Reference Interval Harmonization in Canada

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University of Toronto & The Hospital for Sick Children

Canadian Society for Clinical Chemists (CSCC) Education Roundtables
September 22nd 2022
11:30am-12:30pm EST

Outline & Learning Objectives

Presentation Outline

- Reference Interval Harmonization in Canada
- Analyzing the Data – Approach Taken by CSCC hRI
- Path towards Implementation

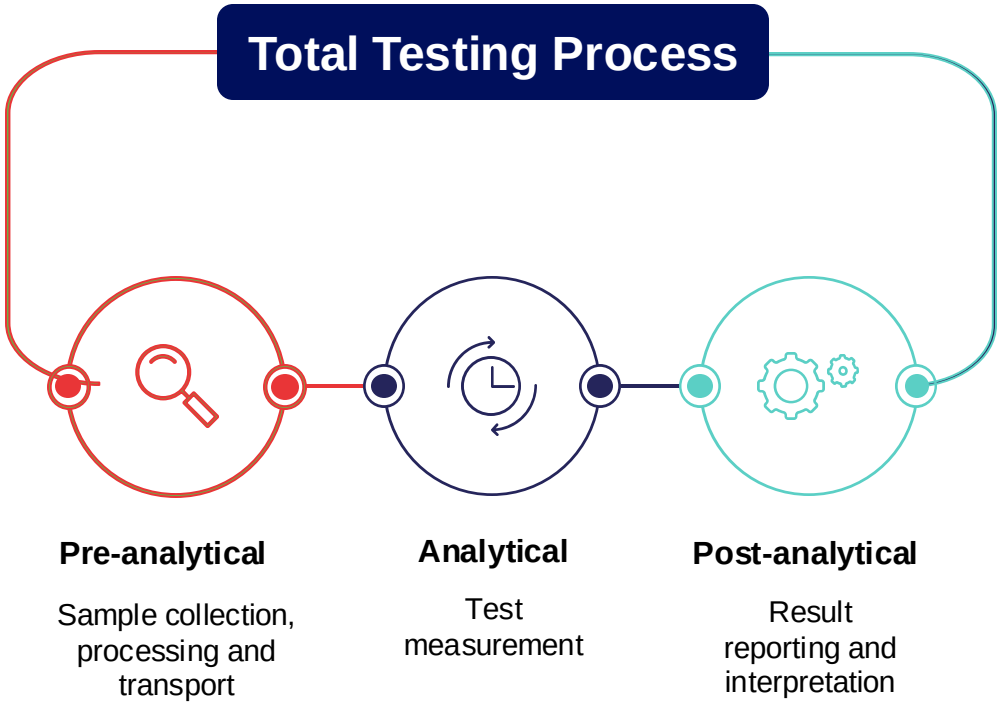
At the end of the session, the participants will be able to:

- Outline the major gaps in reference intervals and the critical need for harmonization across clinical laboratories.
- Describe the major advances made by the CSCC Working Group on Reference Interval Harmonization.
- Discuss the development and verification of common reference intervals and their implementation across Canada.

Harmonization in Laboratory Medicine

Harmonization: "the equivalence of test results and interpretation among different routine measurement procedures over time and space according to defined analytical and clinical quality specifications"

Plebani M. Clinical chemistry and laboratory medicine. 2013 Apr 1;51(4):741-51.



Harmonization in Laboratory Medicine - *Preanalytical*

Preanalytical phase: processes completed prior to laboratory analysis
(e.g. specimen collection, transport, and processing)

- Estimated to account for **50-70% of errors in laboratory medicine.**

Table 1. Pre-analytical errors grouped in relation to identification and sample problems.

Identification	Sample
Unlabeled samples	Hemolyzed
Mislabeled samples	Clotted
Insufficiently labeled samples	Icteric/lipemic
Samples suspected of being from the wrong patient ("wrong blood in tube")	Incorrect filling level
	Inadequate quantity
Irregularities in transfusion labeling requirements (e.g. signature of phlebotomist)	Lost/not received
	Damaged during transportation and improperly stored

http://dx.doi.org/10.11613/BM.2014.012 Biochemia Medica 2014;24(1):105–13

- **Steps towards harmonization**: development of standardized quality indicators to ensure that all clinical laboratories define, report, and benchmark according to defined quality standards.

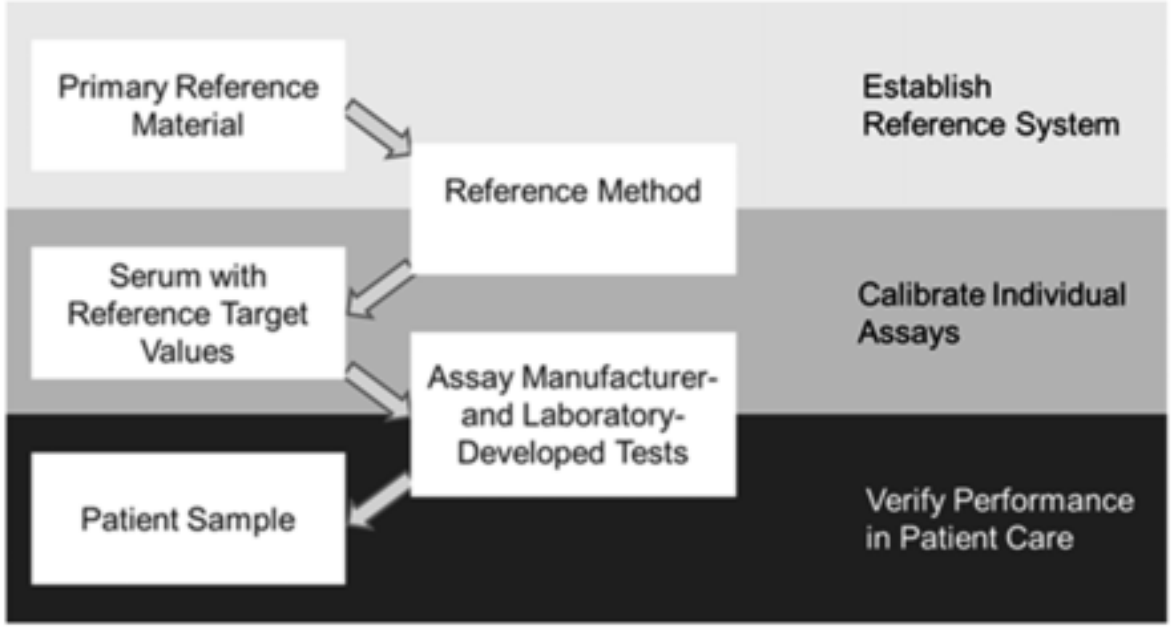
LMP INVESTIGATING DISEASE. IMPACTING HEALTH.

LMP Quality Council at University of Toronto
lmp.utoronto.ca/about-lmp-quality-council

Harmonization in Laboratory Medicine - *Analytical*

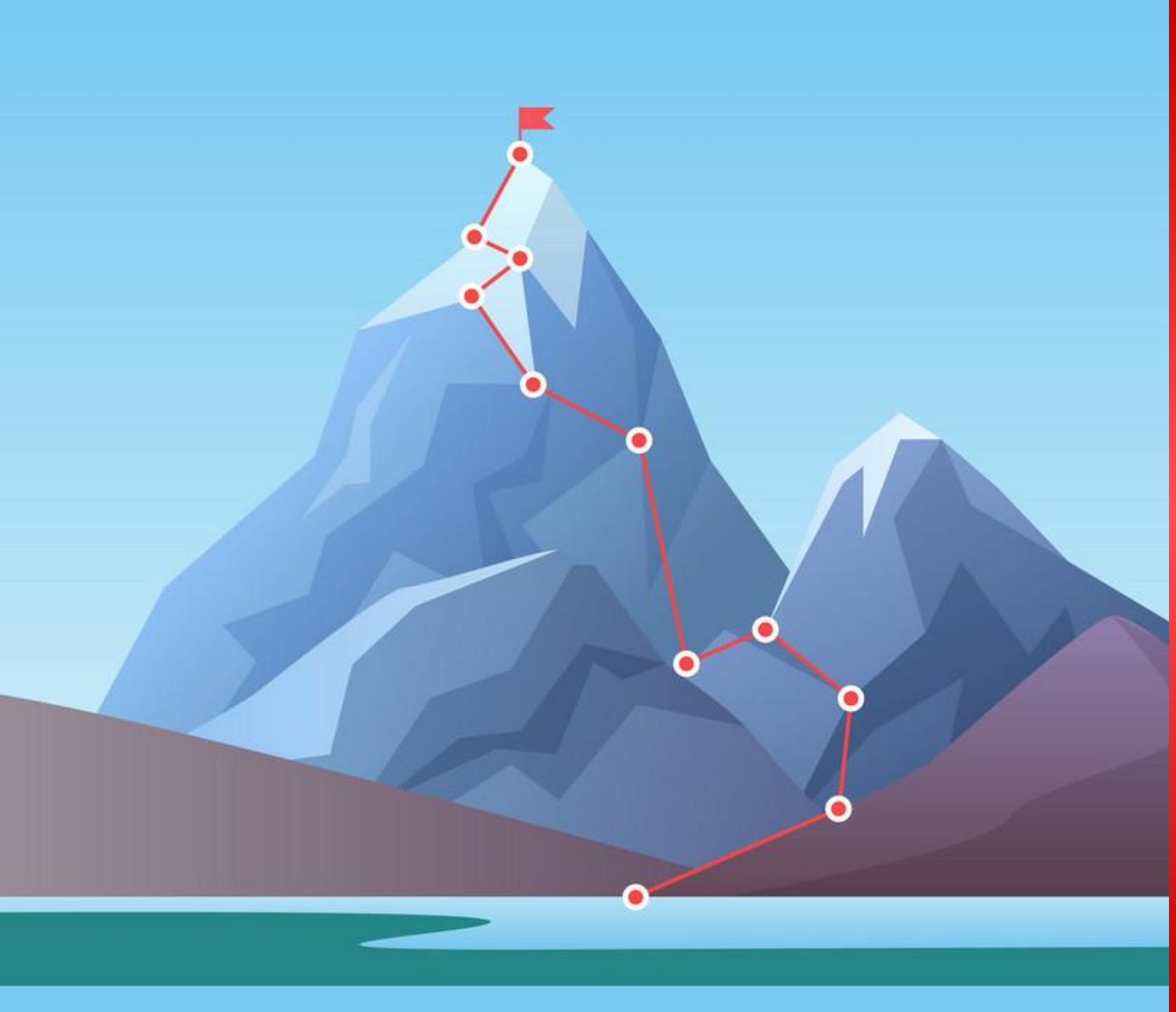
Analytical phase: processes directly related to sample analysis and testing

- Results between different **clinical laboratory measurement procedures** should be equivalent, within clinically meaningful limits.
- **Metrological traceability** to higher order references is ideal to provide reproducible result and stable reference system.
- Current standardization resources are available for approximately **110 measurands** (e.g. HbA1c, cholesterol)



Abbreviated diagram of the 3 basic steps performed in standardization programs, showing the traceability chain.
Adapted from ISO 17511:2020.

The Journal of Applied Laboratory Medicine. 2021 Mar;6(2):510-21.



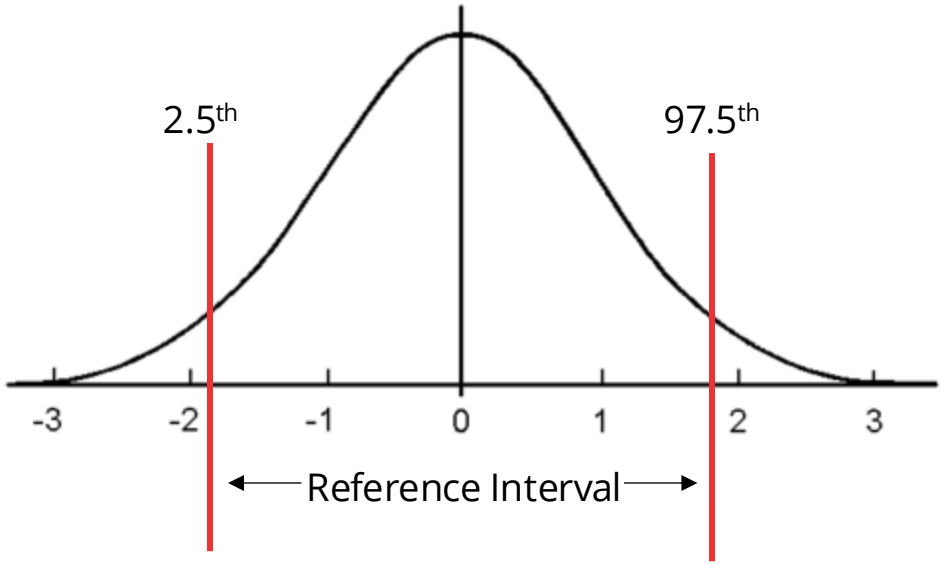
Immense progress!

Primed for RI harmonization

Harmonization in Laboratory Medicine – *Postanalytical*

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).

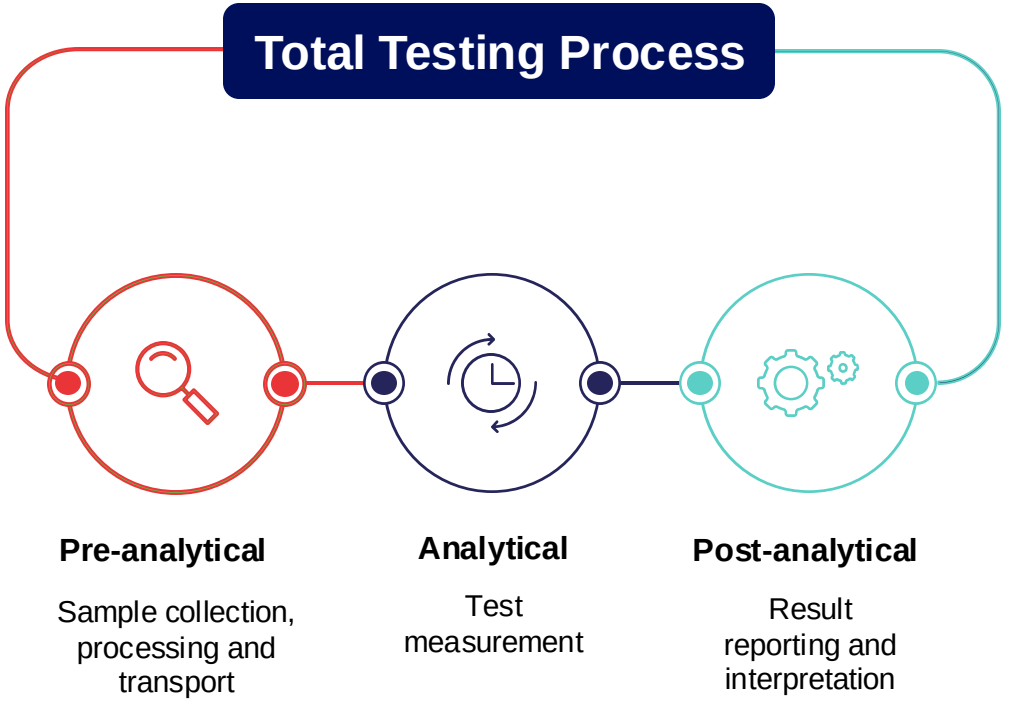


Clinical Decision Limits: threshold values that indicate significant patient risk of clinical outcome or diagnosis of a specific disease.

	HbA1c (%)
Diabetes	≥6.5
Prediabetes	5.7 – 6.4
Normal	~ 5.7

Harmonization in Laboratory Medicine – *Postanalytical*

<u>RI Harmonization</u>: “using one interpretative recommendation that may be age- and/or sex-stratified for an analyte across several laboratories, regardless of analytical assay or patient population”



Harmonized or common RIs are only suitable for assays that demonstrate minimal bias across considered methodologies

Are Reference Intervals Still a Problem?

