates for harmonization

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

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

Renal
- ✓ Creatinine
- ✓ Calcium
- ✓ Phosphate

Endocrine
- ✓Free T3
- ✓Free T4
- ✓TSH

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Selection of reference interval approach

Direct Approach

Involves recruiting healthy subjects into a study in which samples are collected for the sole purpose of determining a reference interval

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

-

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

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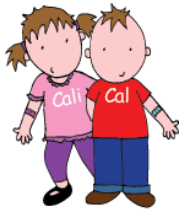
CSCC hRI WG: Path to Reference Interval Harmonization

A Unique Canadian Advantage (Direct Data in Canadian Children & Adults)

- Direct Canadian studies using CLSI-based techniques to derive reference intervals
- **CALIPER**: Pediatric reference intervals for over 185 biomarkers on several analytical platforms
- **CHMS**: Adult and pediatric reference intervals primarily based on Ortho VITROS platform

CALIPER

'ARM' us with the knowledge to help others



Statistics Canada Statistique Canada

Canada

Statistics Canada
www.statcan.gc.ca

Canadian Health Measures Survey

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Selection of reference interval approach

Indirect Approach

Involves using results of a database established for another purpose (i.e. laboratory information systems)

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- Less resources required
- Data easily representative
- Pre-analytical processes reflect routine laboratory practice

-

- Requires in-depth statistical analysis and consideration
- Determination of healthy population relies on statistical methods

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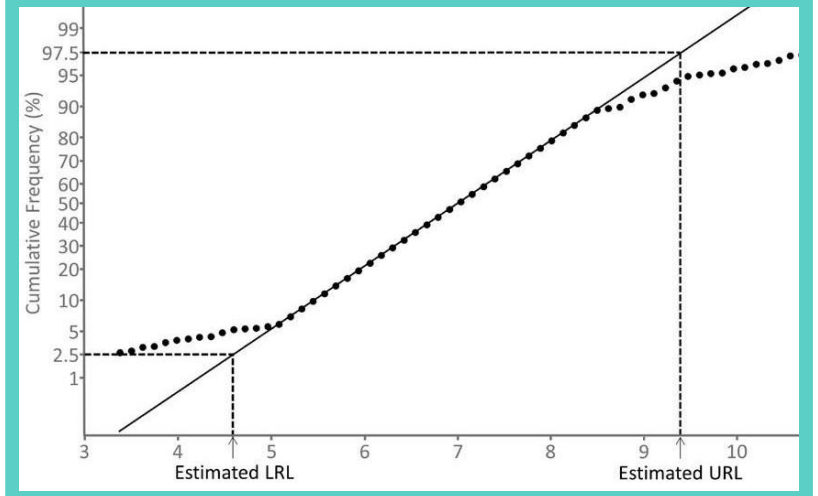
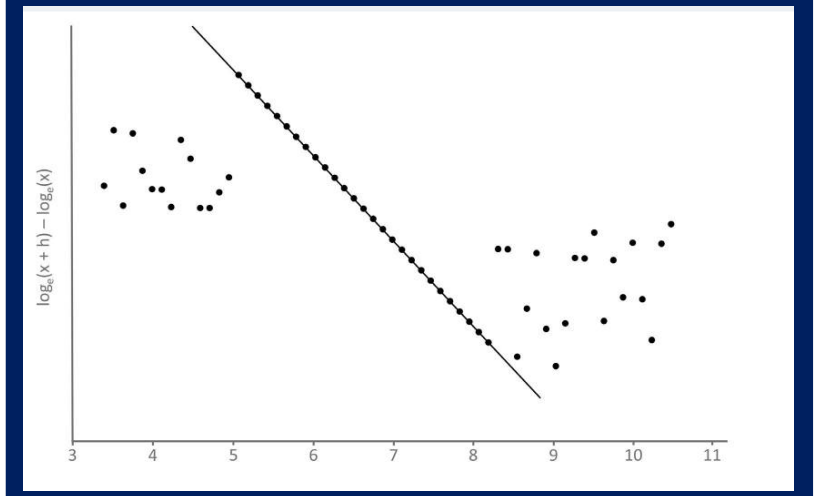
Selection of reference interval approach – available indirect approaches

Hoffman Method (1963)



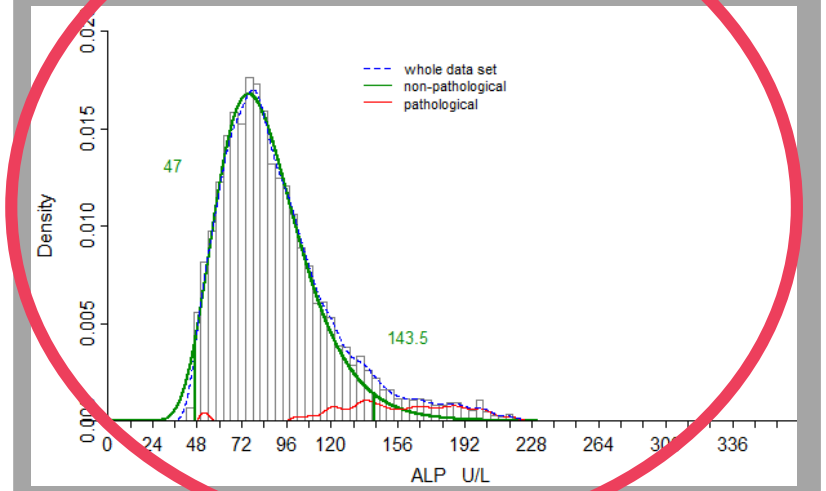
- *Plot the cumulative frequency of the distribution on a normal probability paper*
- *Reference interval extrapolated through linear regression*

Bhattacharya Method (1967)



- *Mathematical straightening of the Gaussian distribution*
- *The slope and intercept are used to determine the mean and SD, and from this, the reference interval*

TML Method (2007)



- *Modern computational power can be leveraged to derive indirect reference intervals using "maximum likelihood estimation"*

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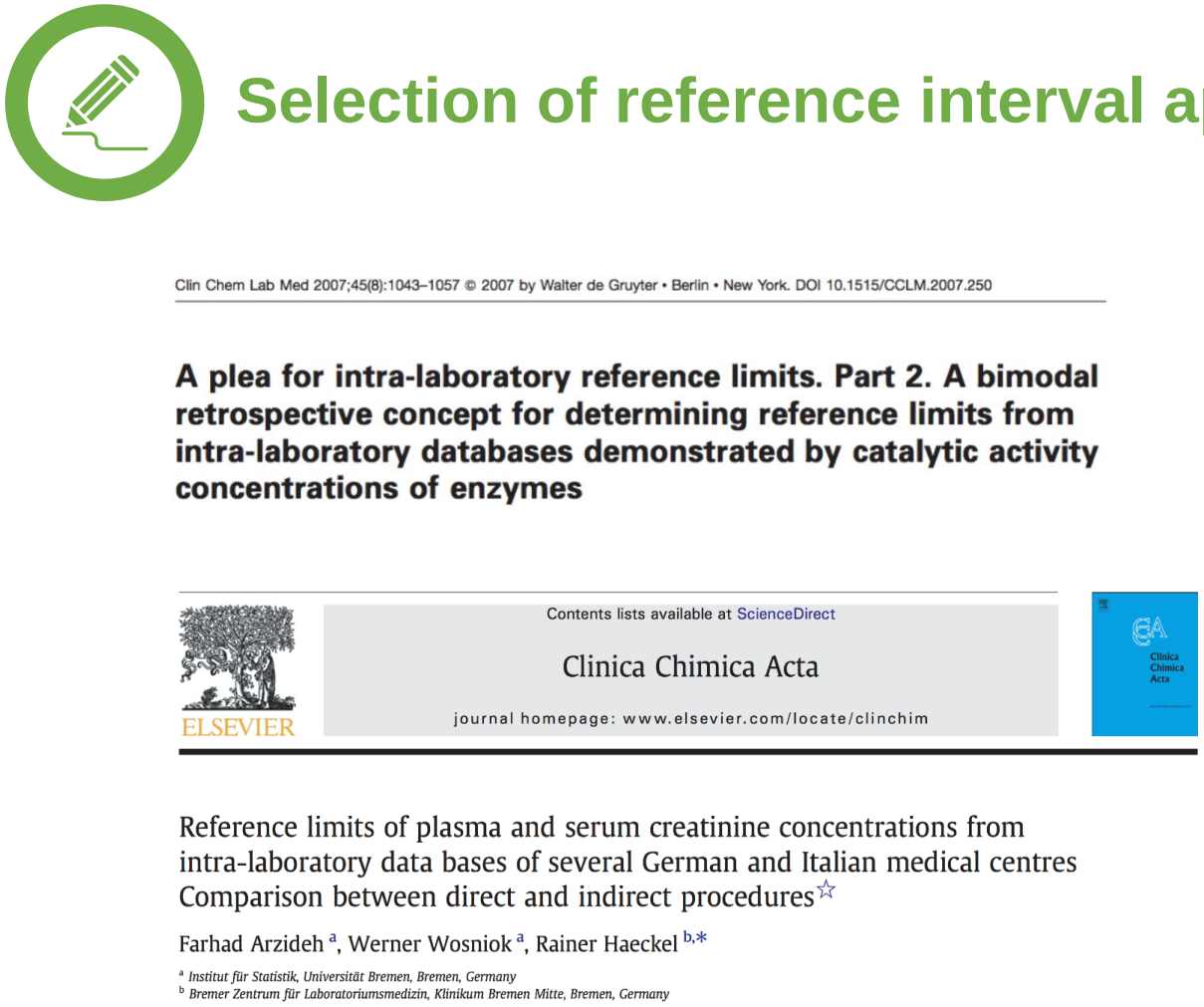
Selection of reference interval approach: TML Approach



Clin Chem Lab Med 2007;45(8):1043–1057 © 2007 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2007.250

A plea for intra-laboratory reference limits. Part 2. A bimodal retrospective concept for determining reference limits from intra-laboratory databases demonstrated by catalytic activity concentrations of enzymes