Yes ➡ for Clinicians

- different reference intervals from different laboratories;
- confusion between **Reference Intervals** and **Decision Limits**

Yes ➡ for Patients

- same value can be considered “normal” or “abnormal” in different laboratories

Reference Interval Harmonization: Around the world

UK Pathology Harmony

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

NORIP

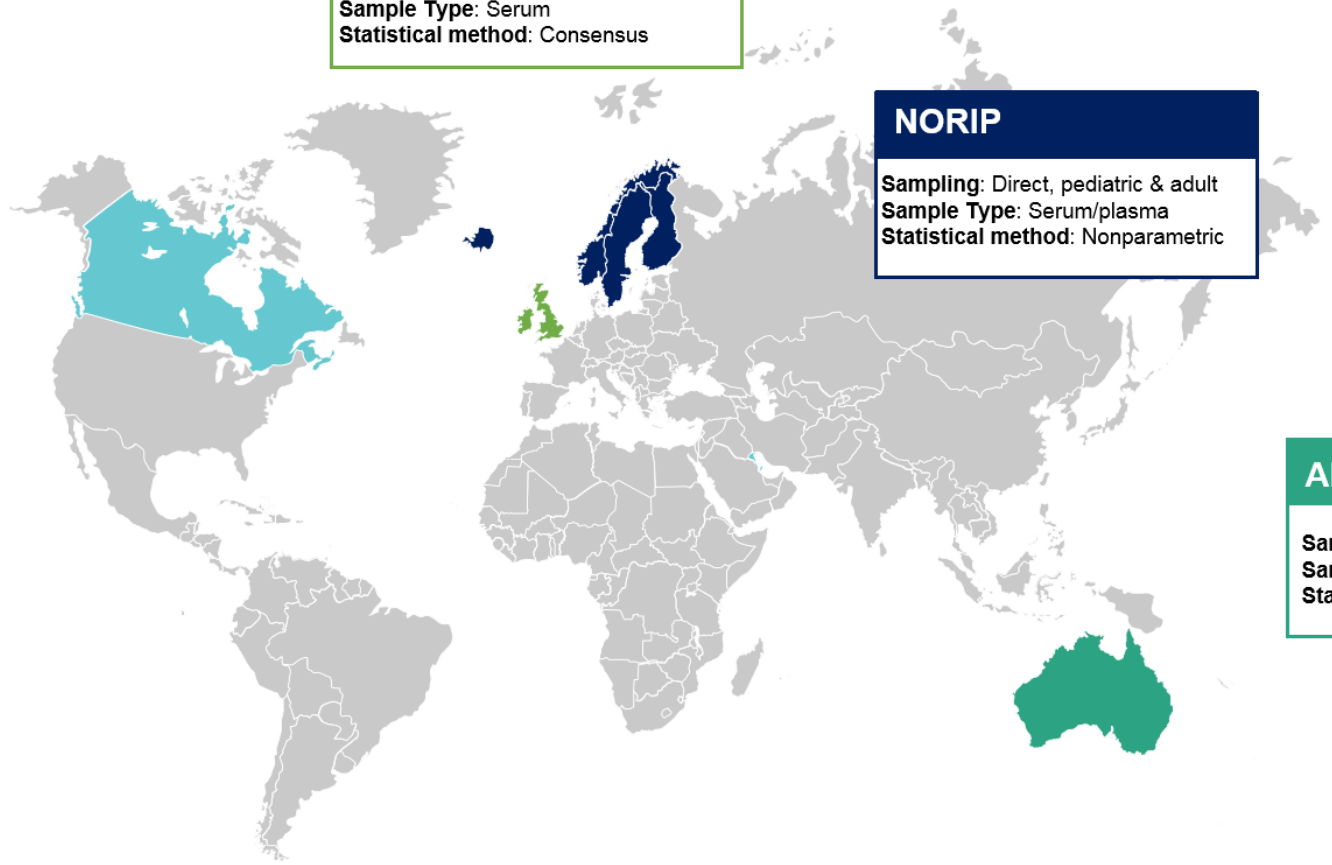
Sampling: Direct, pediatric & adult
Sample Type: Serum/plasma
Statistical method: Nonparametric

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

CSCC Working Group on Reference Interval Harmonization

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

Co-Chairs
Khosrow Adeli
Christine Collier

WG Members
Zahraa Mohammed-Ali
Albert Tsui
Dana Bailey
Cynthia Balion
George Cembrowski
Jake Cosme
James Dalton
Vincent De Guire
Angela Fung
Trefor Higgins
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David Seccombe
Julie Shaw
Julia Stemp
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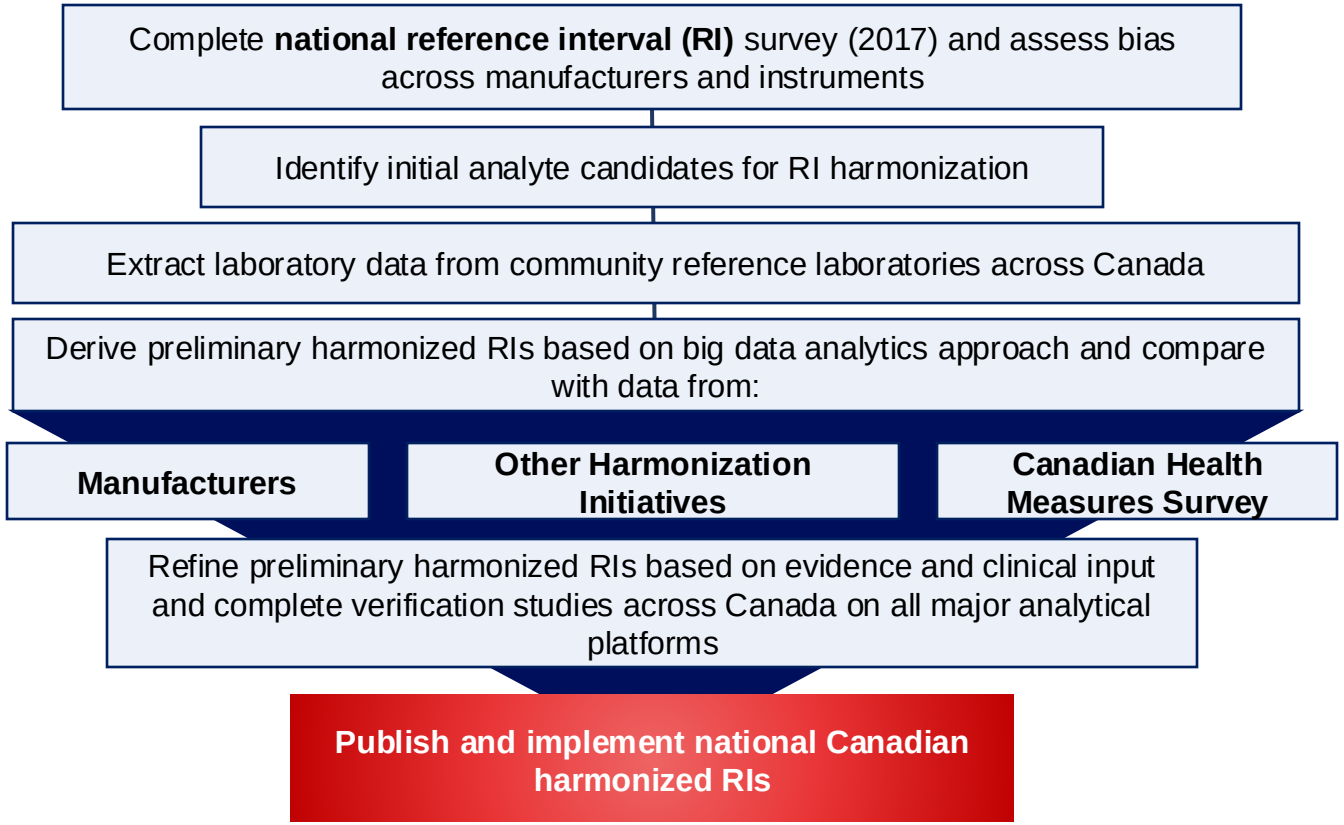
Allison Venner
Nicole White-AlHabeeb



National Survey 2017

Reference Intervals in use across Canada: >30 Clinical Laboratories surveyed

Clinical Biochemistry (2017)

Reference Interval Harmonization in Canada: Current Gaps

- 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

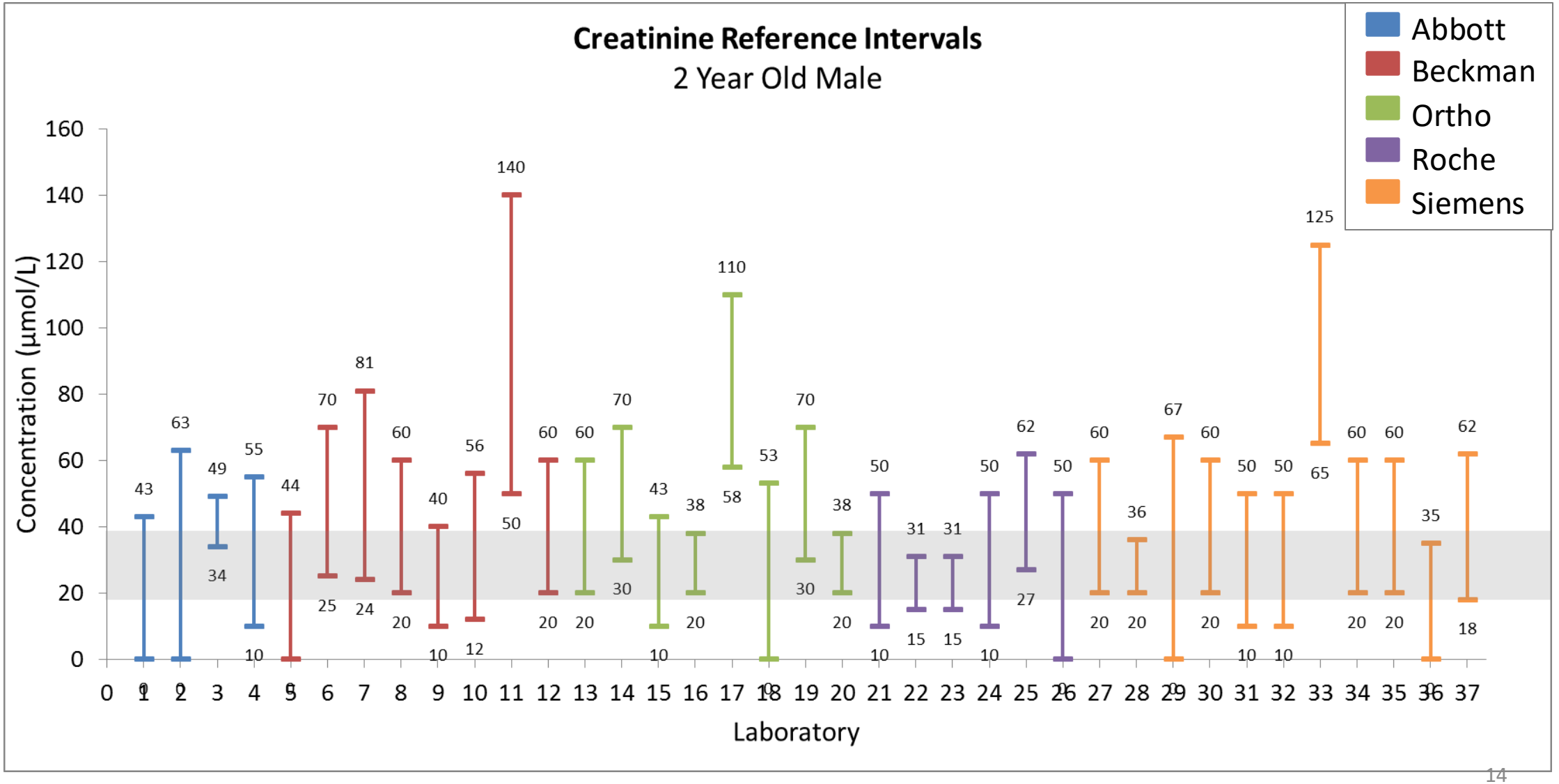
CSCC 2017 National Survey on Reference Interval Variation:

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

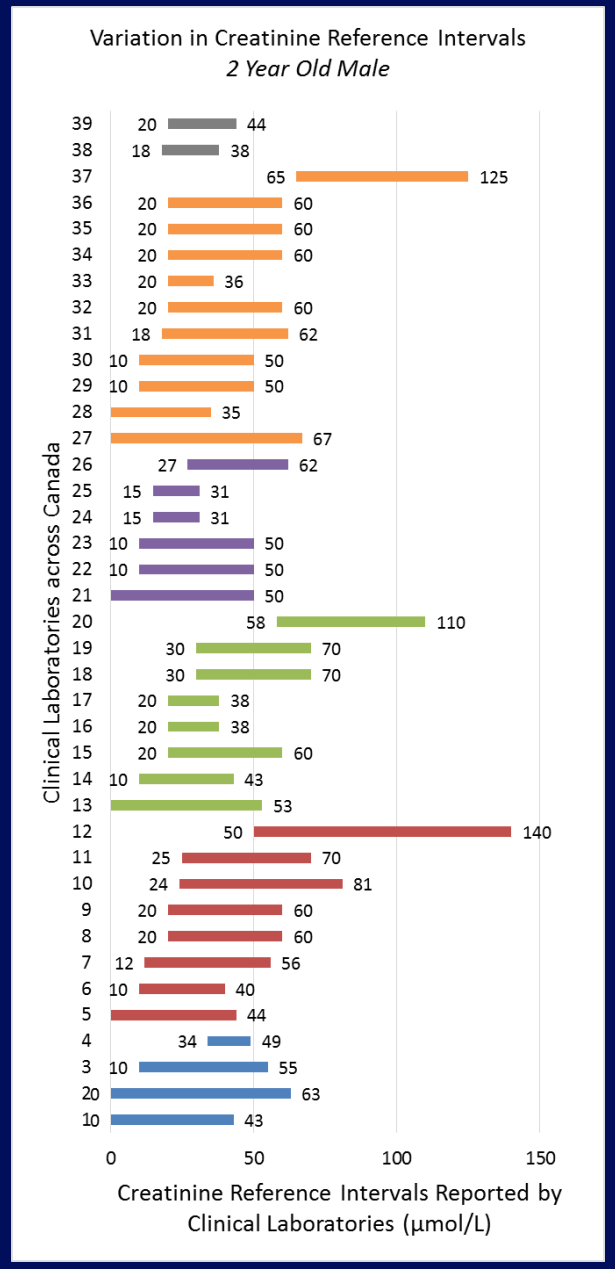
Key Findings:
- Variability in RIs even between laboratories using the same instrumentation
- RI variability exceed test result variability

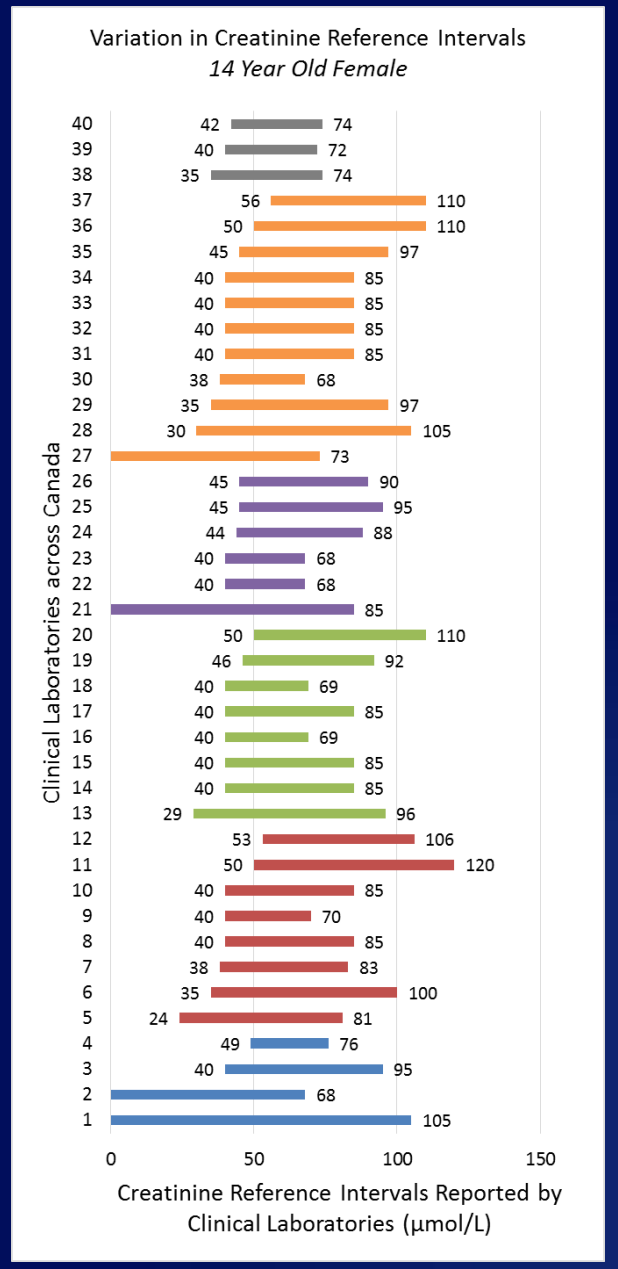
Clinical biochemistry. 2017 Nov 1;50(16-17):925-35.

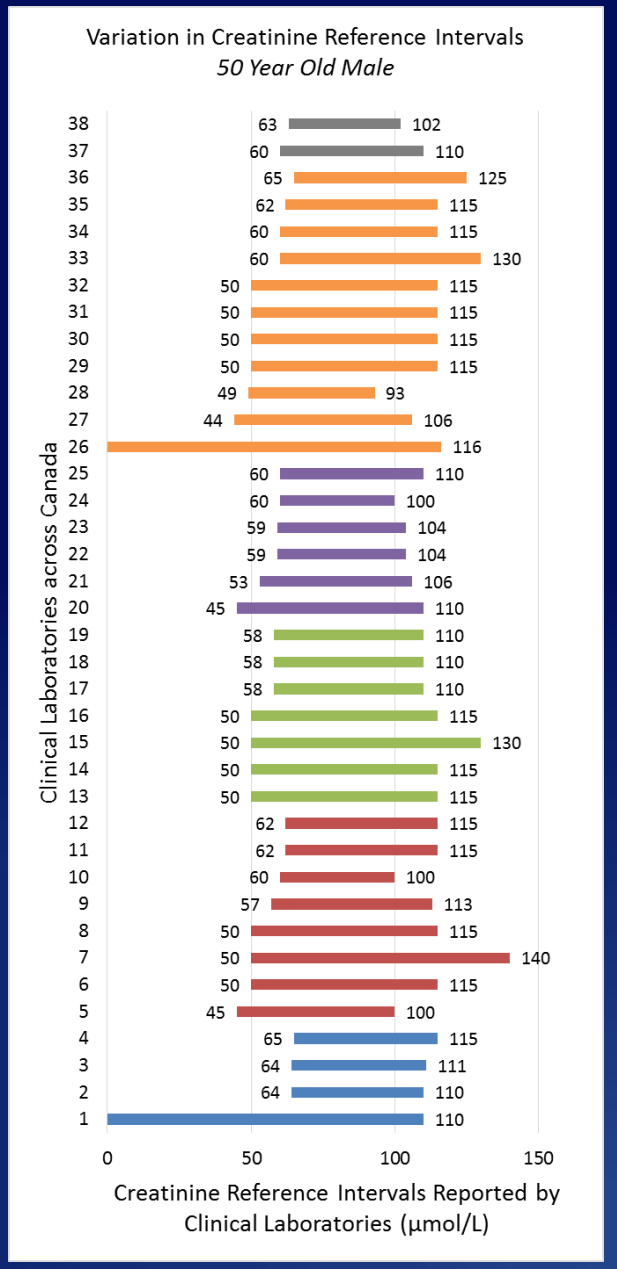
Reference Intervals in Centres across Canada: Creatinine



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


Variation in Creatinine Reference Intervals
2 Year Old Male
Clinical Laboratories across Canada
Creatinine Reference Intervals Reported by Clinical Laboratories (µmol/L)
0
50
100
150


Variation in Creatinine Reference Intervals
14 Year Old Female
Clinical Laboratories across Canada
Creatinine Reference Intervals Reported by Clinical Laboratories (µmol/L)
0
50
100
150


Variation in Creatinine Reference Intervals
50 Year Old Male
Clinical Laboratories across Canada
Creatinine Reference Intervals Reported by Clinical Laboratories (µmol/L)
0
50
100
150


Abbott
Beckman
Ortho
Roche
Siemens

CALIPER Study of Pediatric Reference Intervals

CALIPER = Canadian Laboratory Initiative on Pediatric Reference Intervals

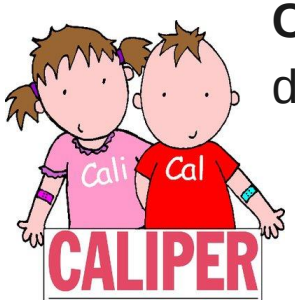
Serum Biobank: > **12,500** samples (males/females)

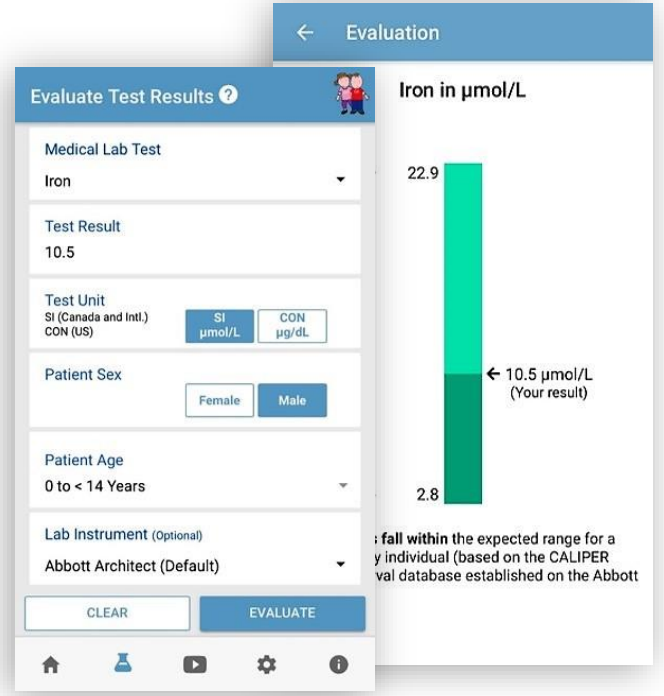
Age Range: Birth to 18 years

Health Information: Family History, Health Status, BMI, Waist Circumference

CALIPER Database: Reference standards for over 200 biomarkers from peer-reviewed publications

CALIPER Mobile and Web Apps for ready access to the database of pediatric reference standards





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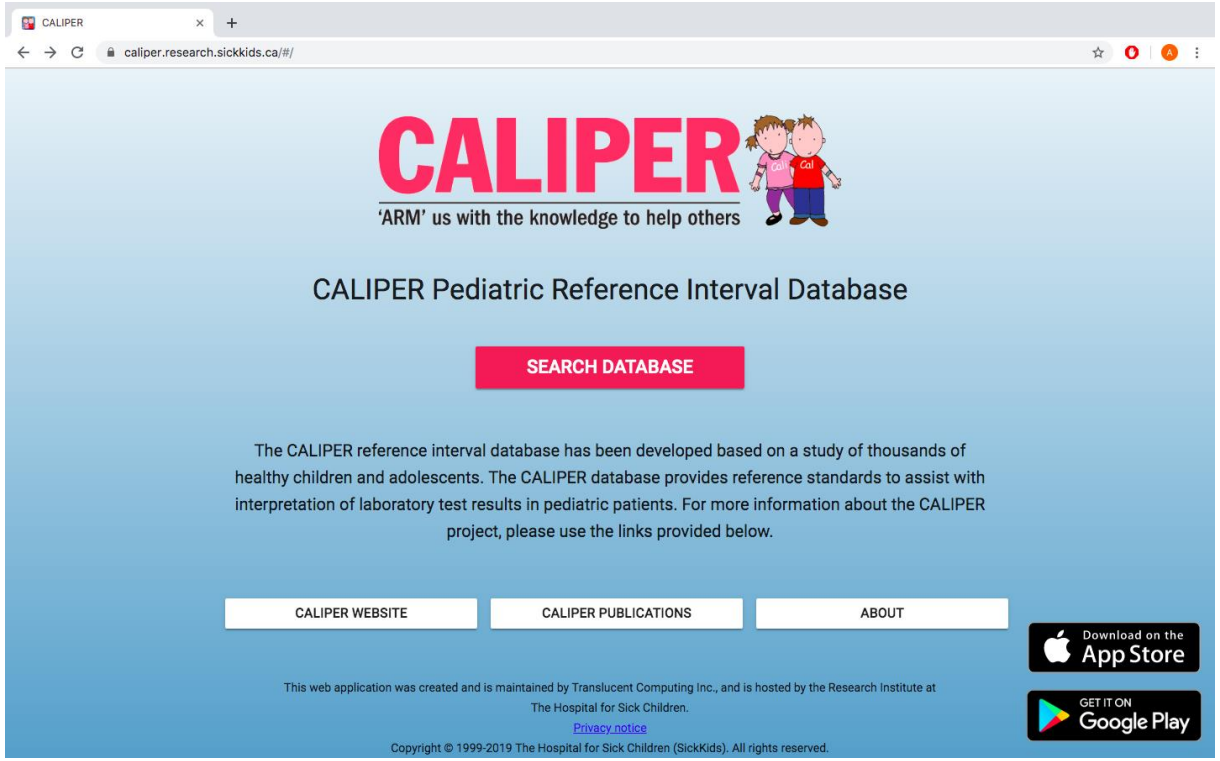
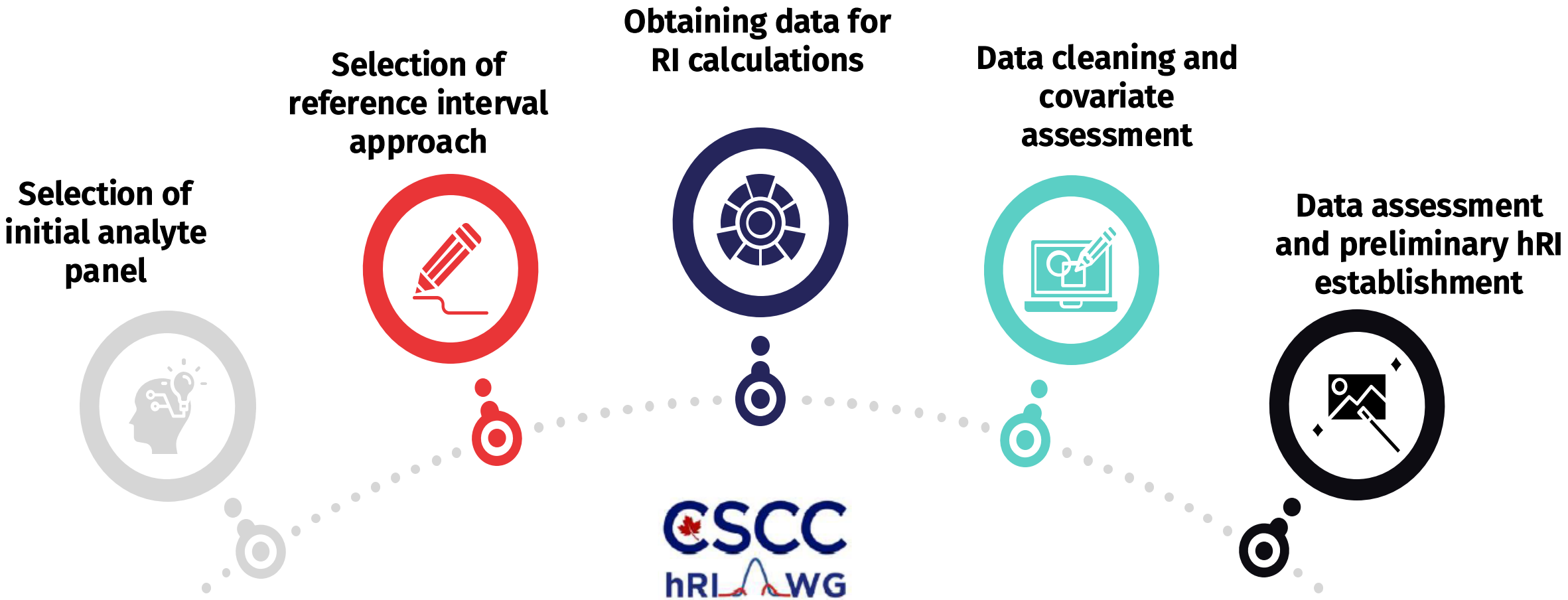
CALIPER Online Database

www.caliperdatabase.org



Many clinical laboratories have implemented CALIPER pediatric RIs for test interpretation in children and adolescents, serving as a form of harmonization for pediatric RIs

Path to Reference Interval Harmonization in Adults



Approach: Selecting Initial Analyte Panel

An initial panel of 16 analytes were selected as candidates for harmonization through: literature review, manufacturer IFU review

Electrolytes

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

Hepatic

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

Renal

- ✓ Creatinine
- ✓ Calcium
- ✓ Phosphate

Endocrine

- ✓Free T4
- ✓Thyroid Stimulating Hormone

Approach: Selecting reference interval approach

How are we going to establish harmonized RIs?

DIRECT:
New prospective RI study

INDIRECT:
Retrospective data mining to establish RIs

Approach: Selecting 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

+

- 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

Approach: Selecting reference interval approach

Available Canadian Direct Data:

- Direct Canadian studies using CLSI-based techniques to derive reference intervals

- **CHMS**: Adult and pediatric reference intervals primarily based on Ortho VITROS platform (n=12,000)

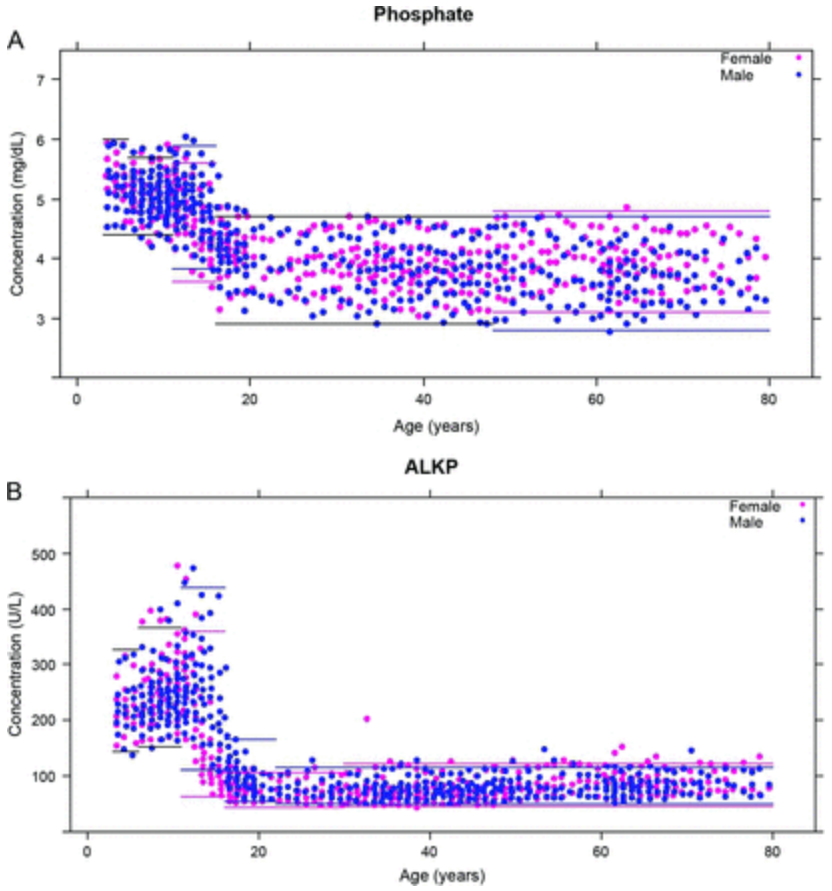
Statistics Canada Statistique Canada

Canada

Statistics Canada
www.statcan.gc.ca

Canadian Health Measures Survey

Clinical chemistry. 2015 Aug 1;61(8):1049-62.
Clinical chemistry. 2015 Aug 1;61(8):1063-74.



Approach: Selecting reference interval approach

Indirect Approach

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

+

- 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

Big Data Era:

Applications in Clinical Biochemistry

A Treasure Trove of Data!

- Medical laboratory data accounts for **70-80%** of objective medical in patient charts.
- Numerous applications in clinical biochemistry and other fields (e.g. pathology, microbiology).
- Poses new opportunities to achieve harmonization in laboratory medicine.

Approach: Obtaining data for RI calculations and harmonization

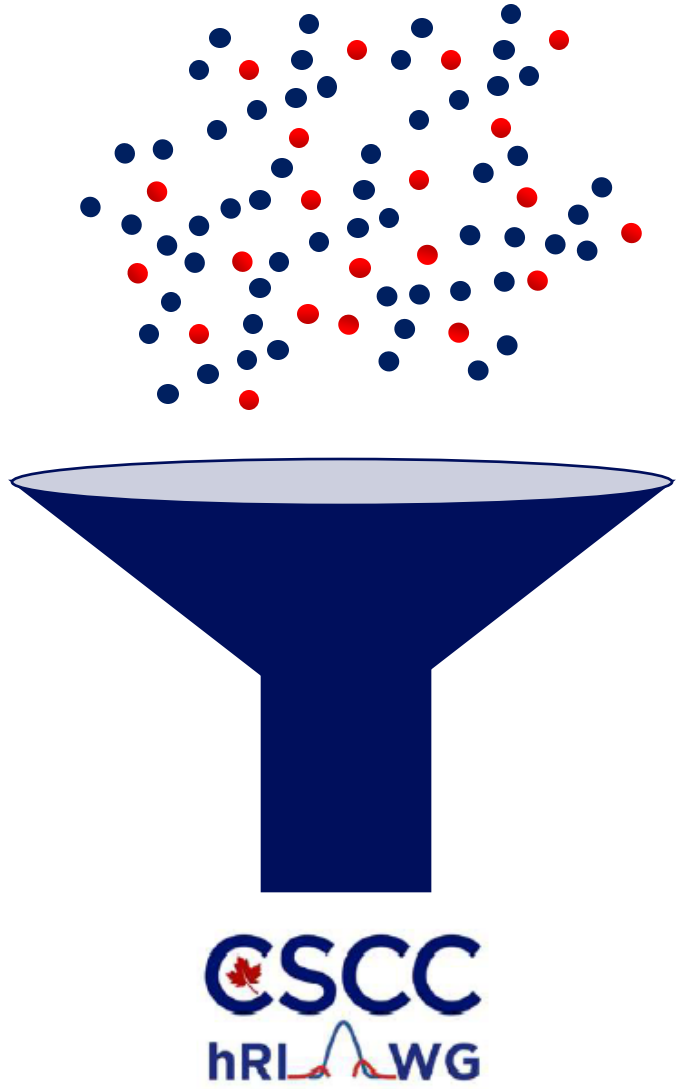
- Appropriate selection of data contributing centres is essential to optimize the performance of indirect methods

Criteria for data centre contribution:

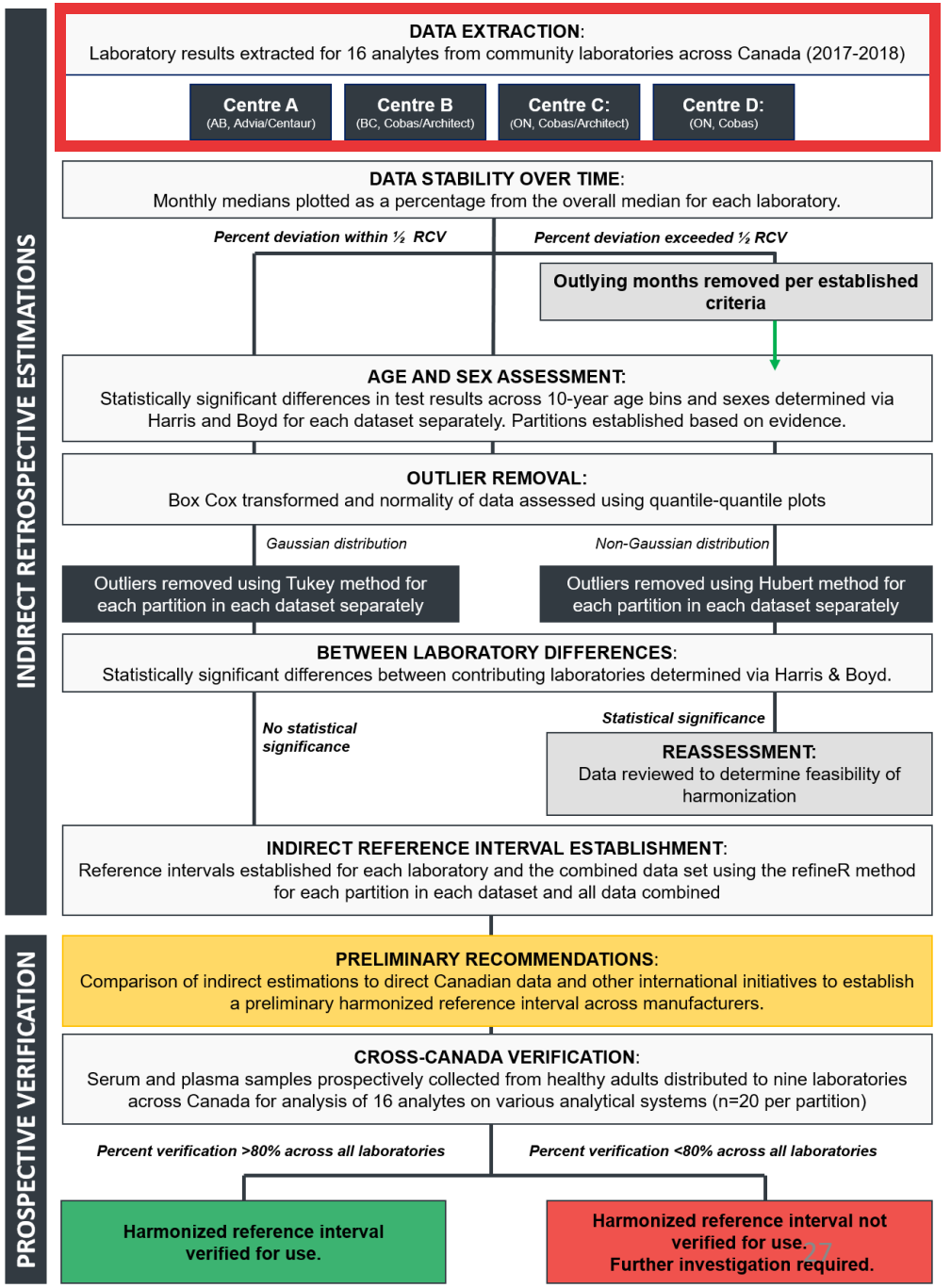
- *Large outpatient population*
- *Representative of Canadian population*
- *Representative of different analytical platforms*
- *Consistent results over time*