Contents lists available at ScienceDirect

Clinica Chimica Acta

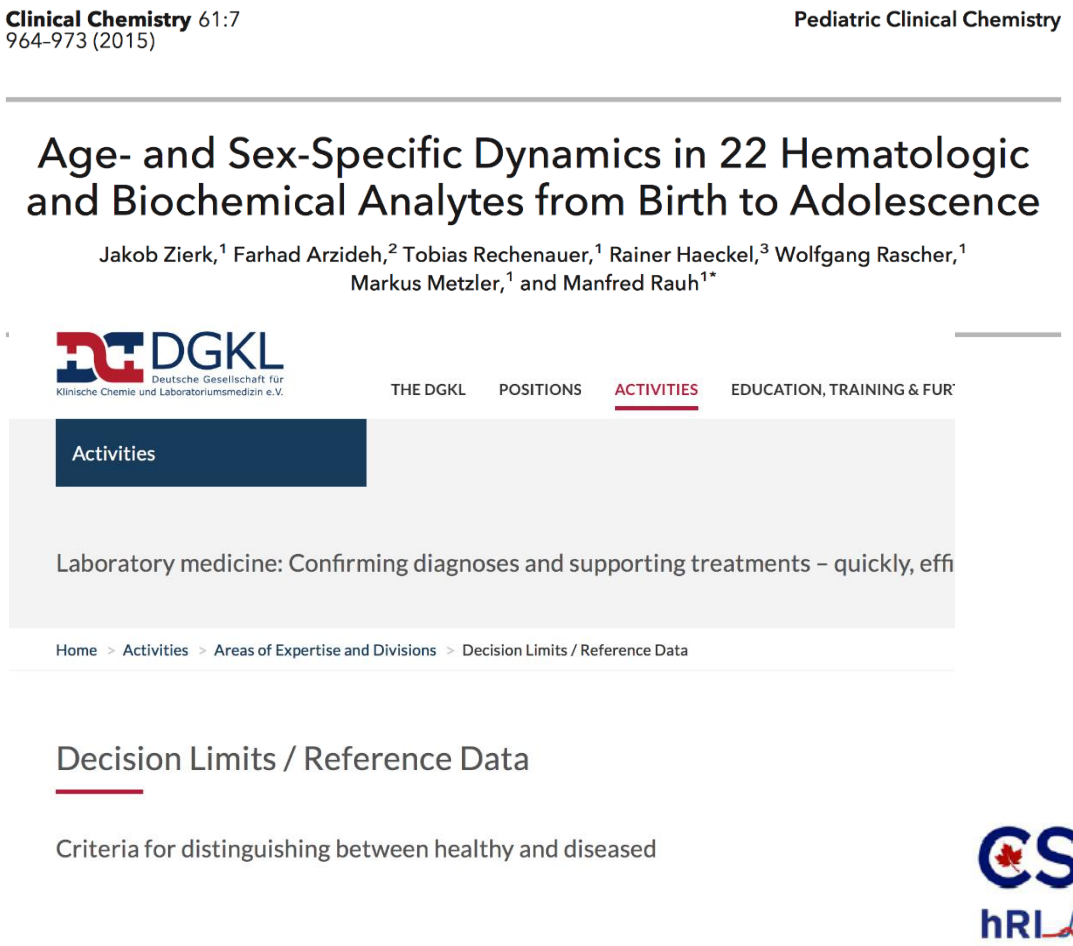
journal homepage: www.elsevier.com/locate/clinchim

ELSEVIER

Reference limits of plasma and serum creatinine concentrations from intra-laboratory data bases of several German and Italian medical centres Comparison between direct and indirect procedures☆

Farhad Arzideh [a], Werner Wosniok [a], Rainer Haeckel [b,*]

[a] Institut für Statistik, Universität Bremen, Bremen, Germany
[b] Bremer Zentrum für Laboratoriumsmedizin, Klinikum Bremen Mitte, Bremen, Germany



Clinical Chemistry 61:7
964–973 (2015)

Pediatric Clinical Chemistry

Age- and Sex-Specific Dynamics in 22 Hematologic and Biochemical Analytes from Birth to Adolescence

Jakob Zierk,[1] Farhad Arzideh,[2] Tobias Rechenauer,[1] Rainer Haeckel,[3] Wolfgang Rascher,[1] Markus Metzler,[1] and Manfred Rauh[1*]

DGKL Deutsche Gesellschaft für Klinische Chemie und Laboratoriumsmedizin e.V.

THE DGKL POSITIONS ACTIVITIES EDUCATION, TRAINING & FUR

Activities

Laboratory medicine: Confirming diagnoses and supporting treatments – quickly, effi

Home > Activities > Areas of Expertise and Divisions > Decision Limits / Reference Data

Decision Limits / Reference Data

Criteria for distinguishing between healthy and diseased

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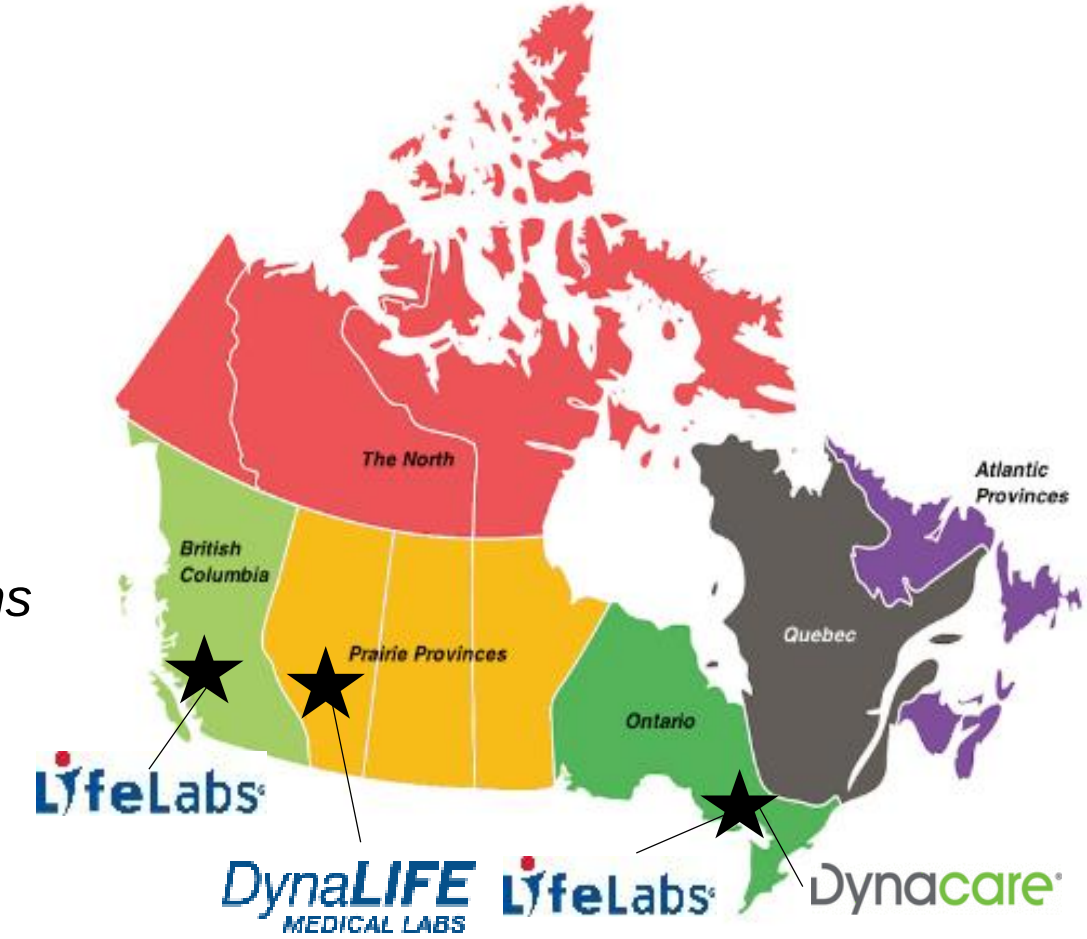
Selection of data contributing centres

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*

Collaboration with community reference laboratories to support this initiative



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Data cleaning and covariate assessment

Prior to executing indirect methodologies, data pre-processing must be discussed:

1. Analytical stability over data extraction period
2. Data exclusion based on clinical criteria:
   - *Should repeat observations be removed?*
   - *Should extreme values be excluded?*

Performance of indirect approaches rely on appropriate data cleaning

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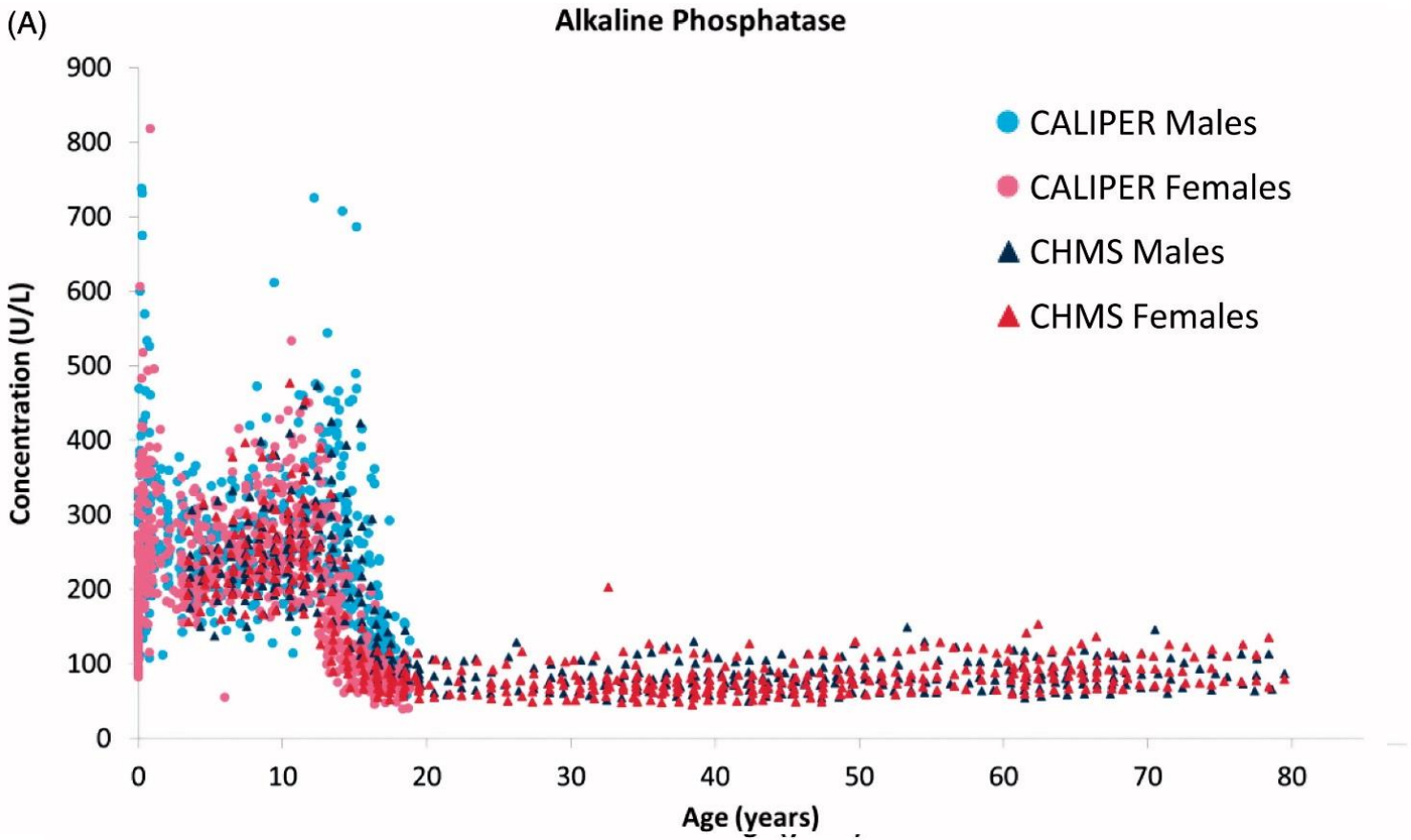
Data cleaning and covariate assessment