Formed collaborations with community laboratories to support this initiative

Analyzing the Data



Analyzing the Data



Analyzing the Data:
Example – Alkaline Phosphatase

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: Cobas
Sample Size: 1062848

DynaLIFE MEDICAL LABS

Province: Alberta
Analytical Platform: Advia
Sample Size: 503169

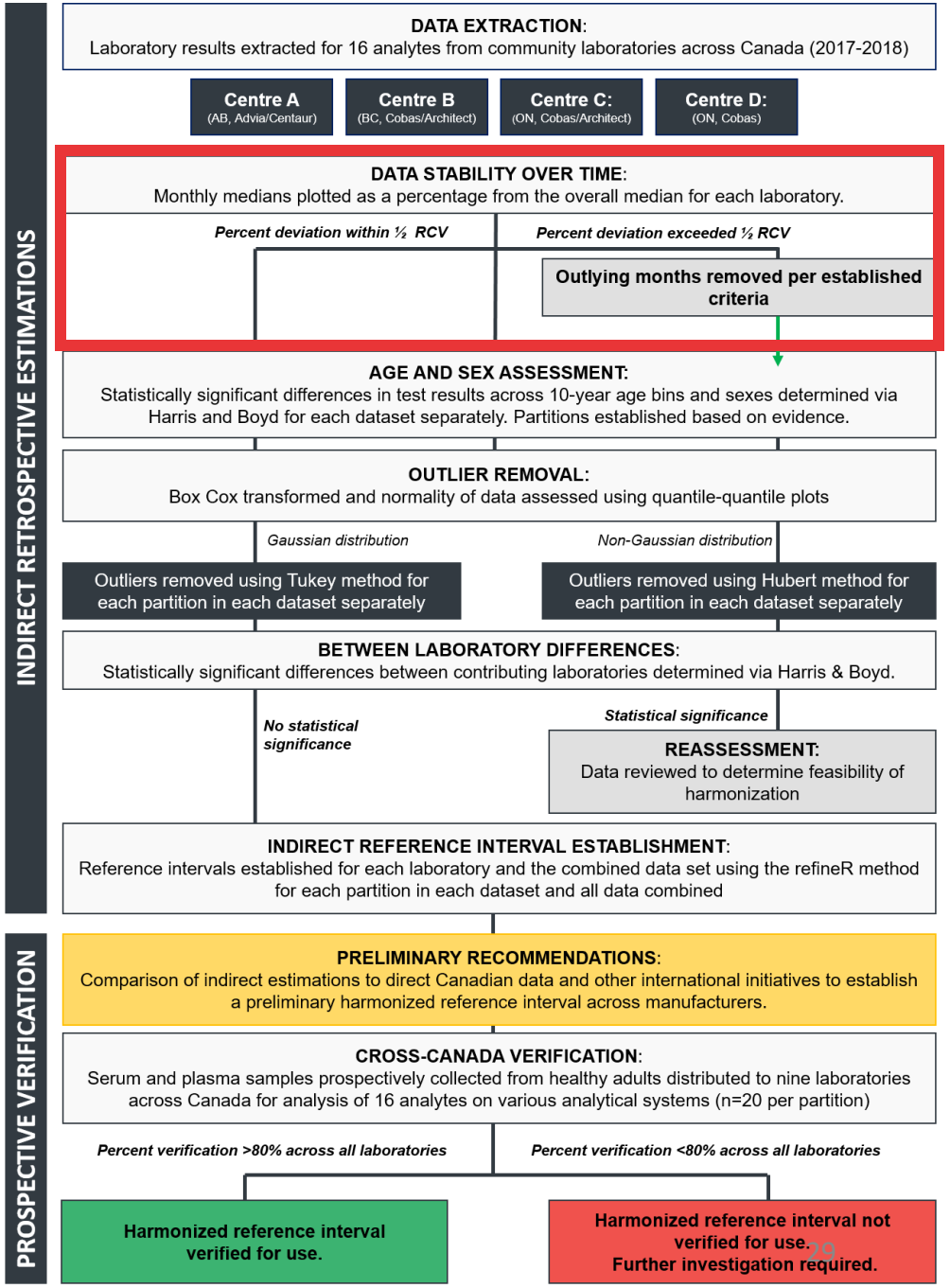
LifeLabs®

Province: Ontario
Analytical Platform: Cobas
Sample Size: 2655240

LifeLabs®

Province: BC
Analytical Platform: Cobas
Sample Size: 781171

Analyzing the Data



Analyzing the Data:

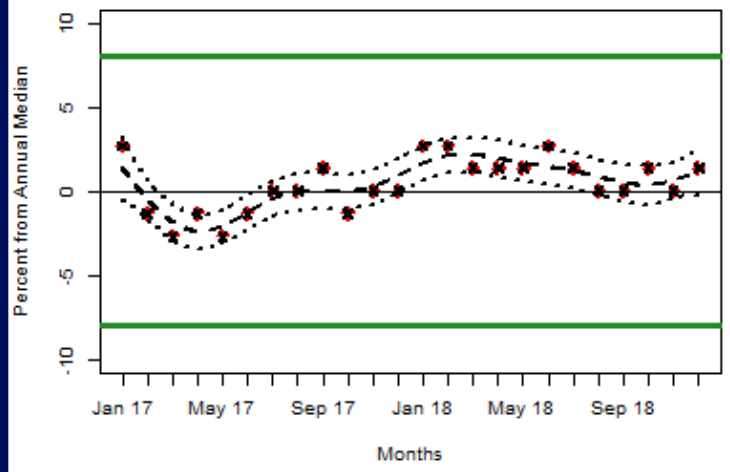
Example – Alkaline Phosphatase

2 ***Data clean up***

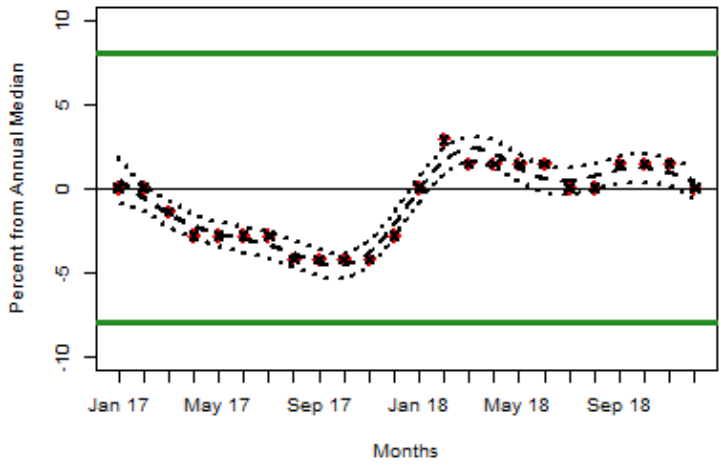
- ✓ *Monthly stability assessed visually*
- ✓ *Percent deviation from median compared to ½ reference change value (RCV) reported by EFLM (8%)*

Monthly Stability: Percent variation from annual median graphed for each laboratory separately and compared to ½ RCV (green line)

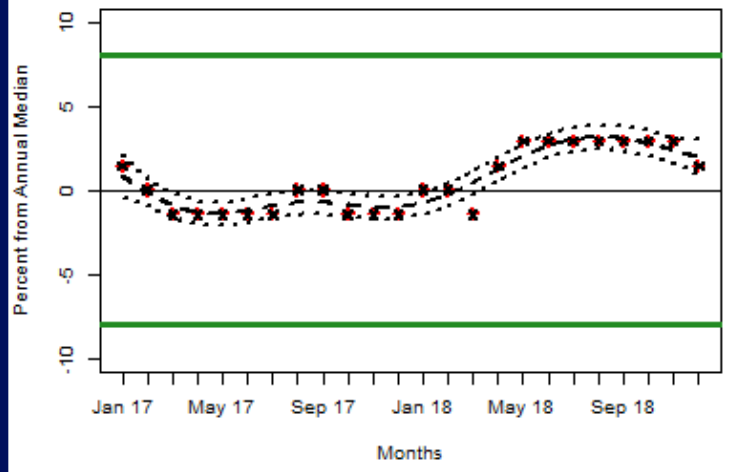
ALP (Advia – Alberta)



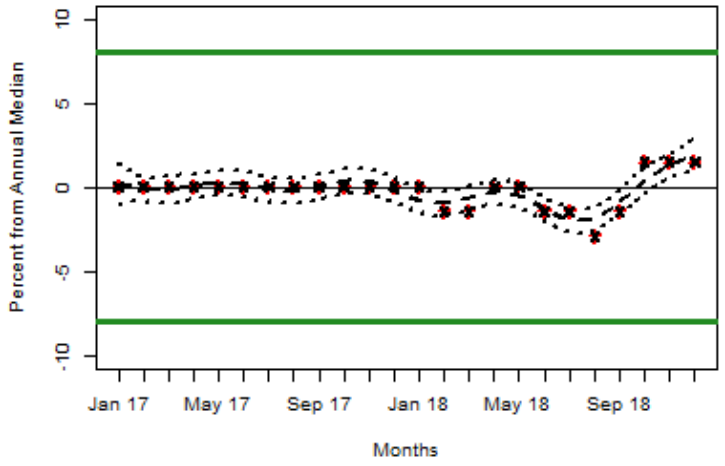
ALP (Cobas – British Columbia)



ALP (Cobas – Ontario)

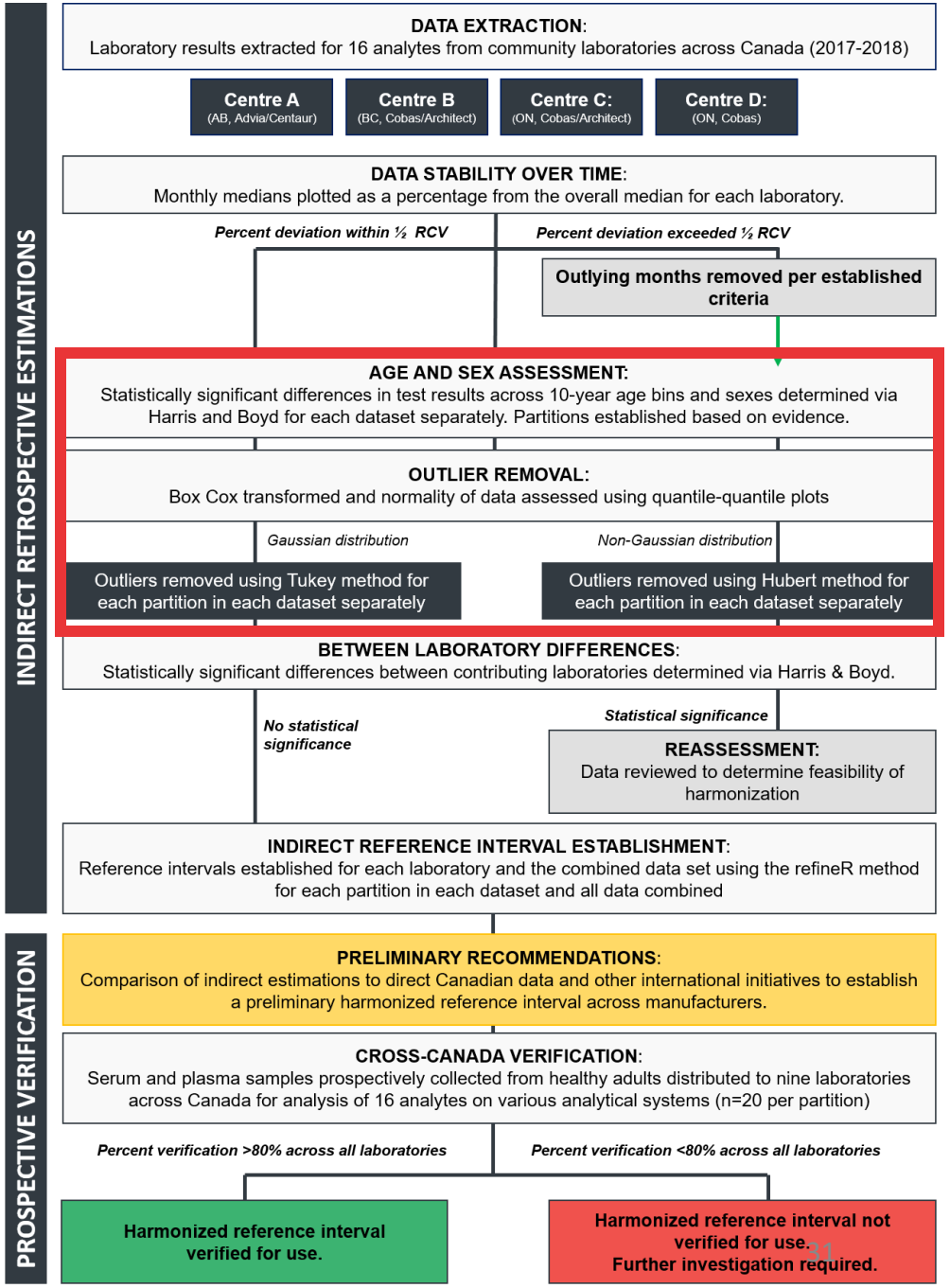


ALP (Cobas – Ontario)



No instability observed

Analyzing the Data



Analyzing the Data:

Example – Alkaline Phosphatase

3 ***Assess age/sex differences***

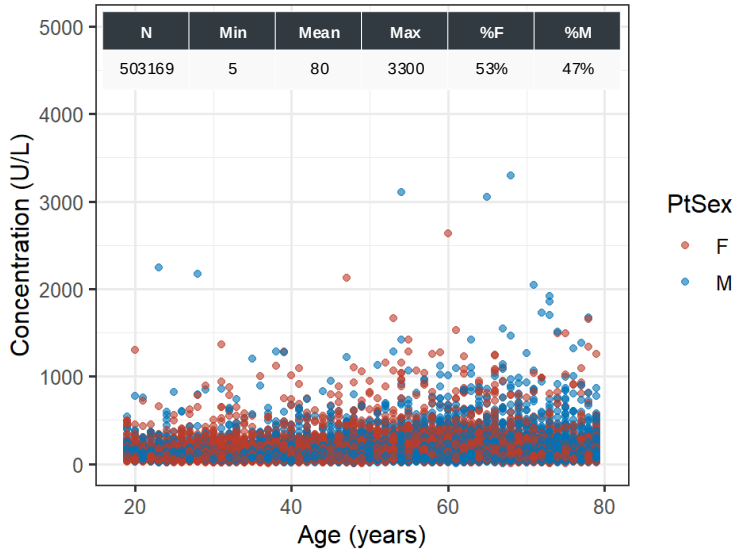
- ✓ **Visually assess raw data across each centre**

Difficult to make conclusions based on simple visualization of raw data

Scatterplot: Raw result values graphed by age and colour-coded by sex for each laboratory

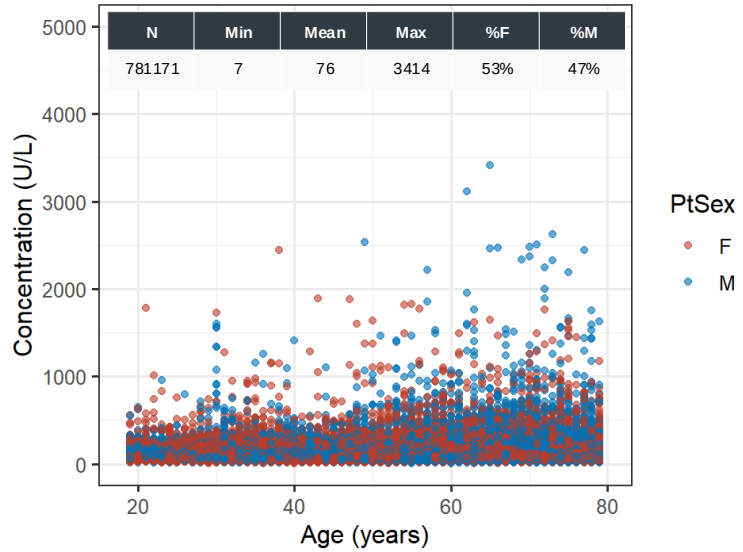
Alkaline Phosphatase (Advia - AB)

N	Min	Mean	Max	%F	%M
503169	5	80	3300	53%	47%



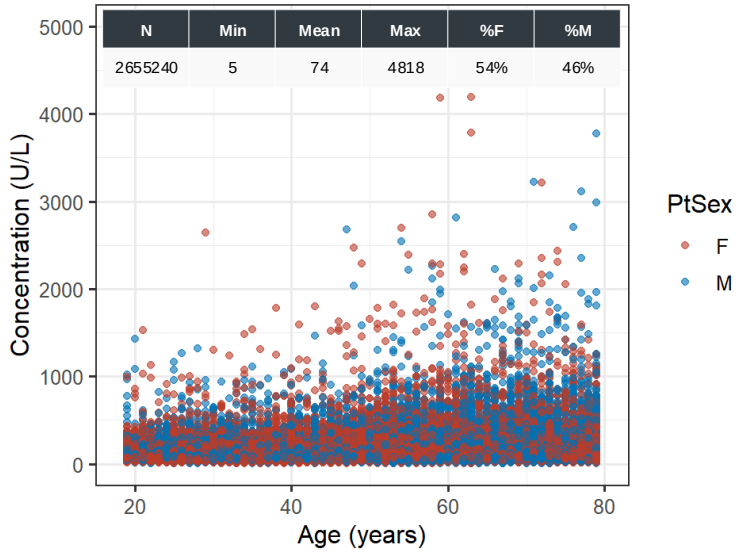
Alkaline Phosphatase (Cobas - BC)