Prior to reference interval establishment, key covariates must also be considered:

Age

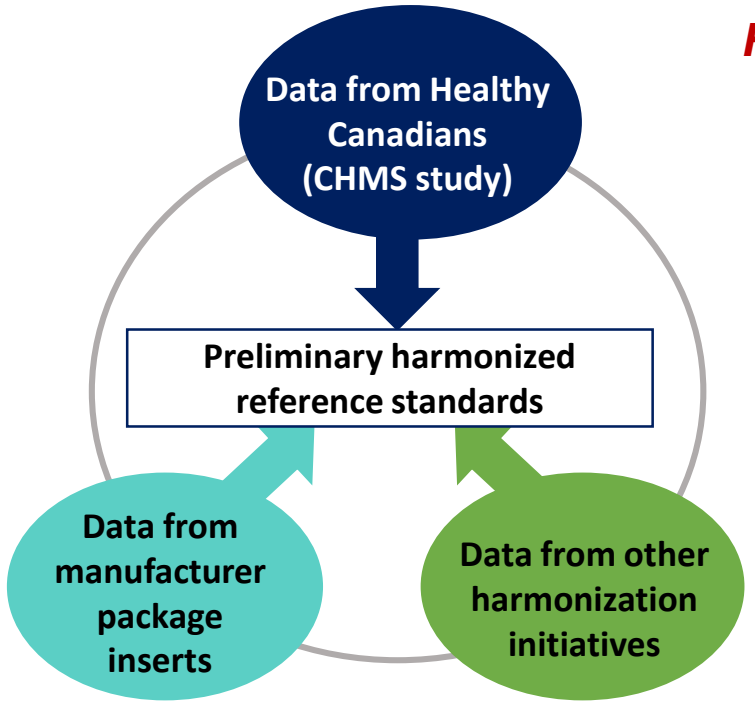
Sex



Bmj. 2018 May 24;361.

CSCC hRI WG: Path to Reference Interval Harmonization

Data assessment and preliminary hRI establishment



Harmonized Reference Intervals Developed for 14 Chemistry and 3 Immunoassays

*Based on the comparison of **preliminary harmonized reference standards**, final recommendations were decided on by CSCC hRI WG members at a workshop in 2020*

CSCC hRI WG: Path to Reference Interval Harmonization

Preliminary Harmonized Reference Intervals derived for 17 Analytes:

Electrolytes

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

Hepatic

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

- ✓ Creatinine
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Endocrine

- ✓Free T3
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Presentation Outline

Path to Harmonization

Speaker: Dr. Khosrow Adeli

- Outline the efforts of CSCC hRI WG in the development of evidence-based harmonized reference intervals in the adult population
- Discuss key considerations in method development

Analyzing the Data

Speaker: Mary Kathryn Bohn

- Outline the statistical approach used to calculate harmonized reference intervals, providing a background and worked example
- Discuss rationale in data analysis measures

Path to Implementation

Speaker: Dr. Dana Bailey

- Discuss the next steps to implementing harmonized reference intervals across Ontario and Canada
- Engage with colleagues through polling questions to provide input

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Analyzing the Data: *Key Steps & Considerations*

- Our team has developed novel R codes to complete the discussed analyses in combination with the RLE software released by DGKL group

- Today, we will go through this multi-step approach for an example analyte as well as provide a preview of recommendations

- **Data Presentations:**
  - ALP

Analyzing the Data: *Key Steps & Considerations*

1. ***Retrieve population dataset with low abnormal rate from each province***
2. ***Assess age- and sex-specific statistical differences for each provincial dataset***
3. ***Clean-up each provincial dataset (e.g. monthly instability, outliers)***
4. ***Assess statistical differences between each provincial dataset***
5. ***Combine clean datasets into Canada-wide file, using TML method to derive the 2.5th and 97.5th percentiles***
6. ***Compare preliminary hRIs to published direct and indirect data***

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Analyzing the Data:
ALP an example

1 ***Retrieve population dataset***

- ✓ **Extract data from multiple centres across two year period**
- ✓ **Remove all repeat observations**
- ✓ **Include key covariates:**
  - **Age**
  - **Sex**
  - **Date of Collection**
  - **Result**

Dynacare®

Province: Ontario
Analytical Platform: Roche
Sample Size: 1062848

DynaLIFE MEDICAL LABS

Province: Alberta
Analytical Platform: Siemens
Sample Size: 503169

LifeLabs®

Province: Ontario
Analytical Platform:
Roche (chemistry)
Abbott (immunoassay)
Sample Size: 2655240

LifeLabs®

Province: BC
Analytical Platform:
Roche (chemistry)
Abbott (immunoassay)
Sample Size: 781171

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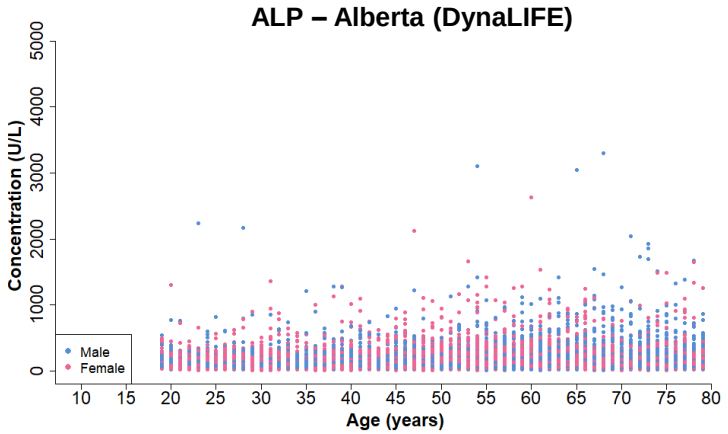
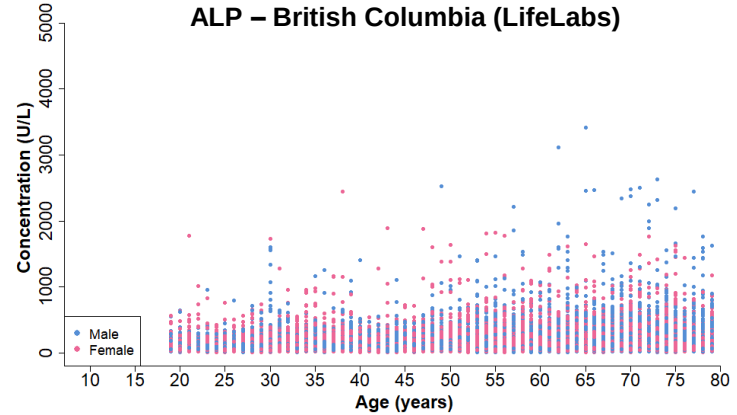
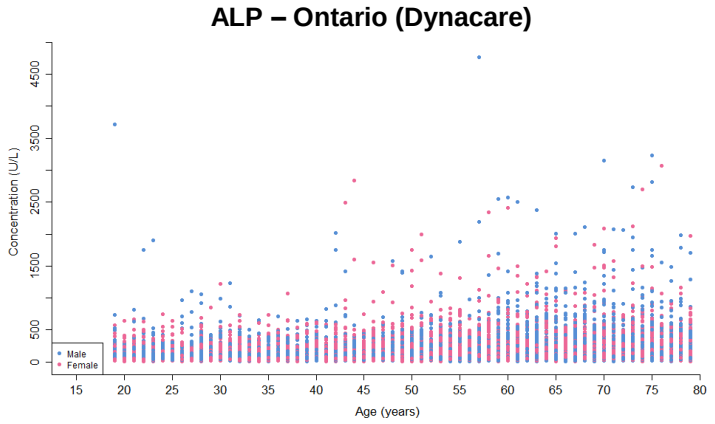
Analyzing the Data:
ALP an example

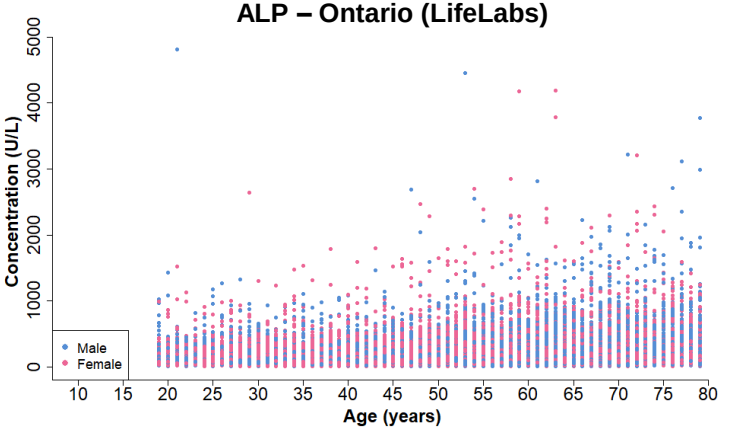
2 ***Assess age/sex differences***

- ✓ **Visually assess raw data across each centre**









Difficult to make conclusions based on simple visualization of raw data

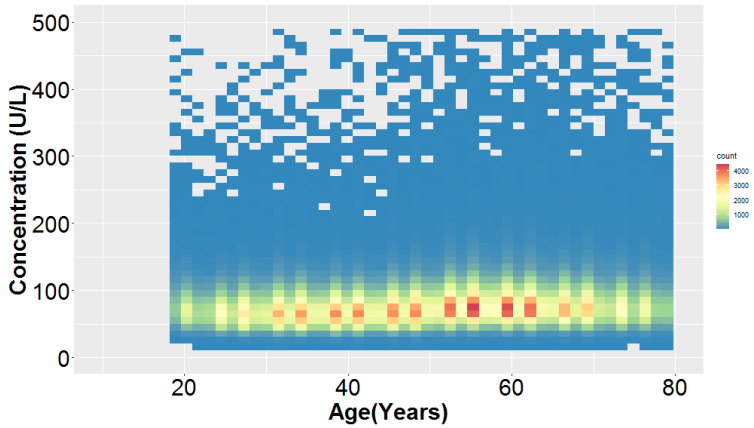
Analyzing the Data:

ALP an example

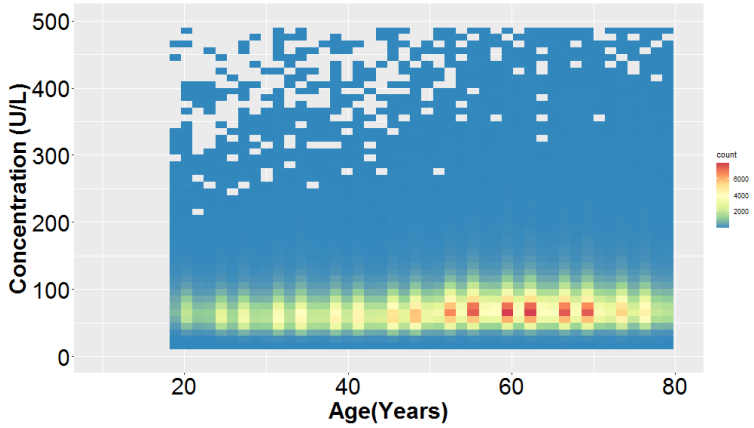
2 ***Assess age/sex differences***

- ✓ **Visually assess raw data across each centre**
- ✓ **Assess data density to evaluate age-specific trends**

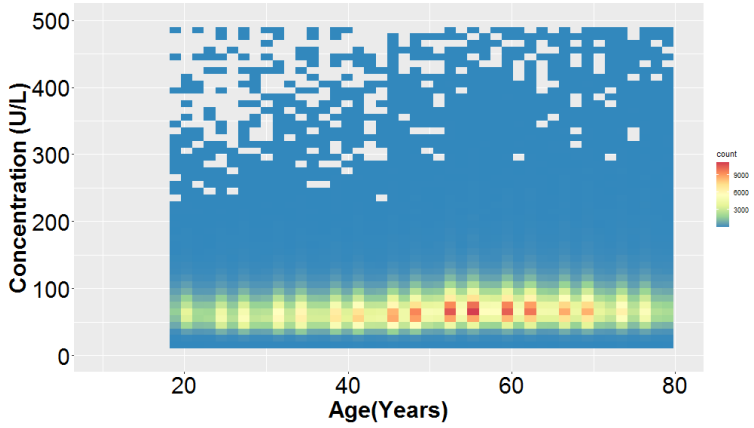
ALP – Alberta (DynaLIFE)



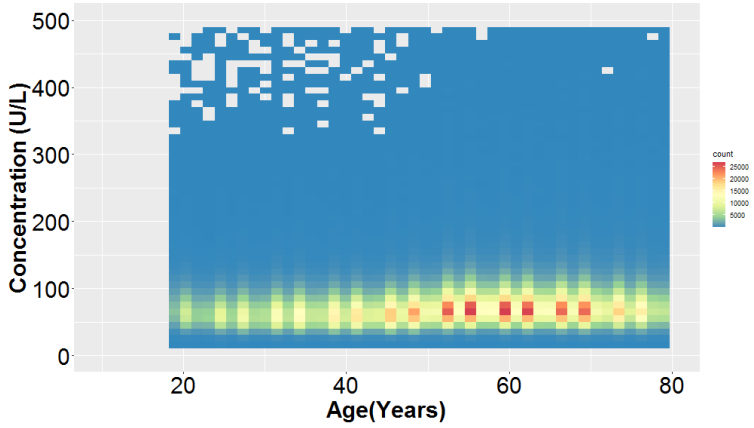
ALP – British Columbia (LifeLabs)



ALP – Ontario (Dynacare)



ALP – Ontario (LifeLabs)



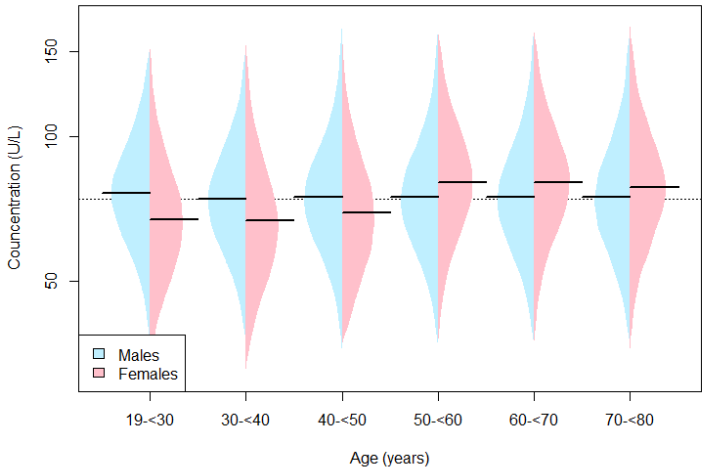
Analyzing the Data:

ALP an example

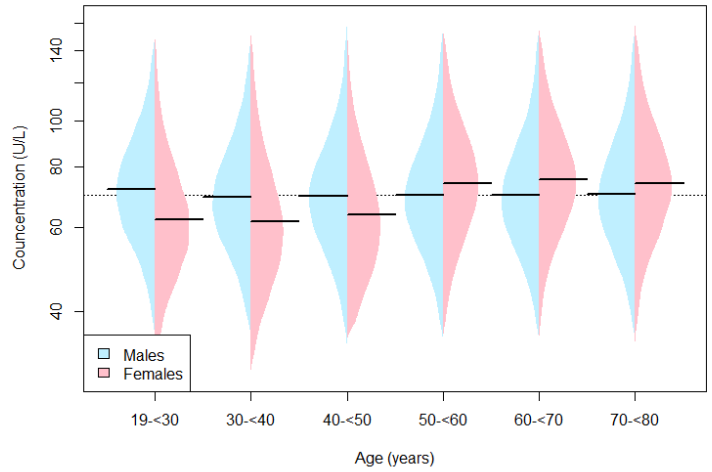
2 *Assess age/sex differences*

- ✓ **Visually assess raw data across each centre**
- ✓ **Assess data density to evaluate age-specific trends**
- ✓ **Use specialized plots to view age- and sex-specific differences**

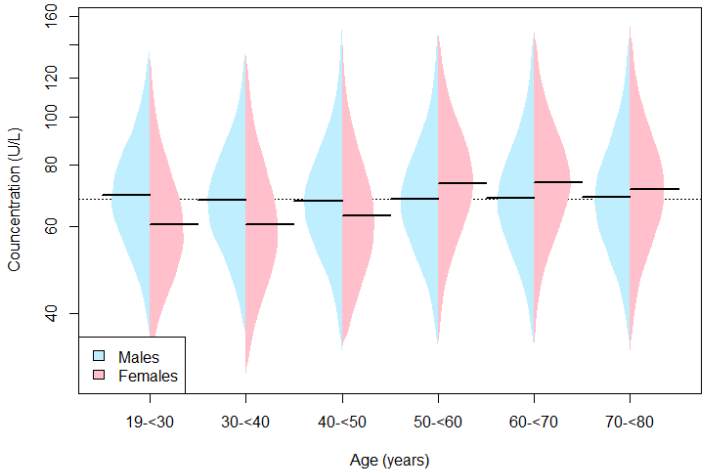
ALP – Alberta (DynaLIFE)



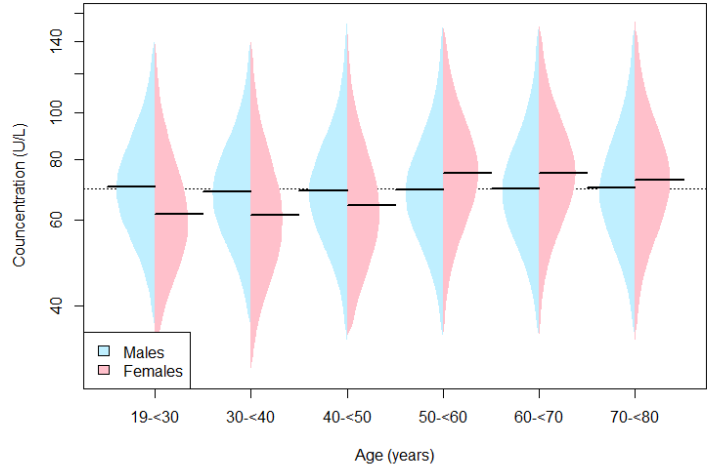
ALP – British Columbia (LifeLabs)



ALP – Ontario (Dynacare)



ALP – Ontario (LifeLabs)



Analyzing the Data:
ALP an example

2 *Assess age/sex differences*

- ✓ **Visually assess raw data across each centre**
- ✓ **Assess data density to evaluate age-specific trends**
- ✓ **Use specialized plots to view age- and sex-specific differences**
- ✓ **Confirm visual assessment statistically using Harris & Boyd Method**

- Determination of statistical significance in the difference of subclass means by the standard normal deviate test

$$z = \frac{\bar{x}_1 - \bar{x}_2}{\left[\left(\frac{s_1^{\,2}}{n_1}\right) + \left(\frac{s_2^{\,2}}{n_2}\right)\right]^{1/2}}$$

$$z^* = 3(n_{average}/120)^{½} = 3[(n_1 + n_2)/240]^{½}.$$

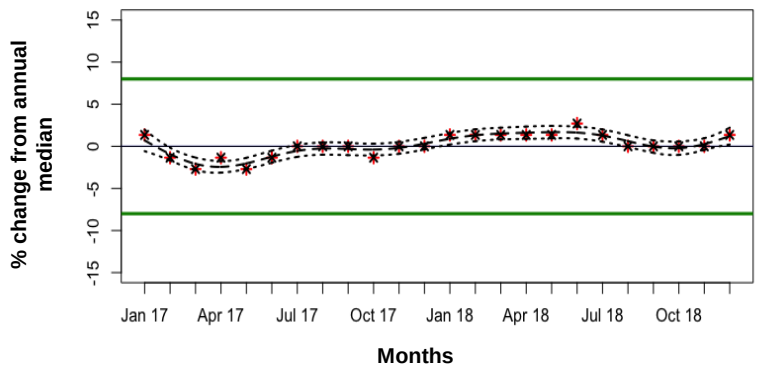
Partitions Identified for ALP:
- **19-<40 years Male**
- **19-<40 years Female**
- **40-<80 years**

Analyzing the Data:
ALP an example

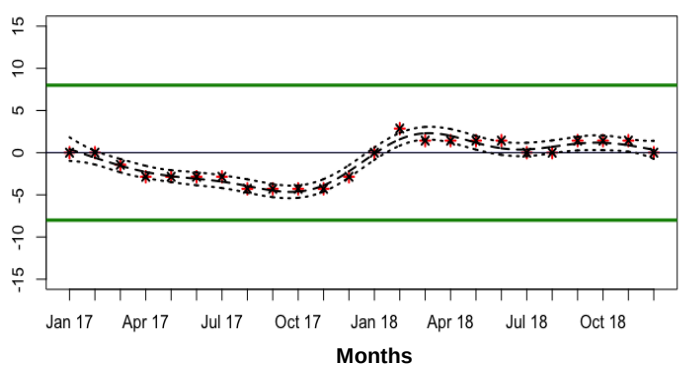
3 ***Data clean up***

- ✓ ***Monthly stability assessed visually***
- ✓ ***Percent deviation from median compared to reference change value (RCV) reported by EFLM.***

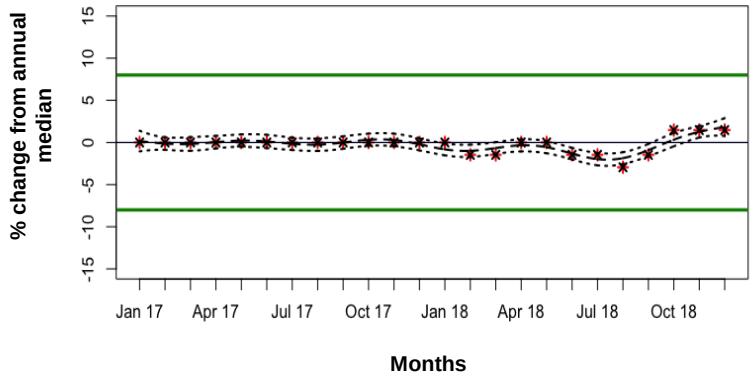
ALP – Alberta (DynaLIFE)



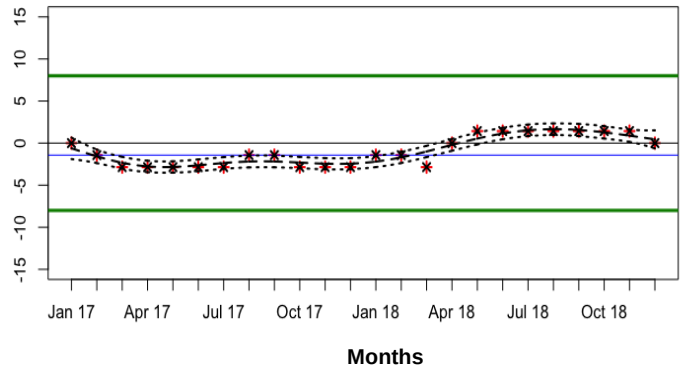
ALP – British Columbia (LifeLabs)



ALP – Ontario (Dynacare)



ALP – Ontario (LifeLabs)

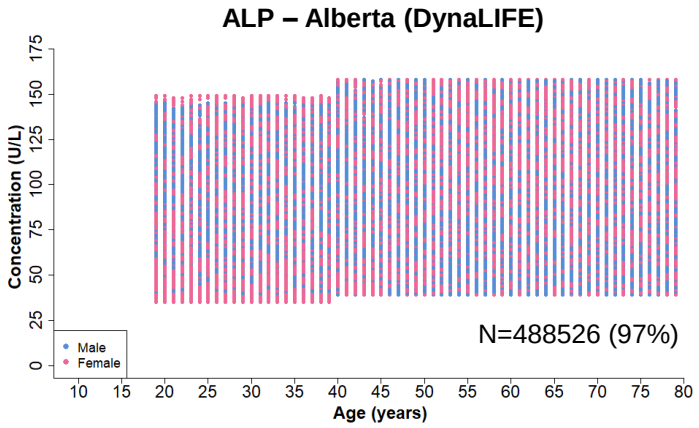


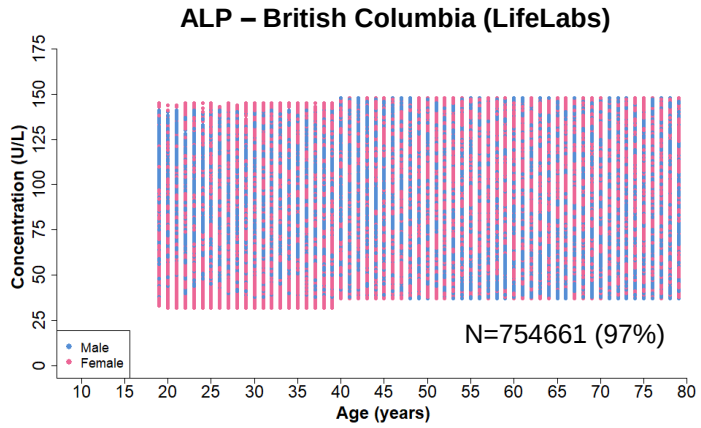
No Instability Observed

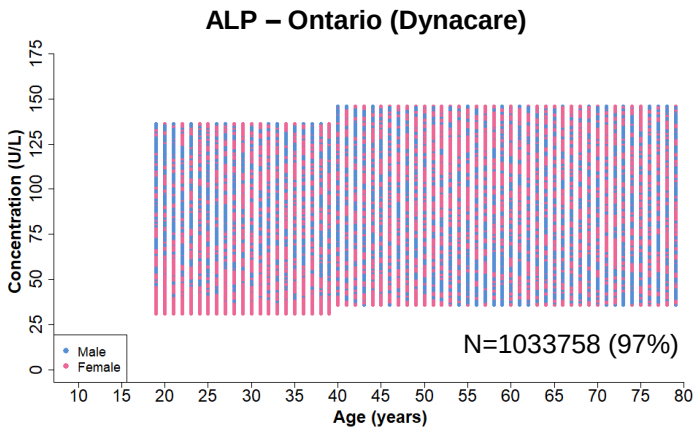
Analyzing the Data:
ALP an example

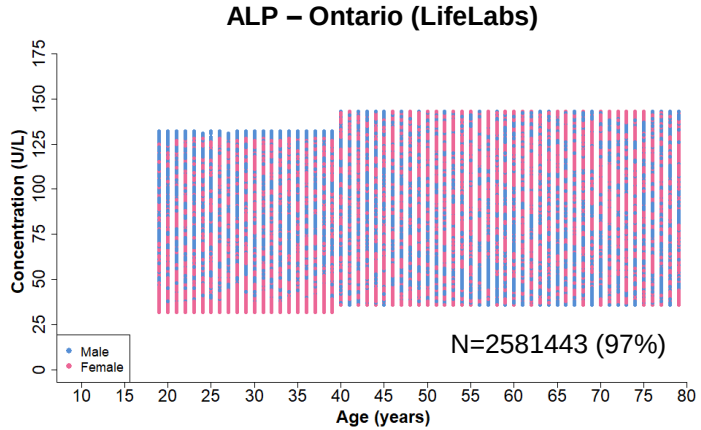
3 ***Data clean up***

- ✓ ***Monthly stability assessed visually***
- ✓ ***Percent deviation from median compared to reference change value (RCV) reported by EFLM.***
- ✓ ***Remove outliers for each centre based on Tukey or Hubert method, depending on data distribution***





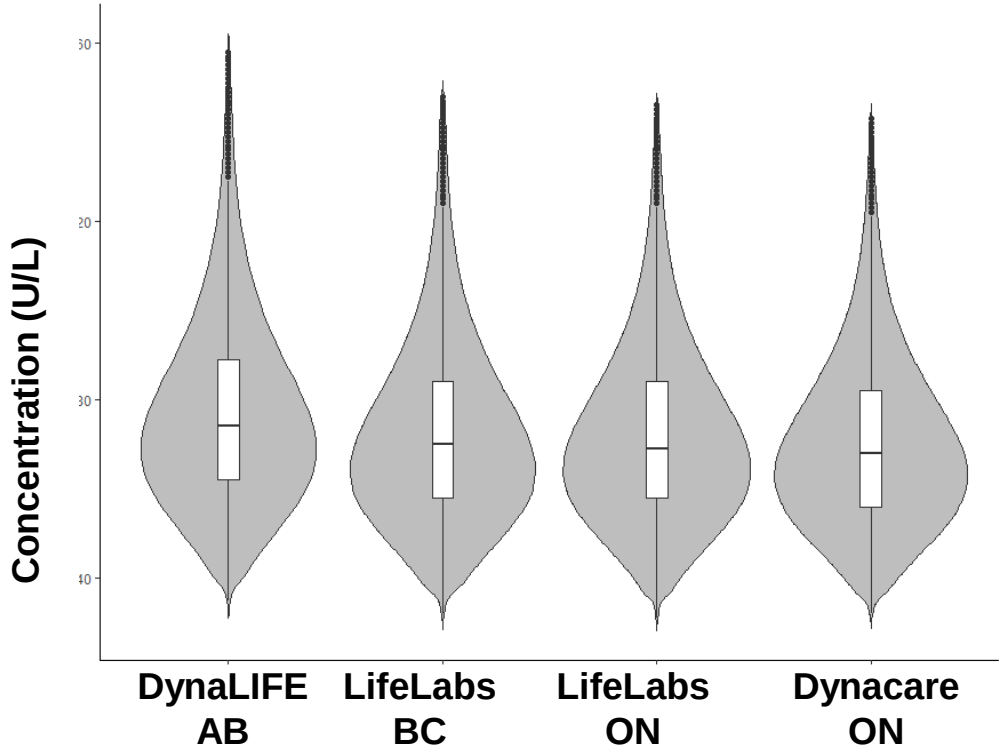




Analyzing the Data:
ALP an example

4 ***Centre-specific differences***

- ✓ ***Assess centre-specific differences using Harris & Boyd method***
- ✓ ***Combine all centres if no significant differences are observed into Canada-Wide file***



Dynacare®
Province: Ontario
Analytical Platform: Roche
Sample Size: 1062848

DynaLIFE MEDICAL LABS
Province: Alberta
Analytical Platform: Siemens
Sample Size: 503169