N	Min	Mean	Max	%F	%M
781171	7	76	3414	53%	47%



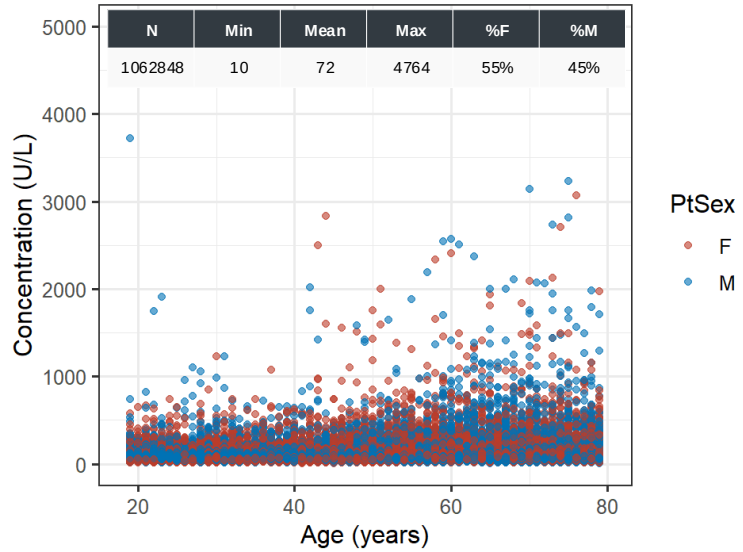
Alkaline Phosphatase (Cobas - ON1)

N	Min	Mean	Max	%F	%M
2655240	5	74	4818	54%	46%



Alkaline Phosphatase (Cobas - ON2)

N	Min	Mean	Max	%F	%M
1062848	10	72	4764	55%	45%



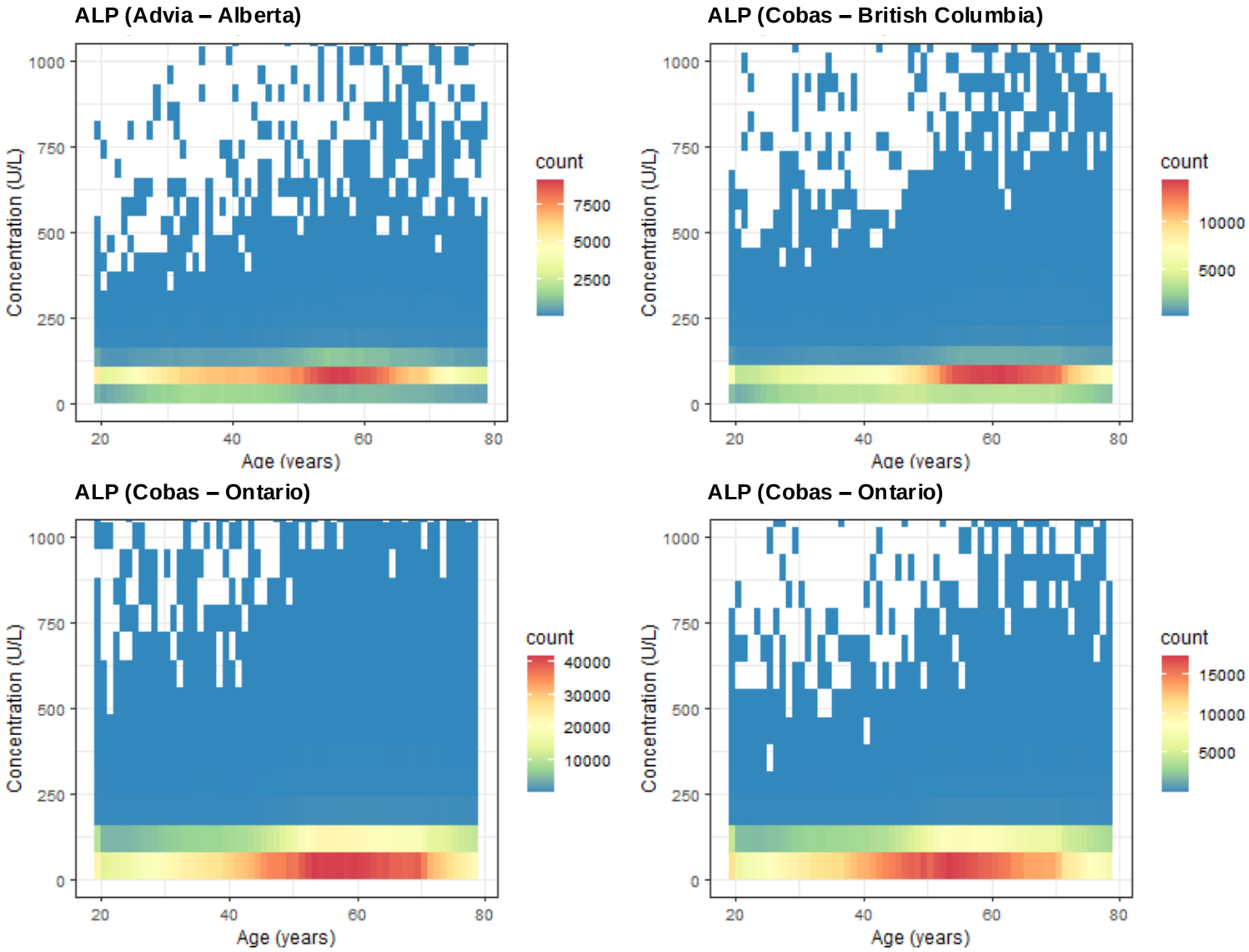
Analyzing the Data:

Example – Alkaline Phosphatase

3 ***Assess age/sex differences***

- ✓ **Visually assess raw data across each centre**
- ✓ **Compare data density across the age range for each laboratory**

Density plot: To visualize density, divides the plot area in a multitude of small fragment and represents the number of points in this fragment.

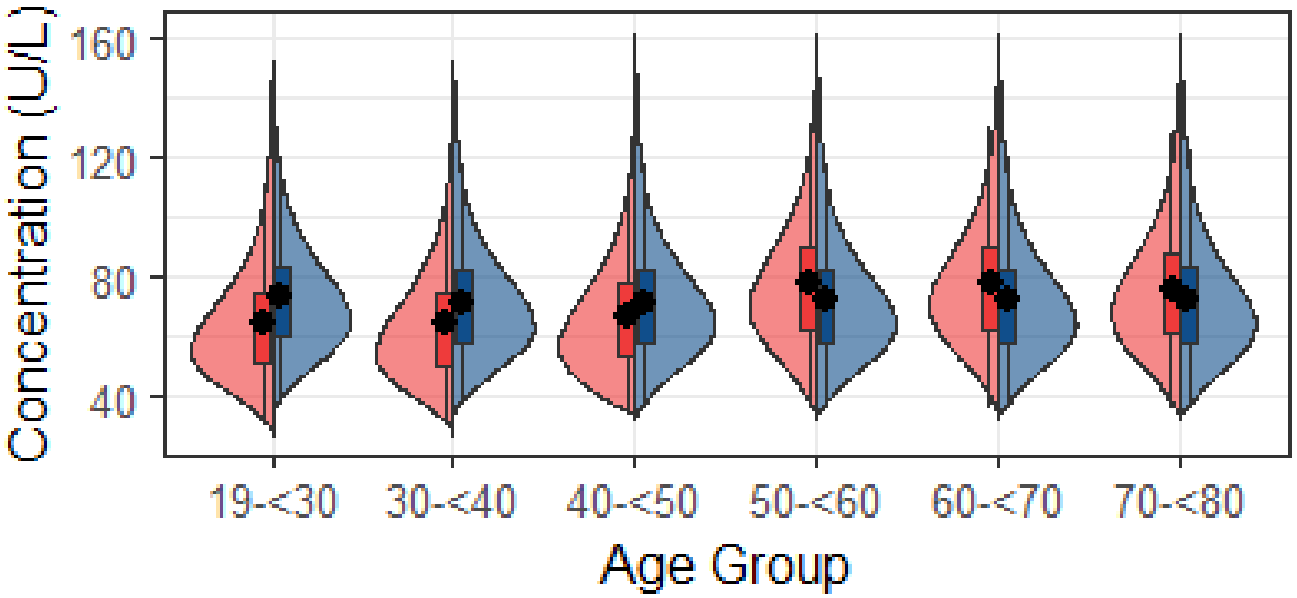


Analyzing the Data:
Example – Alkaline Phosphatase

3 ***Assess age/sex differences***

- ✓ **Visually assess raw data across each centre**
- ✓ **Compare data density across the age range for each laboratory**
- ✓ **Use specialized plots to view age- and sex-specific differences**
- ✓ **Confirm visual assessment statistically using Harris & Boyd Method**

Bean plot: Alternative to boxplot - compares the distributions of different groups by graphing a two-sided histogram (helpful to identify bimodal distributions etc.)



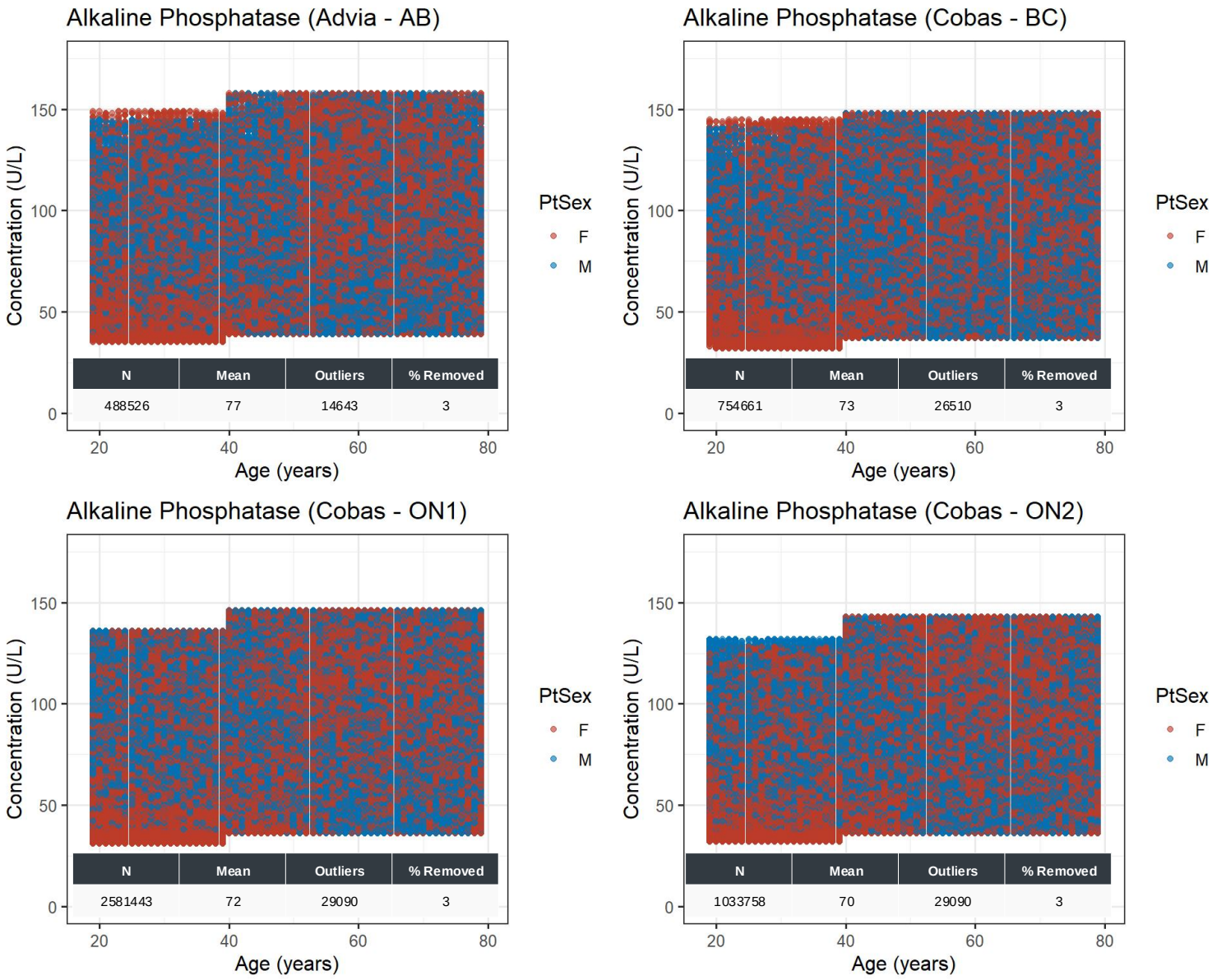
Established age partitions:
19-39 years M/F
40-80 years

Analyzing the Data:

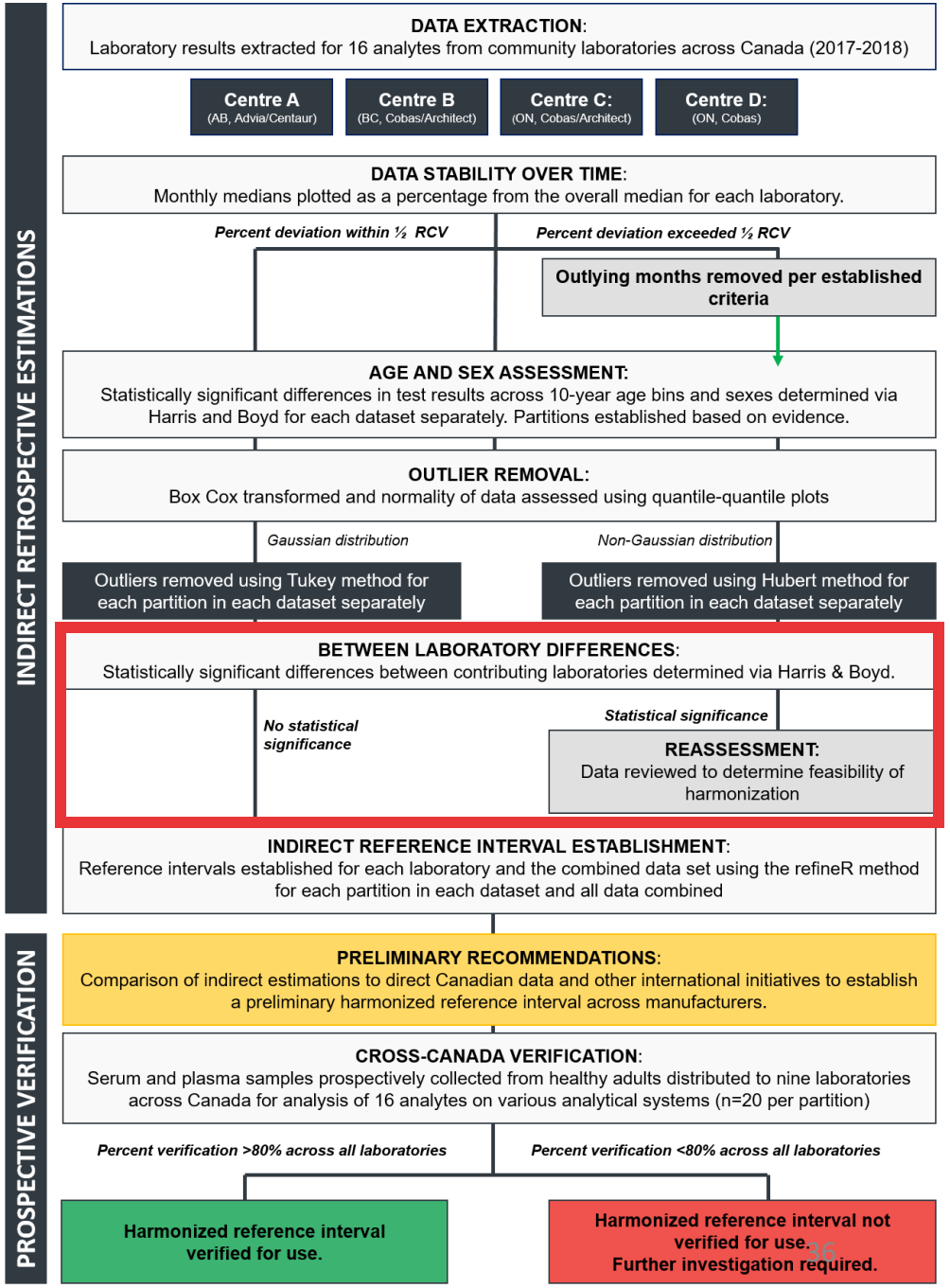
Example – Alkaline Phosphatase

3 ***Assess age/sex differences***

- ✓ **Visually assess raw data across each centre**
- ✓ **Compare data density across the age range for each laboratory**
- ✓ **Use specialized plots to view age- and sex-specific differences**
- ✓ **Confirm visual assessment statistically using Harris & Boyd Method**
- ✓ **Remove outliers**



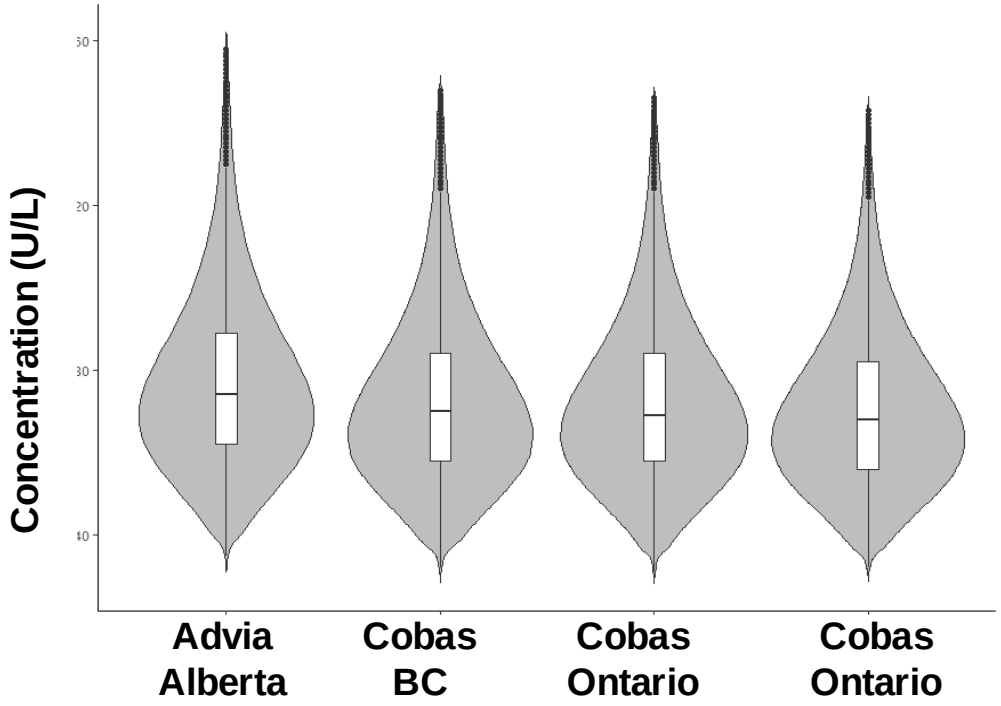
Analyzing the Data



Analyzing the Data:
Example – Alkaline Phosphatase

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 (Cobas)
Sample Size: 1062848