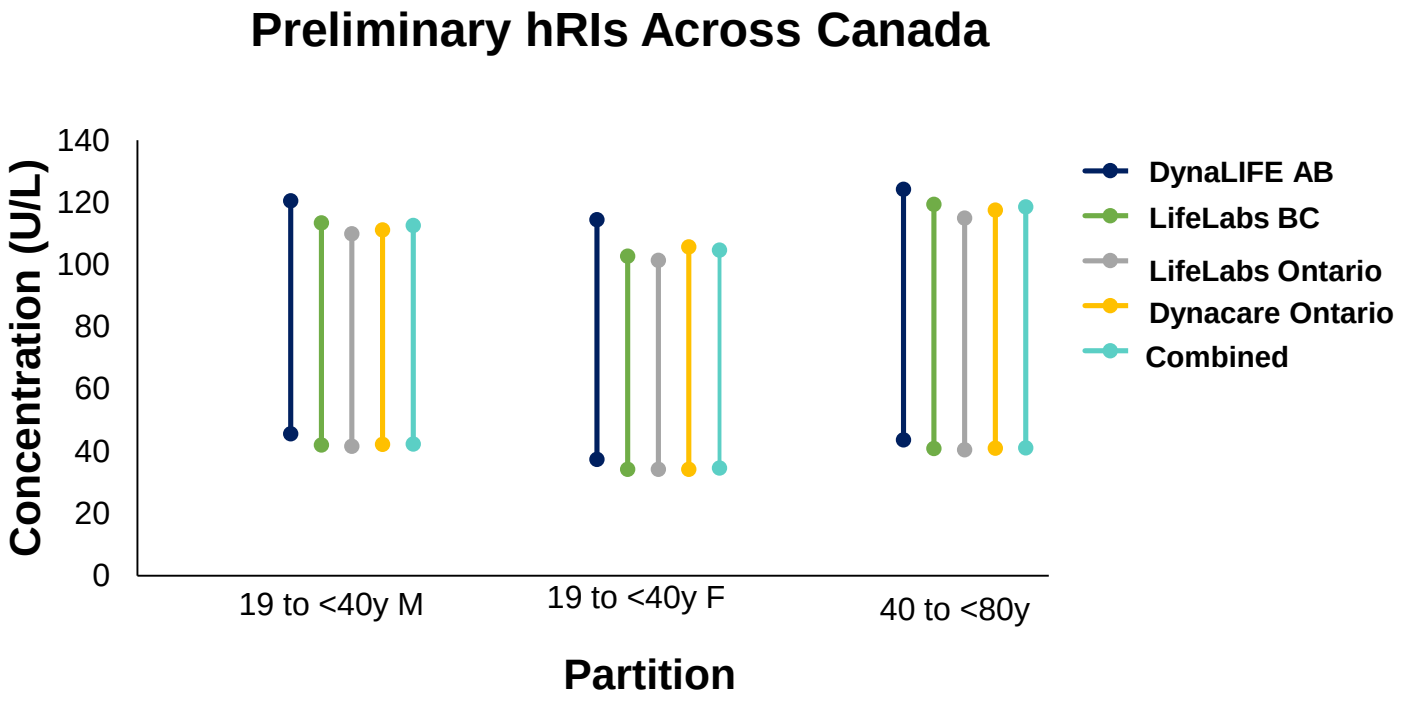
LifeLabs®
Province: Ontario
Analytical Platform: Roche
Sample Size: 2655240

LifeLabs®
Province: BC
Analytical Platform: Roche
Sample Size: 781171

Analyzing the Data:
ALP an example

5 *Establish RI for each partition*

- ✓ *Use TML method to establish reference intervals for each partition*
- ✓ *Compare established reference intervals across provinces and reference intervals*



Partition	Dynacare AB Siemens	LifeLabs BC Roche	LifeLabs ON Roche	Dynacare ON Roche	Canada-Wide
19 to <40y M	46-121	42-114	42-110	42-111	42-113
19 to <40y F	37-115	34-103	34-101	34-106	35-105
40 to <80y	44-124	41-119	41-115	41-118	41-119

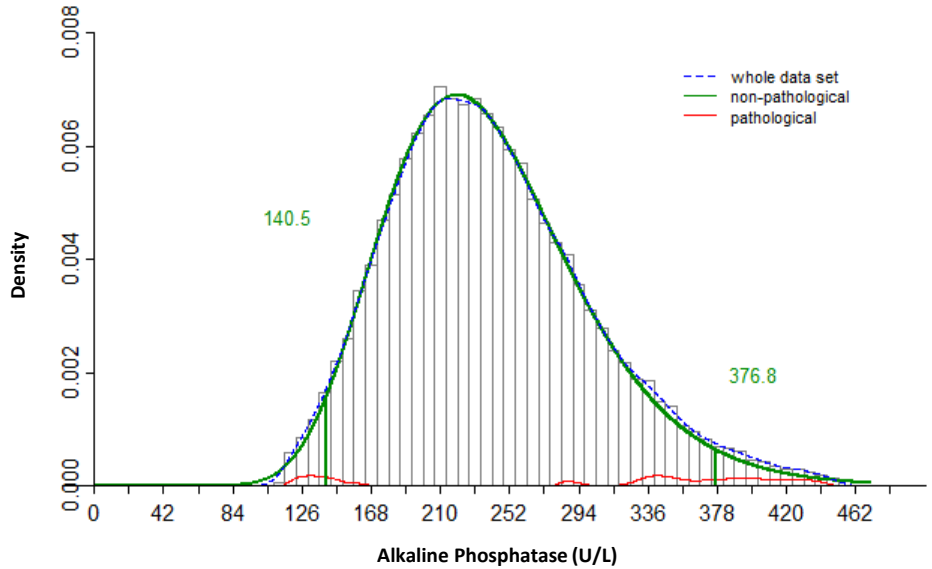
*displayed in U/L

CSCC hRI WG

TML Method: *A Closer Look*

Truncated Maximum Likelihood Method:

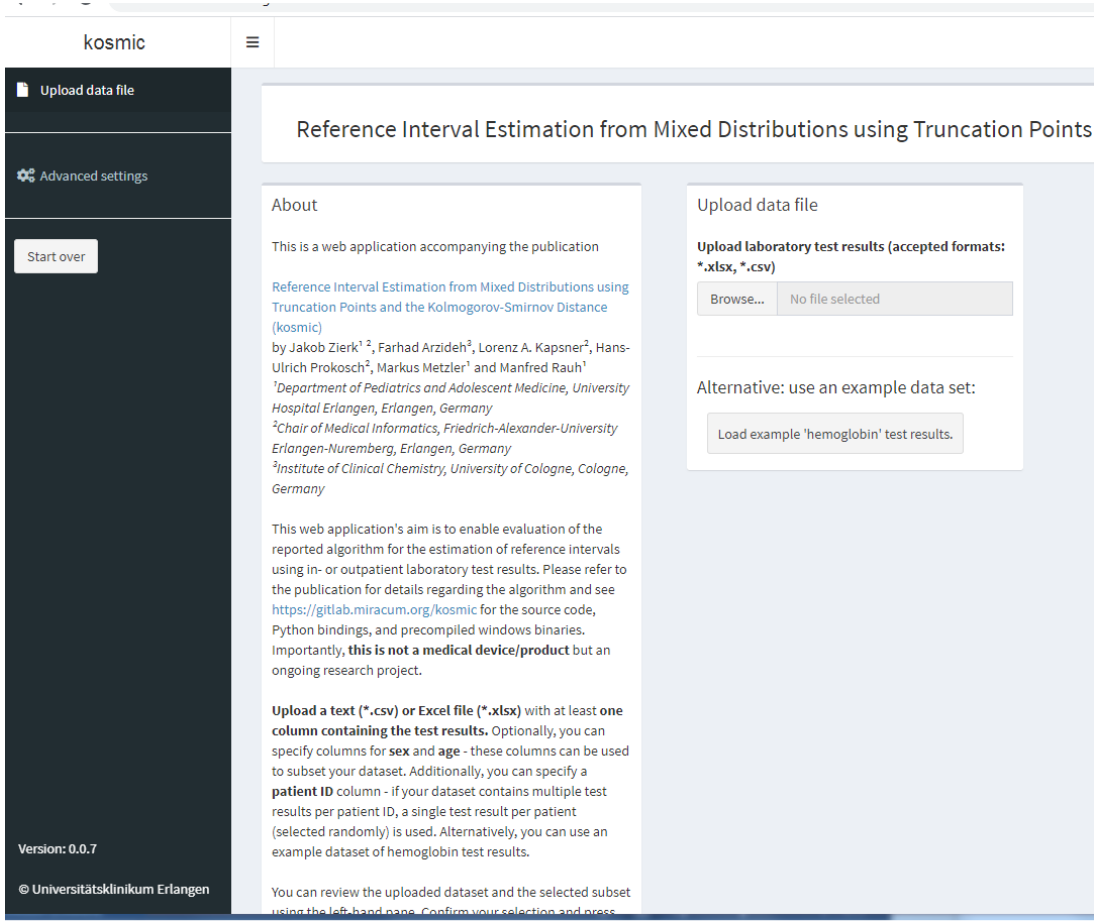
- Described in 2007 by Arzideh and colleagues (CCLM, 2007;45(8))
- **Overall methodology:** Use maximum likelihood estimation techniques to determine the central component of a mixed population dataset
- **Main Assumptions:**
    1. The central part of the distribution curve contains the great majority of results for non-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).

TML Method: *A Closer Look - Advantages*

Truncated Maximum Likelihood Method:



https://kosmic.diz.uk-erlangen.de/
Scientific reports. 2020 Feb 3;10(1):1-8.

- High computational power (millions of data points)
- MLE technique reduces overfitting and enables high distribution resolving power
- No assumptions are made regarding the “diseased” distribution
- Only the “non-diseased” distribution undergoes transformation, if necessary

- Require front-end cleaning and detailed considerations
- No clinical comparator

Beyond Indirect Techniques: *Comparing to Other Approaches*

Comparing preliminary hRIs to various studies and sources can help provide confidence in their recommendation

International Initiatives

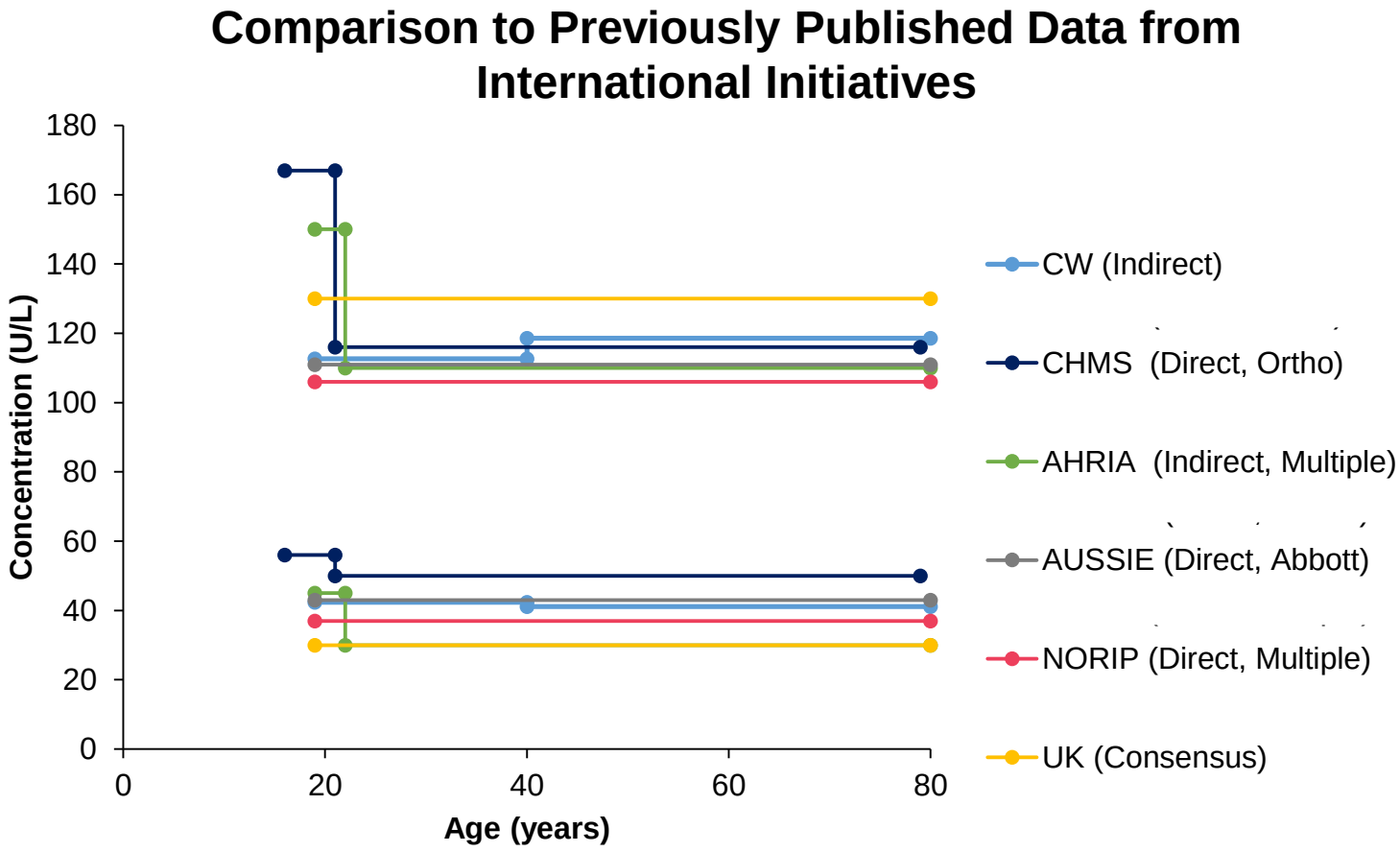
Manufacturer Package Inserts

Current Laboratory Centers

Analyzing the Data:
ALP an example

5 ***Compare and assess***

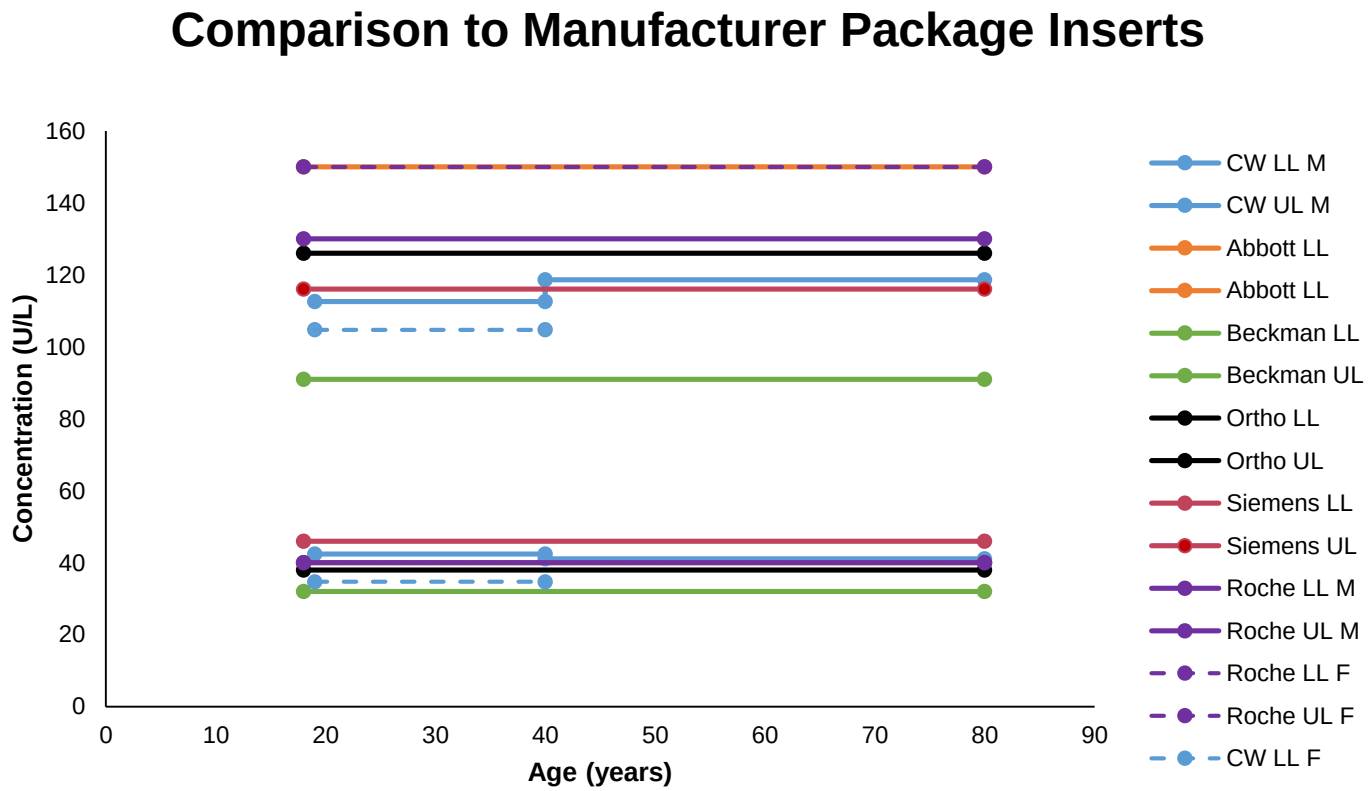
- ✓ ***Compare to indirect and direct data published by international initiatives***



Analyzing the Data:
ALP an example

5 ***Compare and assess***

- ✓ ***Compare to indirect and direct data published by international initiatives***
- ✓ ***Compare to manufacturer package insert data***



Partition	CW		Roche	Abbott	Beckman	Ortho	Siemens
19-<40y M	42-113	**Adult M**	40-130	40-150	32-91	38-126	46-116
19-<40y F	35-105	**Adult F**	35-105				
40-<80y	41-119						

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Analyzing the Data:
ALP an example

5 ***Compare and assess***

- ✓ ***Compare to indirect and direct data published by international initiatives***
- ✓ ***Compare to manufacturer package insert data***
- ✓ ***Compare to what is currently used at each centre***

Comparison to Current Reference Intervals

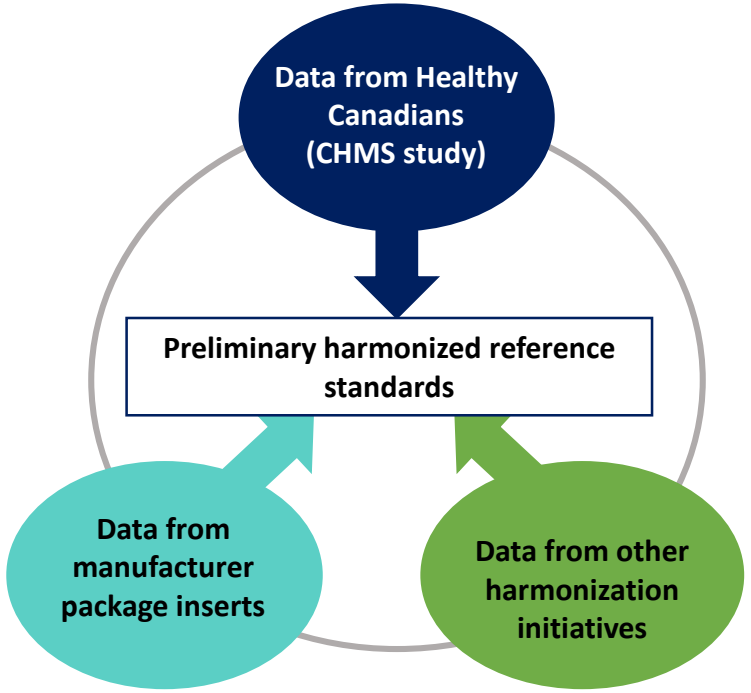
Canada Wide RI (U/L)		DynaLIFE RI (U/L) Siemens		LifeLabs RI (U/L) Roche		Dynacare RI (U/L) Roche	
19 to <40y M	42-114	**Adult**	40-120	**Adult M**	40-145	**Adult M**	40-129
19 to <40y F	34-103			**Adult F**	35-120	**Adult F**	35-122
40 to <80y	41-119						

Analyzing the Data:
ALP an example

5 ***Compare and assess***

- ✓ *Compare to indirect and direct data published by international initiatives*
- ✓ *Compare to manufacturer package insert data*
- ✓ *Compare to what is currently used at each centre*
- ✓ *Internal discussion and finalization*

Preliminary Recommendations



Proposed Harmonized RI	
19 to <40y M	40-115
19 to <40y F	35-105
40 to <80y	40-120

CSCC hRI WG

CSCC hRI WG: Path to Reference Interval Harmonization

Preliminary Harmonized Reference Intervals derived for 17 Analytes:

Electrolytes

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

Hepatic

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

Renal

- ✓ Creatinine
- ✓ Calcium
- ✓ Phosphate

Endocrine

- ✓Free T3
- ✓Free T4
- ✓TSH

Preliminary hRI Recommendations

Electrolytes

Analyte	Calculated Canada-Wide RI		Recommended Harmonized RI	
Sodium (mmol/L)	19 to <80y	138-145	19 to <80y	**137-145**
Potassium (mmol/L)	19 to <80y	3.8-5.1	19 to <80y	**3.8-5.1**
Magnesium (mmol/L)	19 to <80y	0.73-1.00	19 to <80y	**0.73-1.00**
Total CO2 (mmol/L)	19 to <80y	22-32	19 to <80y	**22-30**
Chloride (mmol/L)	19 to <80y	97 – 107	Not finalized	Not finalized