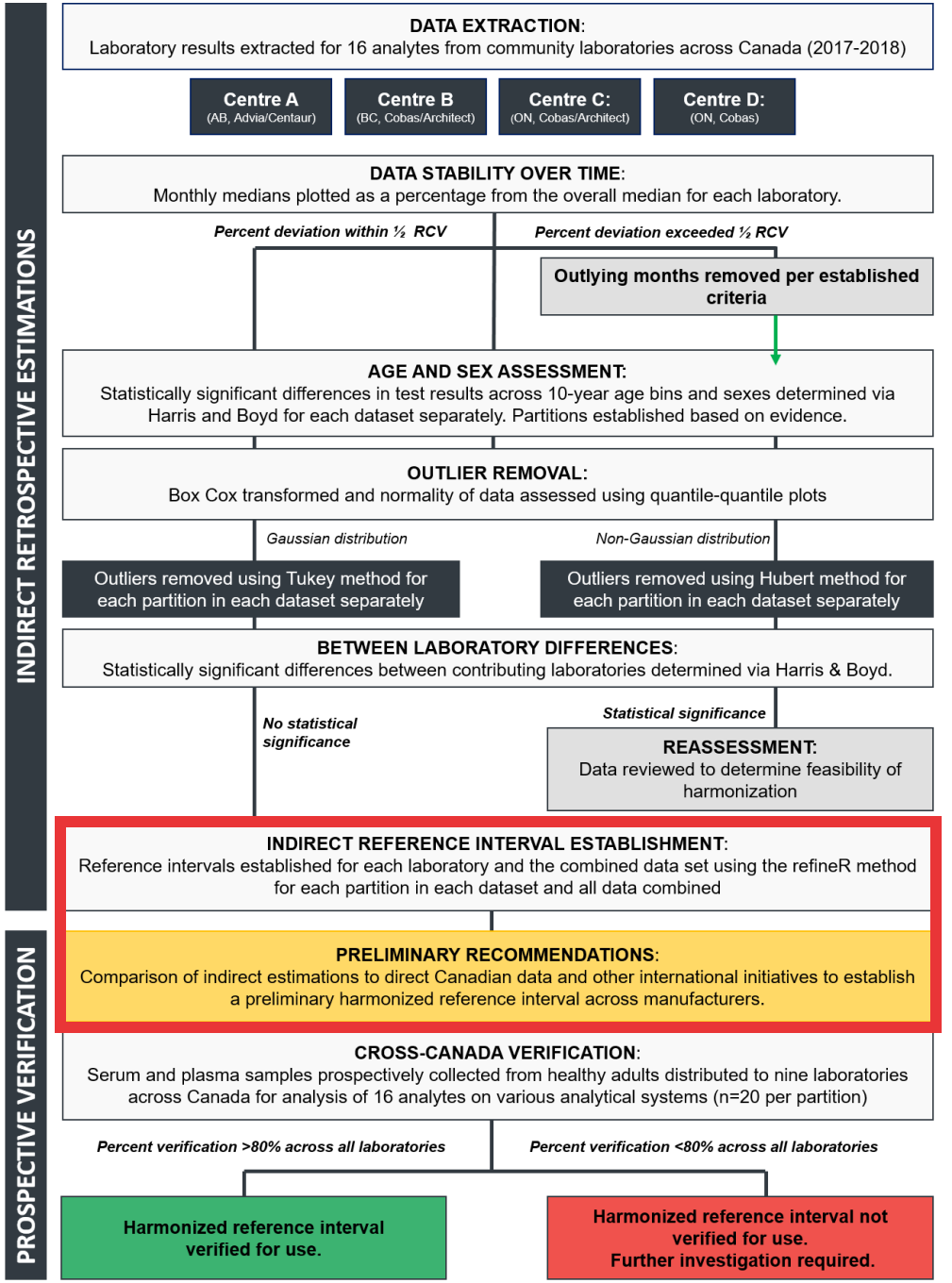
DynaLIFE MEDICAL LABS
Province: Alberta (Advia)
Sample Size: 503169

LifeLabs®
Province: Ontario (Cobas)
Sample Size: 2655240

LifeLabs®
Province: British Columbia (Cobas)
Sample Size: 781171

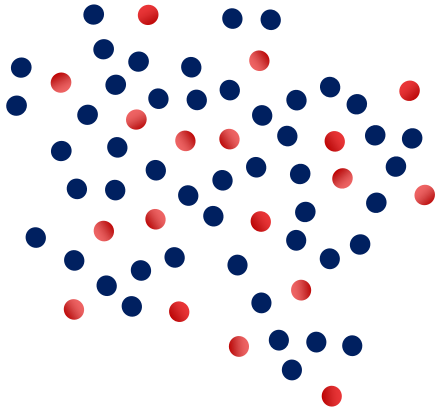
No significant laboratory differences

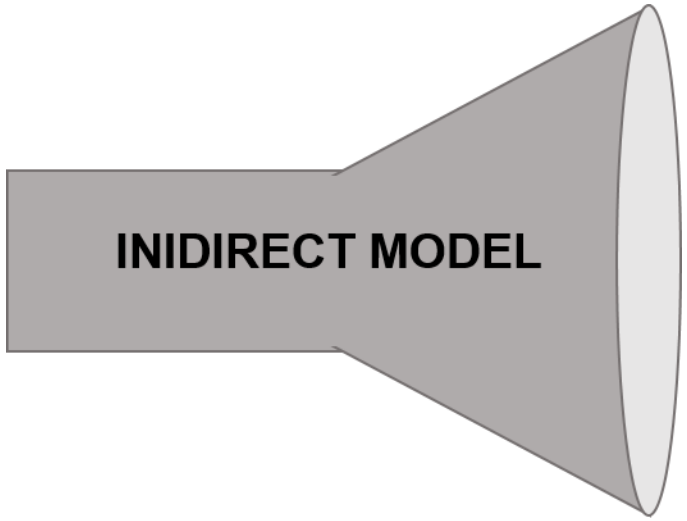
Analyzing the Data



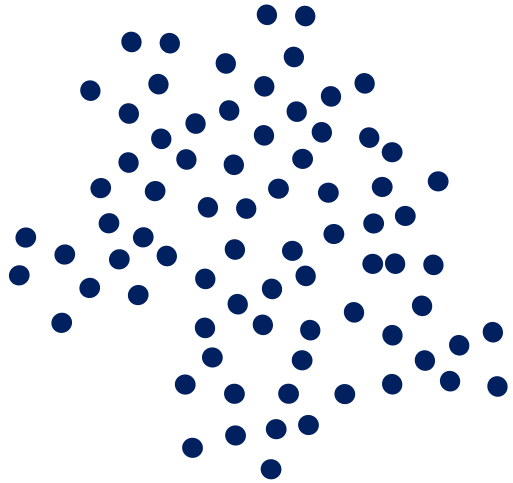
Approach: Selecting reference interval approach

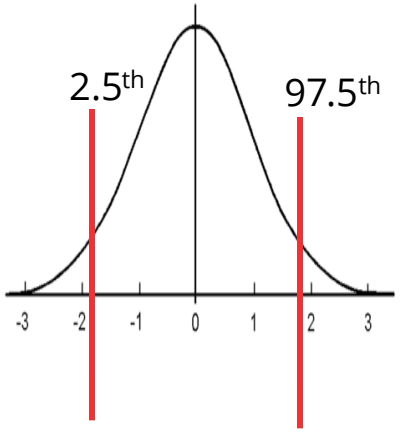
LIS



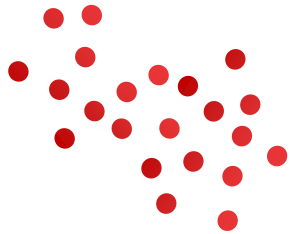


"healthy" subpopulation





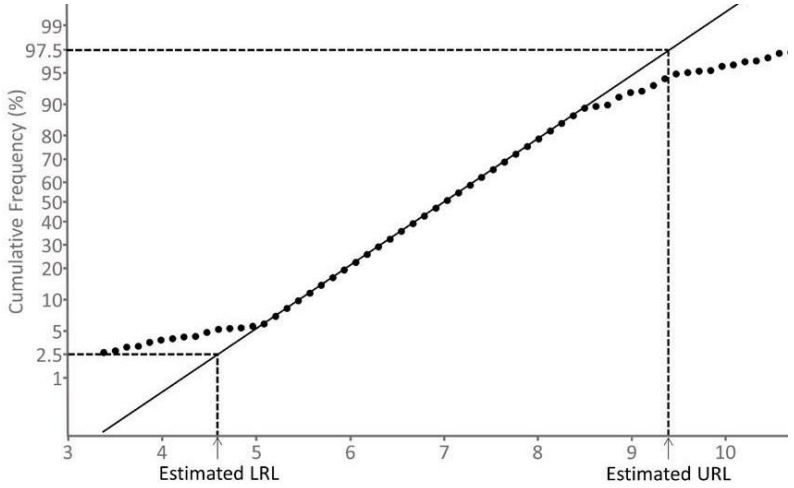
"non-healthy" subpopulation



Approach: Selecting reference interval approach

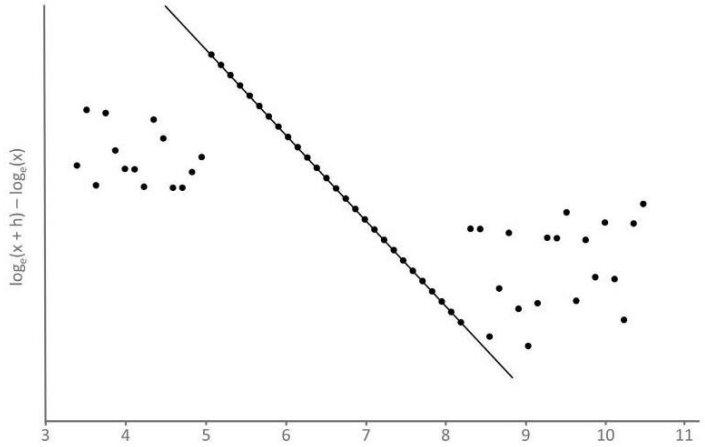
Available Indirect Approaches (1960-2007)

Hoffman Method (1963)



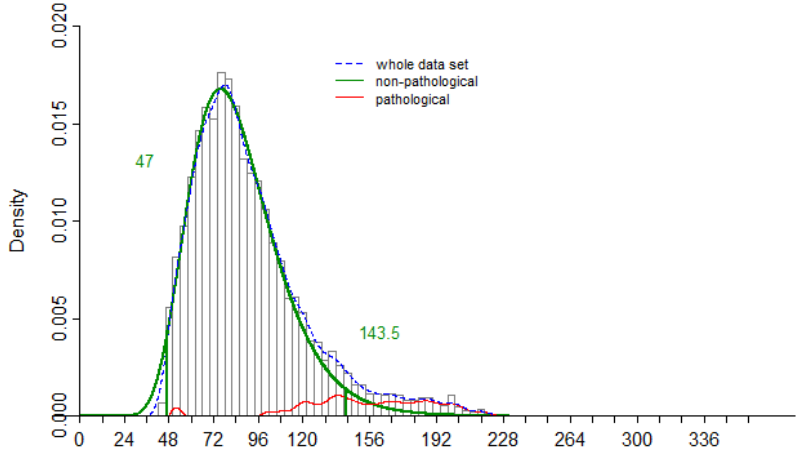
- *Plot the cumulative frequency of the distribution on a normal probability paper*
- *Reference interval extrapolated through linear regression*

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"*

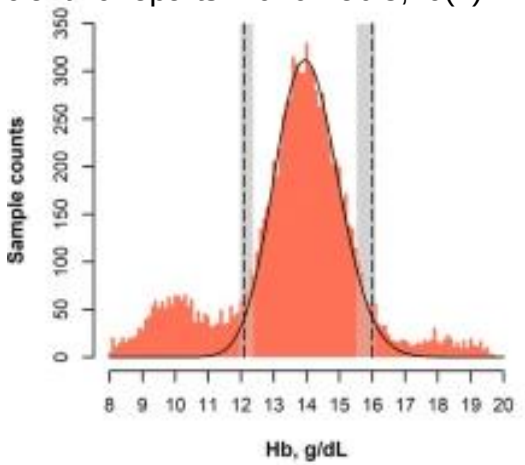
The Clinical biochemist Reviews. 2019 May;40(2):99.

Approach: Selecting reference interval approach

Available Indirect Approaches (2020-2022)

Kosmic (2020)

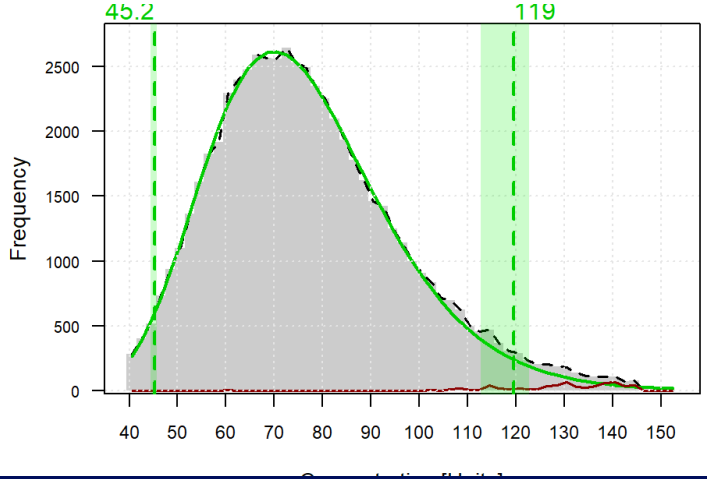
Scientific reports. 2020 Feb 3;10(1):1-8.



- More recent generation of the TML method
- Establishes reference limits from mixed distributions using truncation points and the Kolmogorov-Smirnov distance
- Computational advances (time for RI calculation)

RefineR (2021)

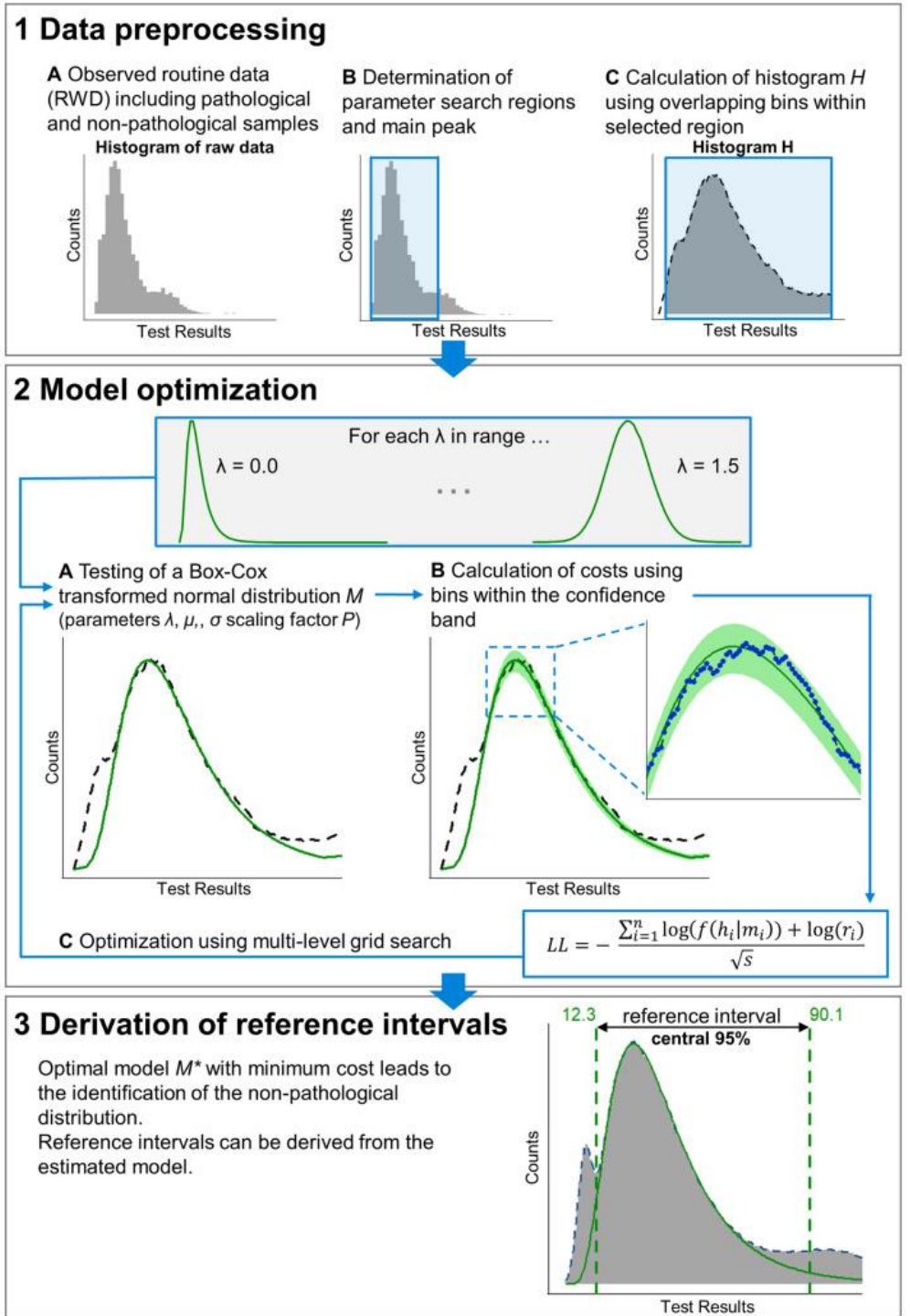
Scientific reports. 2021 Aug 6;11(1):1-7.



- Uses an inverse and unbiased modeling approach with no input parameters
- Yields superior results to kosmic when challenged with a high proportion of pathological samples
- Computational advances (CI calculation)

RefineR Algorithm

Ammer T, Schützenmeister A, Prokosch HU, Rauh M, Rank CM, Zierk J. refineR: a novel algorithm for reference interval estimation from real-world data. Scientific reports. 2021 Aug 6;11(1):1-7.

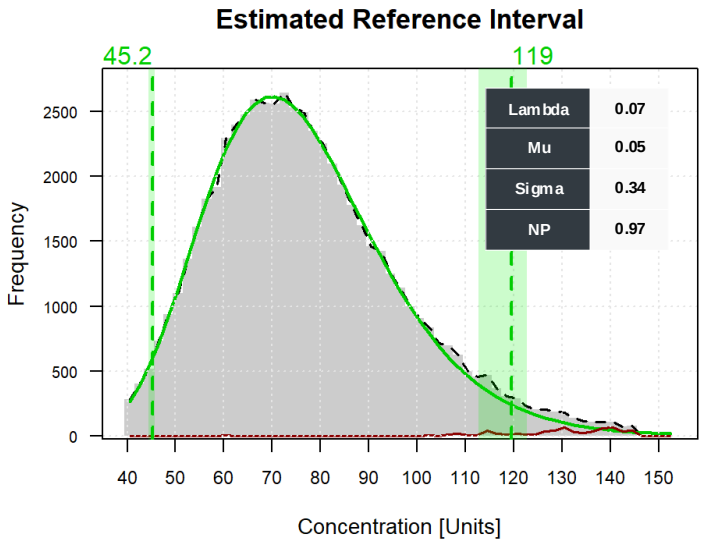


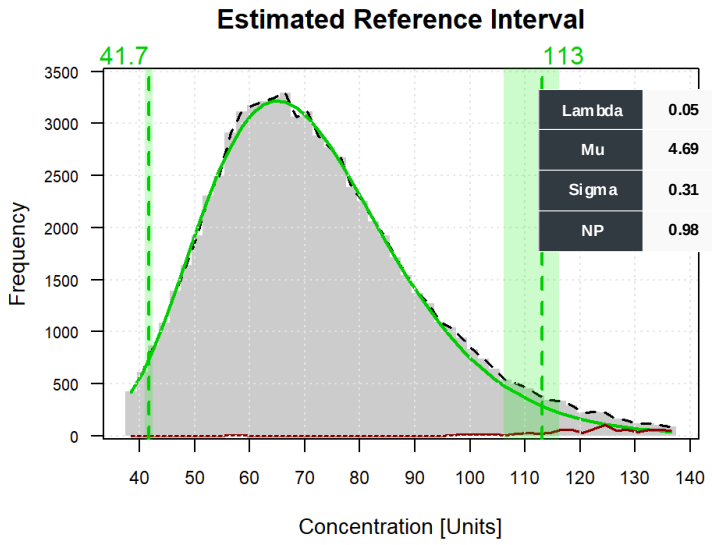
Analyzing the Data:

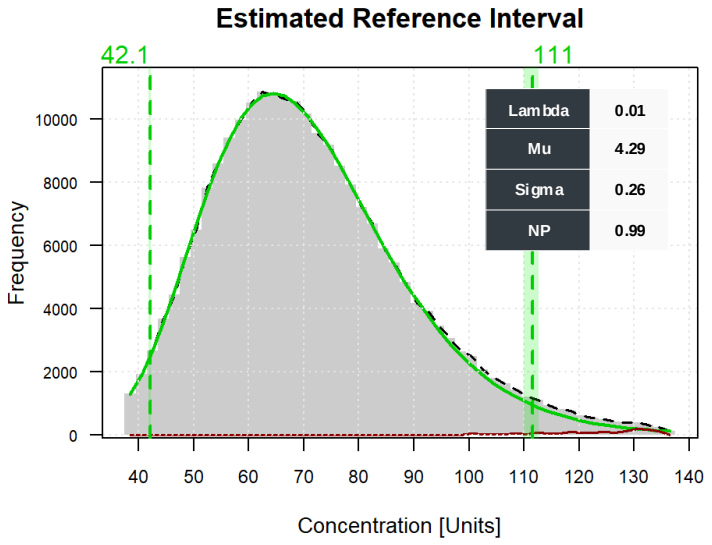
Example – Alkaline Phosphatase

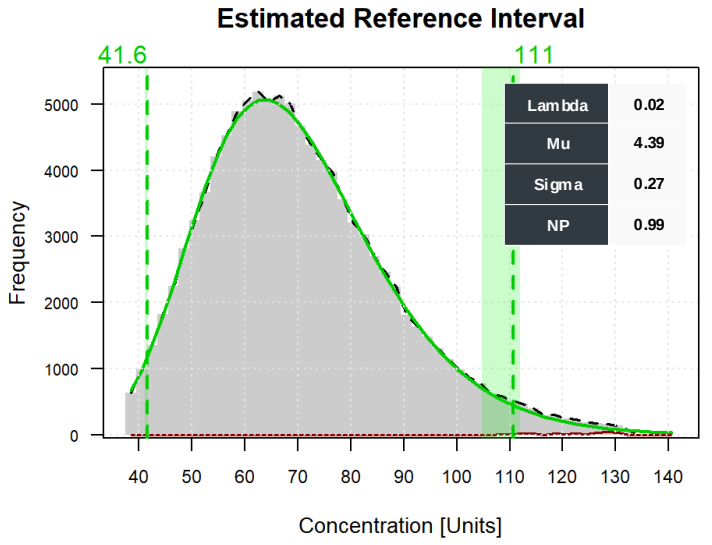
5 ***Establish RI for each partition***

- ✓ ***Use refineR method to establish reference intervals for each partition***







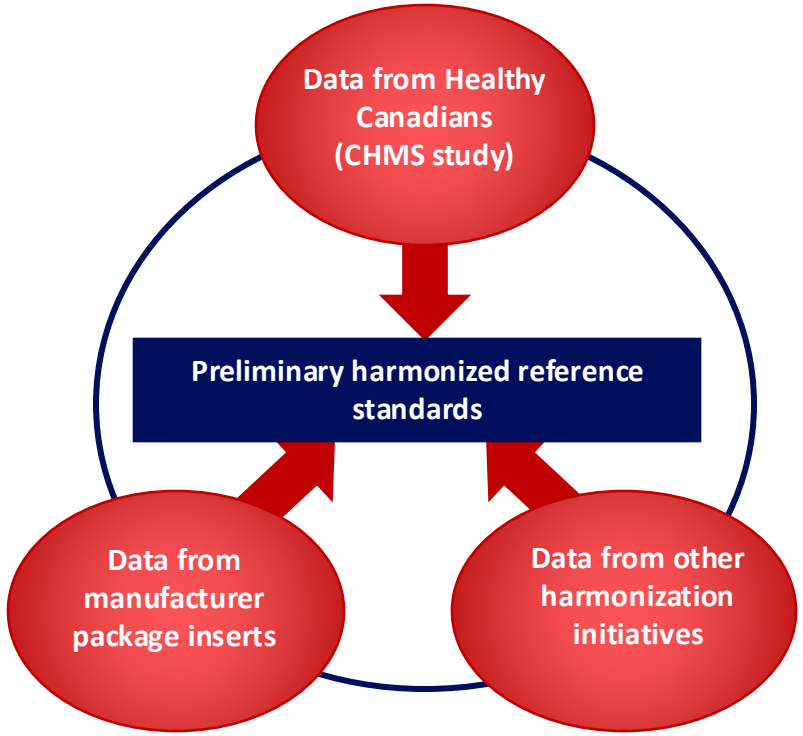


*displayed in U/L

Analyzing the Data:
Example – Alkaline Phosphatase

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*



	Indirect Analysis of Provincial Data					Direct International Initiatives*					hRI
	Advia – AB	Cobas – BC	Cobas – ON1	Cobas – ON2	All	CHMS	AHRIA	AUSS	NORIP	UK	
N	488526	754661	2581443	1033758	4858388						*19-39y M:* **40-115 U/L**
LL *19-39y M*	45 [44, 46]	42 [41, 42]	42 [42, 42]	42 [41, 42]	42 [42, 42]	50	30	43	35	30	*19-39y F:* **35-105 U/L**
UL *19-39y M*	119 [113, 123]	113 [106, 116]	111 [110, 113]	111 [105, 112]	113 [111, 113]	116	110	112	105	130	
LL *19-39y F*	37 [37, 38]	34 [34, 35]	35 [34, 35]	35 [34, 35]	35 [34, 35]	46		32			*40-79y:* **40-120 U/L**
UL *19-39 F*	115 [111, 117]	102 [93, 104]	100 [90, 106]	95 [87, 101]	100 [91, 104]	122		96			
LL *60-79y*	43 [42, 45]	40 [40, 41]	40 [40, 42]	40 [39, 40]	41 [40, 41]						
UL *60-79y*	122 [113, 128]	115 [113, 121]	115 [113, 120]	119 [112, 120]	120 [114, 121]						

CSCC hRI WG: Preliminary Recommendations & Next Steps

Analyte	Partition	hRI
Analyte	**Partition**	**hRI (SI)**
Alkaline Phosphatase (ALP)	19 to 39 years M	40–115 U/L
	19 to 39 years F	35–105 U/L
	40 to 79 years	40–120 U/L
Alanine Aminotransferase (ALT)	19 to 79 years M	<33 U/L
	19 to 79 years F	<25 U/L
Albumin (BCG only)	19 to 79 years	40–50 g/L
Bilirubin, total	19 to 79 years M	<20 µmol/L
	19 to 79 years F	<16 µmol/L
Calcium	19 to 79 years	2.15–2.55 mmol/L
Carbon Dioxide, total	19 to 79 years	22–30 mmol/L
Chloride	19 to 79 years	97–107 mmol/L
Creatinine	19 to 79 years M	65–106 µmol/L
	19 to 79 years F	50–90 µmol/L
Free Thyroxine (FT4)	19 to 79 years	None
Lactate Dehydrogenase (LDH)	19 to 79 years	120–240 U/L
Magnesium	19 to 79 years	0.73–1.00 mmol/L
Phosphate	19 to 79 years	0.80–1.45 mmol/L
Potassium	19 to 79 years	3.8–5.1 mmol/L
Sodium	19 to 79 years	135–145 mmol/L
Thyroid Stimulating Hormone (TSH)	19 to 79 years	0.60–4.00 mIU/L

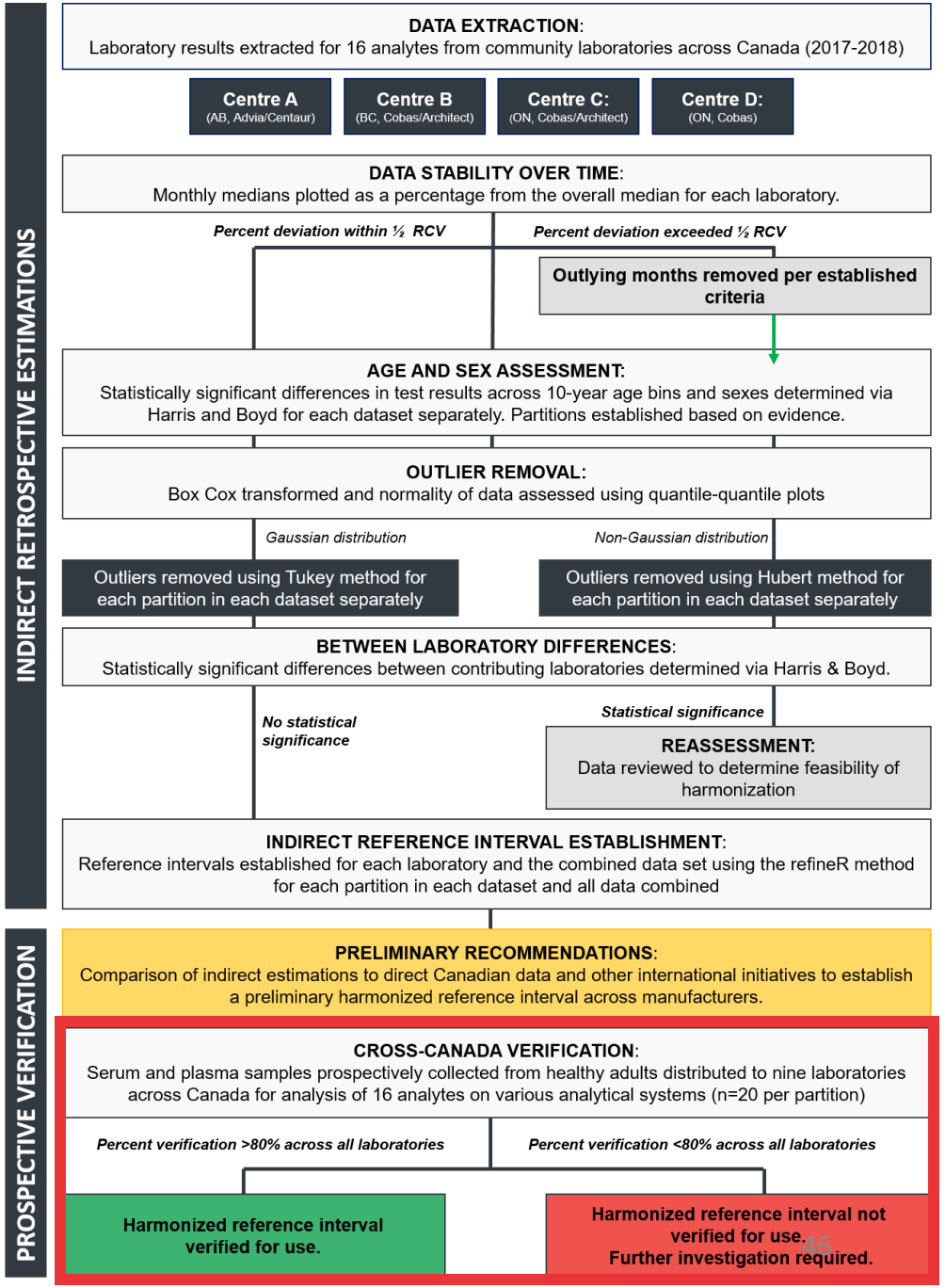
Establishment of preliminary hRIs for 16 parameters

Limitations to the current data:

- *Only three manufacturers represented*
- *Only three provinces represented*
- *All data contributing centres use serum as preferred matrices*

How can they be addressed prior to implementation?

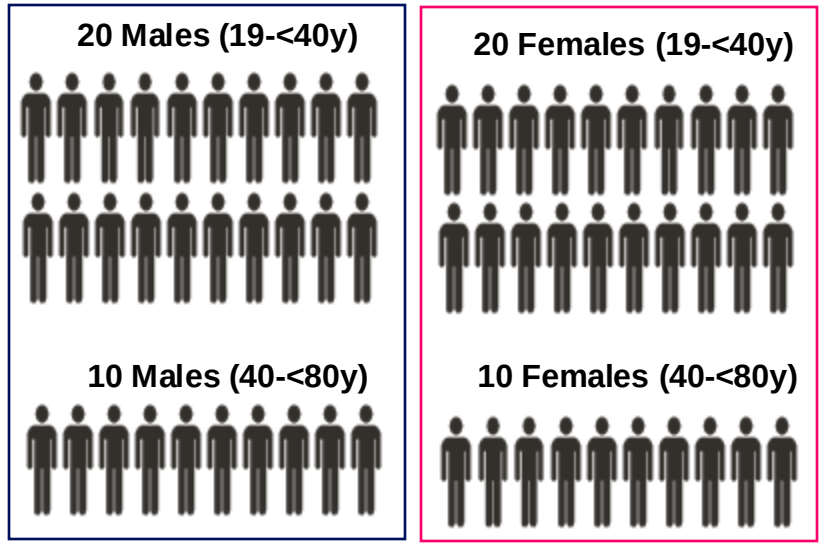
Verifying the Data



CSCC hRI WG: Cross-Canadian Verification Study

Objective: To verify proposed hRIs on major analytical platforms across Canada using serum and plasma samples prospectively collected from healthy adults.

Study Design:



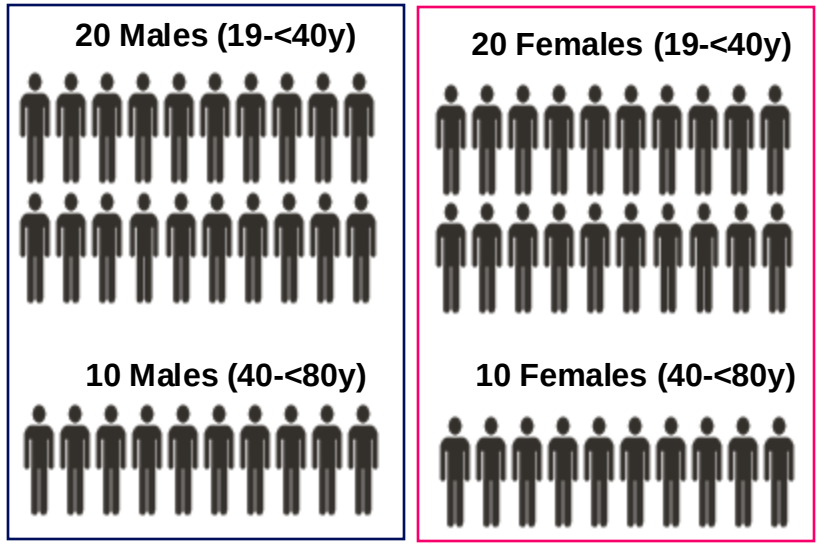
60 adult volunteers *recruited from the community with the following age/sex distribution.*

- 30 individuals were recruited from Ontario
- 30 individuals were recruited from Alberta
- Ethnic distribution is proportional to the 2016 Canadian Census
- **Exclusion criteria included**:
  - Pregnancy
  - History of chronic illness
  - History of acute illness within 7 days of collection
  - Regular use of prescribed medication

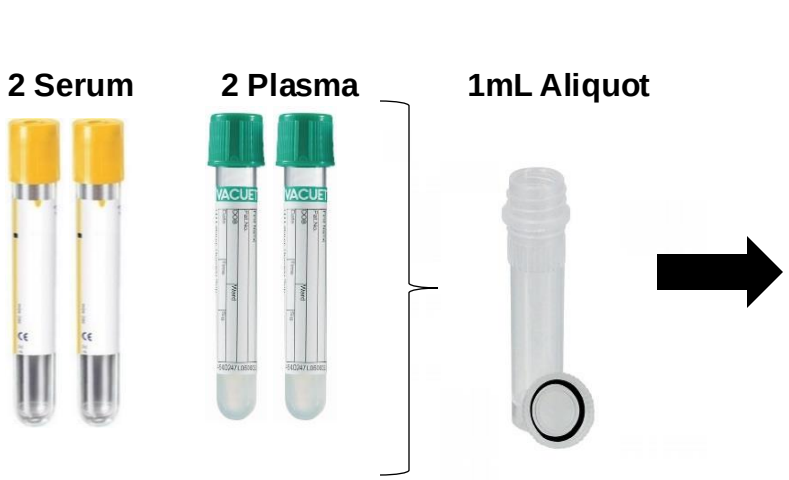
CSCC hRI WG: Cross-Canadian Verification Study

Objective: To verify proposed hRIs on major analytical platforms across Canada using serum and plasma samples prospectively collected from healthy adults.