Preliminary hRI Recommendations

Hepatic

Analyte	Calculated Canada-Wide RI		Recommended Harmonized RI	
Alanine aminotransferase (U/L)	19 to <80y M	11-53	19 to <80y M	**RI: 11-53, CDL: <33**
	19 to <80y F	8-35	19 to <80y F	**RI: 8-35, CDL: <25**
Albumin BCG (g/L)	19 to <60y M	40-51	19 to <80 years	**40-50**
	19 to <60y F	39-49		
	60 to <80y	39-49		
Alkaline Phosphatase (U/L)	19 to <40y M	42-114	19 to <40y M	**40-115**
	19 to <40y F	34-103	19 to <40y F	**35-105**
	40 to <80y	41-119	40 to <80y	**40-120**
Lactate Dehydrogenase (U/L)	19 to <80y	122-237	19 to <80 y	**120-240**
Total Bilirubin (umol/L)	19 to <80y M	3.5-20.0	19 to <80 y M	**3-20**
	19 to <80y F	2.8-15.8	19 to <80 y F	**3-16**
Total Protein (g/L)	19 to <80y	61-79	19 to <80y	**60-80**

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Preliminary hRI Recommendations

Renal

Analyte	Calculated Canada-Wide RI		Recommended Harmonized RI	
Phosphate (mmol/L)	19 to <60y	0.79 – 1.45	19 to <80y	**0.80– 1.45**
	60 to <80y M	0.77 – 1.43		
	60 to <80y F	0.86 – 1.47		
Calcium (mmol/L)	19 to <40y M	2.21 - 2.54	19 to <80y	**2.15 – 2.55**
	19 to <40y F	2.16 – 2.50		
	40 to <80y	2.16 – 2.52		
Creatinine (umol/L)	19 to <80y M	63-117	*Not finalized*	*Not finalized*
	19 to <80y F	48-95		

Preliminary hRI Recommendations

Endocrine

Analyte	Calculated Canada-Wide RI		Recommended Harmonized RI	
FT3 (pmol/L)	19 to <80y	3.01 – 5.68	19 to <80y	**3.0 to 5.7**
FT4 (pmol/L)	19 to <80y	9.7 - 15.5	19 to <80y	**9.5 to 15.5**
TSH (mIU/L)	19 to <80y	0.60-4.55	19 to <80y	**RI: 0.60-4.55, CDL: 0.1-4.12**

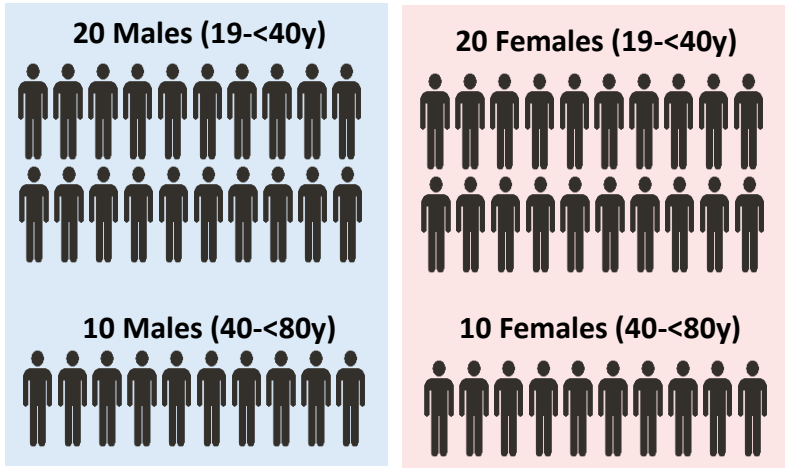
Preliminary hRI Recommendations – Next Steps

- **Limitations to the current data:**
  - *Only three manufacturers represented (Roche, Siemens, Abbott (immunoassays only))*
  - *Only three provinces represented (Ontario, British Columbia, Alberta)*
  - *All data contributing centres use serum as preferred matrices*

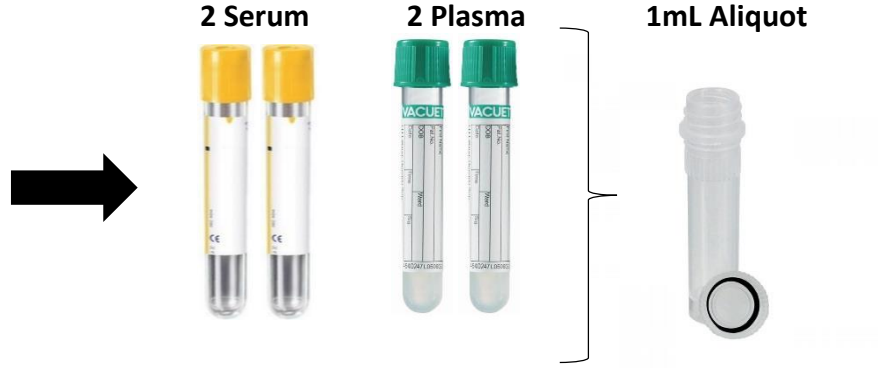
How can these be addressed?

Next Steps: *Cross Canada Verification Study*

Study Design:



60 adult volunteers *will be recruited from the community with the following age/sex distribution. Health will be assessed using a questionnaire.*



2 serum and 2 plasma tubes will be collected from each participant. ***Estimate volume****: ~10mL serum, ~10mL plasma. 1mL aliquots will be stored at -80C*

Distribution to 5-10 laboratories across Canada for analysis of all 17 analytes, ideally on both matrices (two labs per platform ideally).

Roche

Ortho Clinical Diagnostics

SIEMENS

BECKMAN COULTER

Abbott

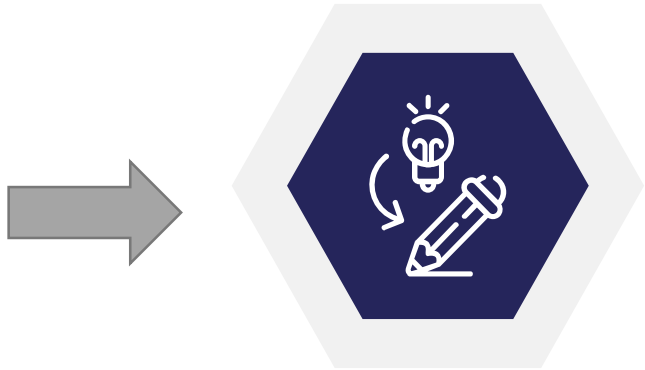
CSCC hRI WG

Next Steps: *Cross Canada Verification Study*

Study aims/outcomes:

1. Demonstrate that the proposed hRIs are valid across laboratories and analytical platforms
2. Demonstrate that the results for each analyte are equivalent across analytical platforms

If significant differences are observed between laboratories, hRI recommendations will be modified accordingly



Final harmonization recommendations

Are you interested in participating?
Please contact us!

CSCC hRI WG

Presentation Outline

Path to Harmonization

Speaker: Dr. Khosrow Adeli

- Outline the efforts of CSCC hRI WG in the development of evidence-based harmonized reference intervals in the adult population
- Discuss key considerations in method development

Analyzing the Data

Speaker: Mary Kathryn Bohn

- Outline the statistical approach used to calculate harmonized reference intervals, providing a background and worked example
- Discuss rationale in data analysis measures

Path to Implementation

Speaker: Dr. Dana Bailey

- Discuss the next steps to implementing harmonized reference intervals across Ontario and Canada
- Engage with colleagues through polling questions to provide input

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Polling question #1

Reference intervals currently reported by my laboratory are derived from:

A. Manufacturer package inserts
B. Publications or textbooks
C. Internal direct studies
D. Internal indirect studies
E. They were set when I started
F. Other

Path to Implementation: Barriers & Feedback

Goal of CSCC hRI WG is not only to establish evidence based harmonized reference intervals, but support their implementation

- Harmonization initiatives around the world have undertaken different approaches to support the implementation of proposed RIs, including:
  - *Assisting in completing verification studies*
  - *Using retrospective data to assess differential flagging rates*
  - *Working with representative societies to support implementation*

Path to Implementation: *Planned Engagement*

After completion of verification program, circulate proposed harmonized practice guidelines to target groups for input:

Finalize & Publish!

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Polling question #2

Would your laboratory be interested in considering RI harmonization?

A. Yes
B. Not at this time
C. I need more information!

Let's discuss!

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Polling question #3

What do you see as the main barriers to implementation of harmonized reference intervals:

A. Scientific concern
B. Resources associated with verification
C. IT resources for LIS implementation
D. Other

Path to Implementation: *Planned Support*

A

Knowledge-translation toolbox

Website

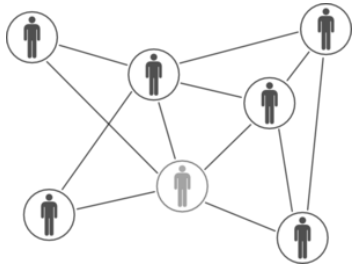
Instructional Video

Other items:

- Relevant publications and links
- Excel template for verification
- Summary of recommendations
- Communication letter to clinicians

B

On-site training workshops in regions across Canada



C

Nation-wide surveys to assess degree of harmonization achieved

CSCC

We want to hear from you!

CSCC hRI WG

Discussion point

How can we best support implementation in laboratories across Canada?

Discussion point

How can we best support maintenance of harmonized RIs in laboratories across Canada?

Path to Implementation: *What's Next*

- Based on our established approach, we plan to expand the initial panel of 17 analytes to include additional laboratory tests!
- Continue to update and assess implementation of hRIs on a prospective basis
- **Stayed tuned for recommendations on harmonized lipid reporting in pediatrics and adults across Canada!**

CSCC hRI WG

Polling question #4

What other analytes would you like to see addressed?

A. Hematology
B. Additional endocrine (e.g. sex hormones)
C. Additional chemistry
D. Vitamins
E. Others

Acknowledgements

CSCC Working Group on Reference Interval Harmonization

Co-Chairs
Khosrow Adeli
Christine Collier

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Mary Kathryn Bohn
Jake Cosme
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Julie Shaw
Janet Simons
Uvaraj Uddayasankar
Dorothy Truong

Community Reference Laboratory Partners

Dynacare®
LifeLabs®
DynaLIFE MEDICAL LABS

CSCC hRI WG

Questions?

Khosrow Adeli, PhD, FCACB, DABCC, FACB
Dana Bailey, MSc, PhD, FCACB, DABCC
Mary Kathryn Bohn, PhD Candidate

On Behalf of the CSCC Reference Interval Harmonization Working Group