Study Design:



60 adult volunteers *recruited from the community with the following age/sex distribution.*



2 serum and 2 plasma tubes will be collected from each participant

Distribution to 9 laboratories across Canada for analysis of all 16 analytes

CSCC hRI WG: Participating Laboratories

Province	Manufacturer
Newfoundland	Architect
Quebec	Atellica
Alberta	Cobas
Ontario	Cobas
Ontario	Cobas
Alberta	DxC
British Columbia	Integra
New Brunswick	Vitros
Ontario	Vitros

SIEMENS Roche BECKMAN COULTER Abbott Ortho Clinical Diagnostics

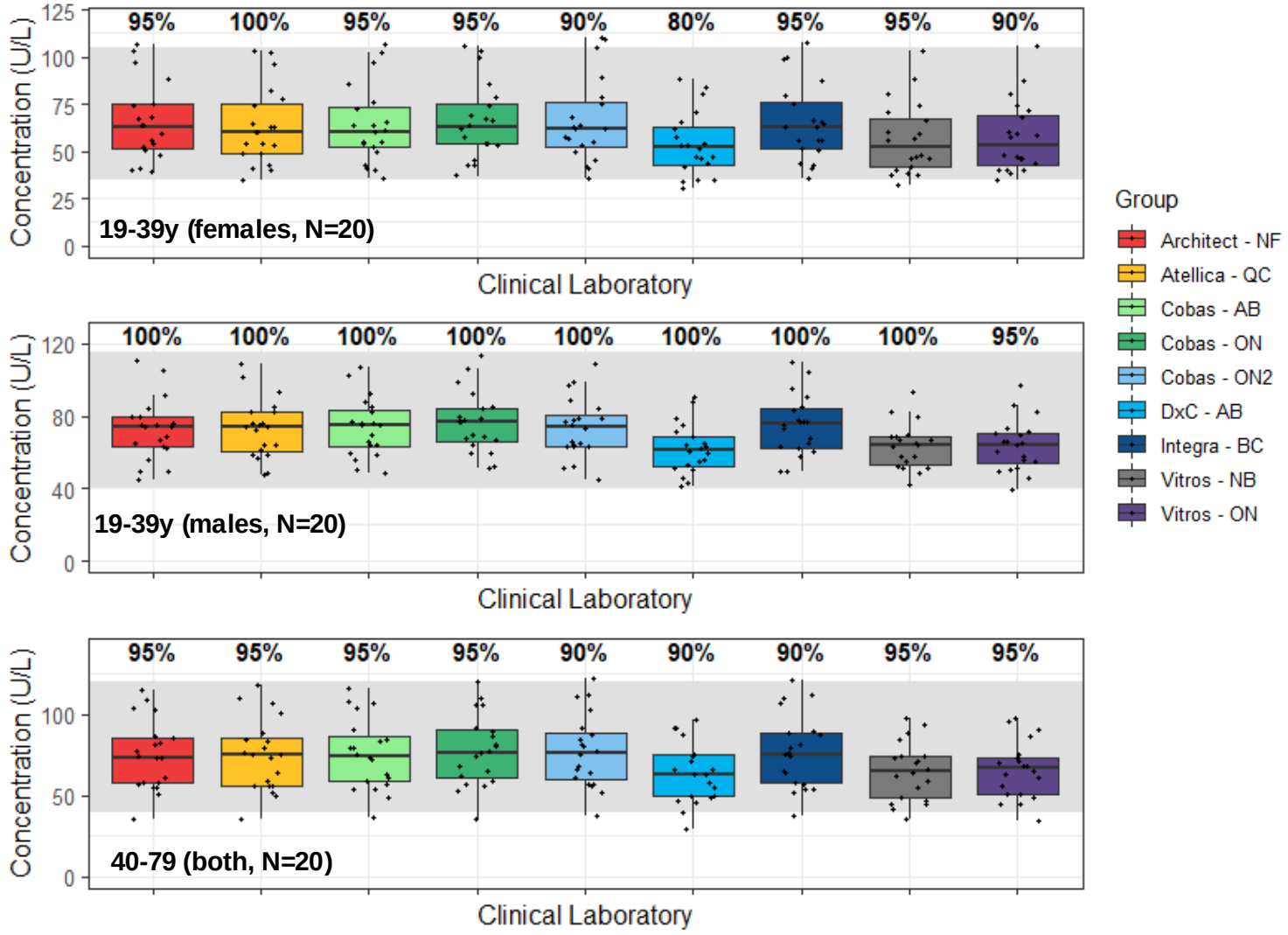
Verifying the Data:

Example – Alkaline Phosphatase

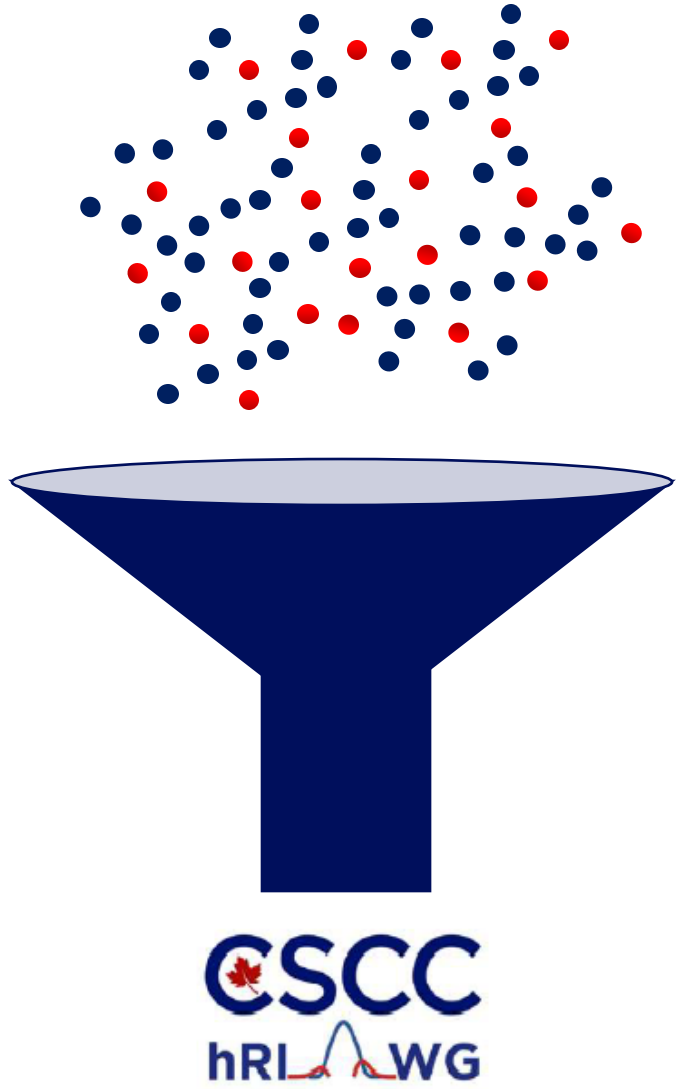
6 ***Compare and assess***

- ✓ ***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***

Verification plot: Results from samples collected for healthy Canadian adults graphed by laboratory using boxplot (median, IQR, tails: Q1/Q3+IQR). Percent verification notated for each laboratory, grey area indicates proposed hRI



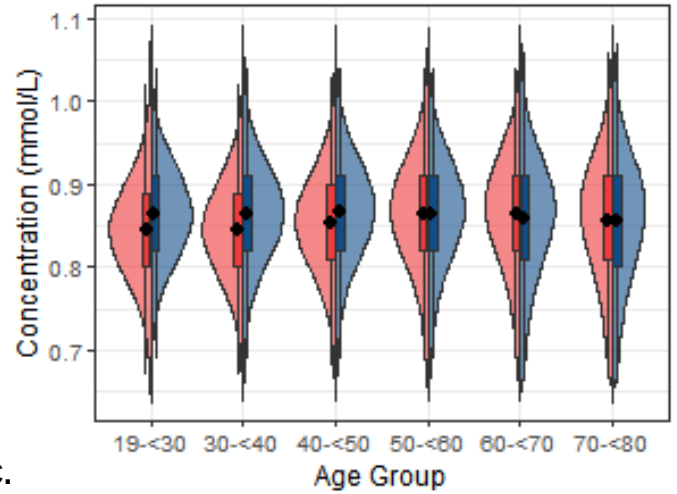
Reviewing the Data



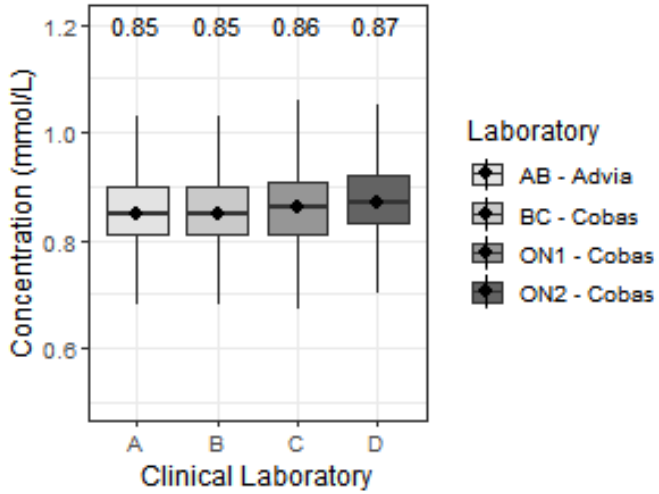
Magnesium

Direct and Indirect Canadian Data Supports Harmonization

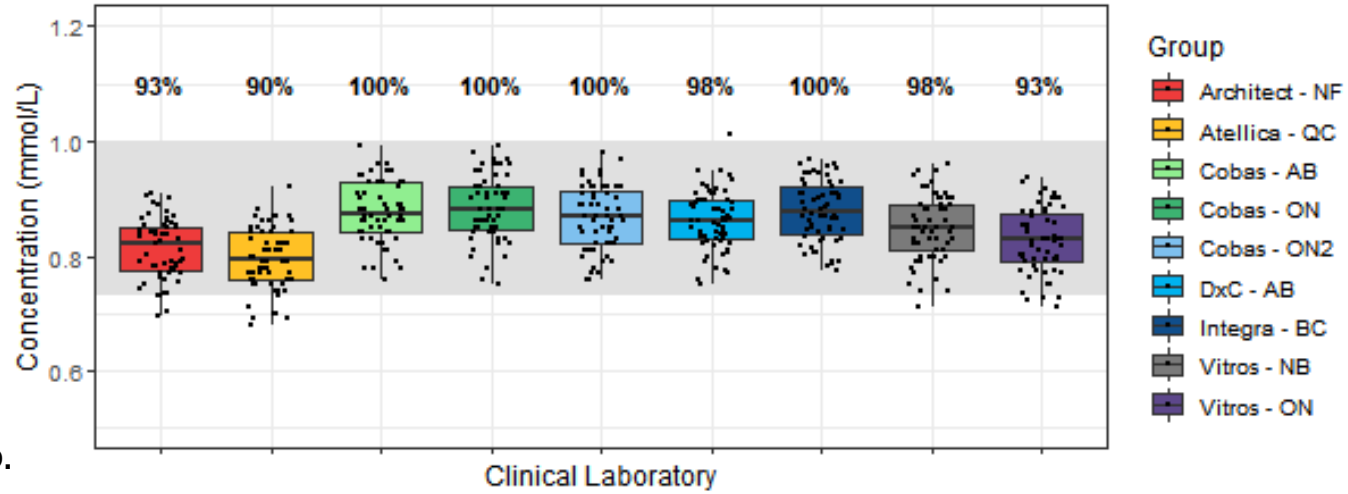
A.



B.



C.



D.

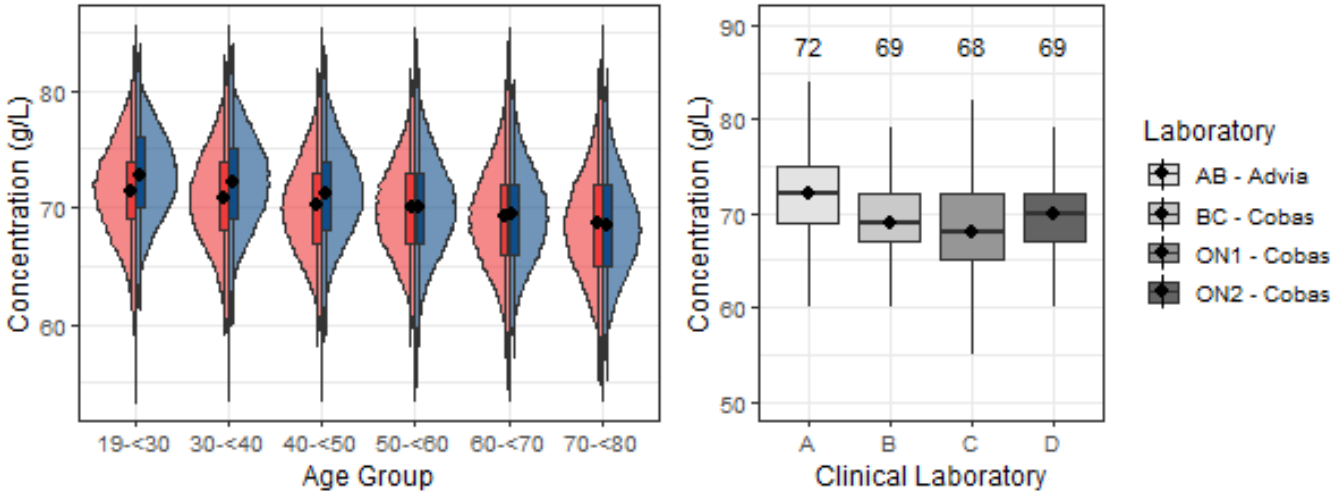
	Indirect Analysis of Provincial Data					Direct International Initiatives*				hRI
	Advia – AB	Cobas – BC	Cobas – ON1	Cobas – ON2	All	AHRIA	AUSSIE	NORIP	UK	
N	203541	124417	423031	157662	908651					*19-79y:* **0.73-1.00 mmol/L**
LL *19-79y*	0.73 [0.73, 0.73]	0.74 [0.72, 0.75]	0.73 [0.72, 0.74]	0.75 [0.74, 0.76]	0.73 [0.73, 0.74]	0.70	0.77	0.71	0.70	
UL *19-79y*	0.97 [0.97, 0.98]	0.99 [0.98, 0.99]	0.99 [0.99, 1.00]	1.00 [1.00, 1.01]	1.00 [0.99, 1.00]	1.10	1.04	0.94	1.00	

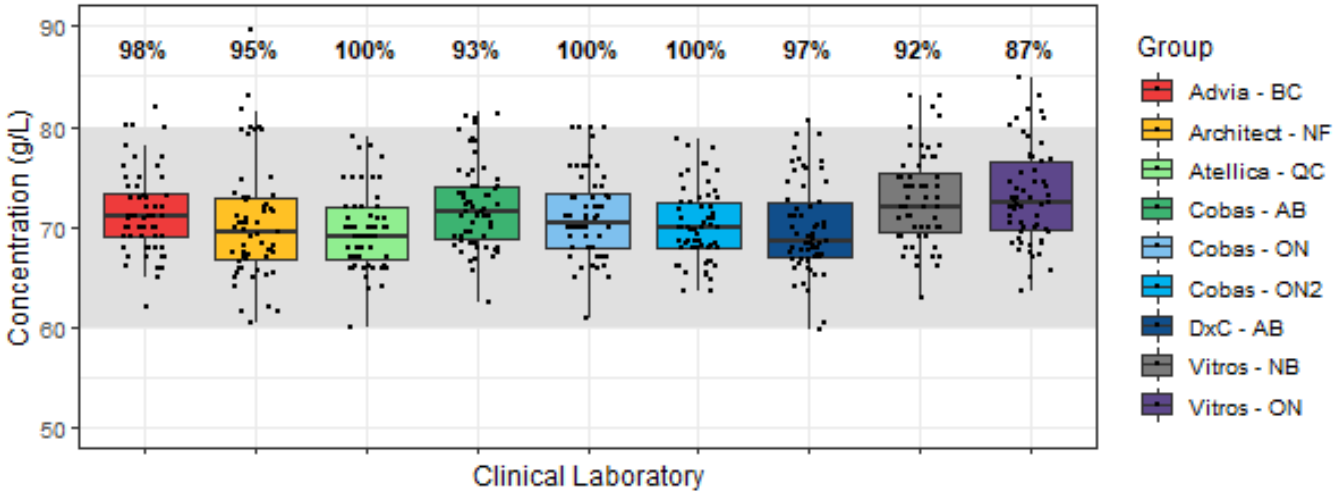
Result Summary:

- Approximately **900,000 results** evaluated
- No age/sex-specific differences observed
- Recommend hRI verified in all nine Canadian Laboratories participating in cross-Canada verification program (*serum and plasma*)

Total Protein

Direct and Indirect Canadian Data Supports Harmonization





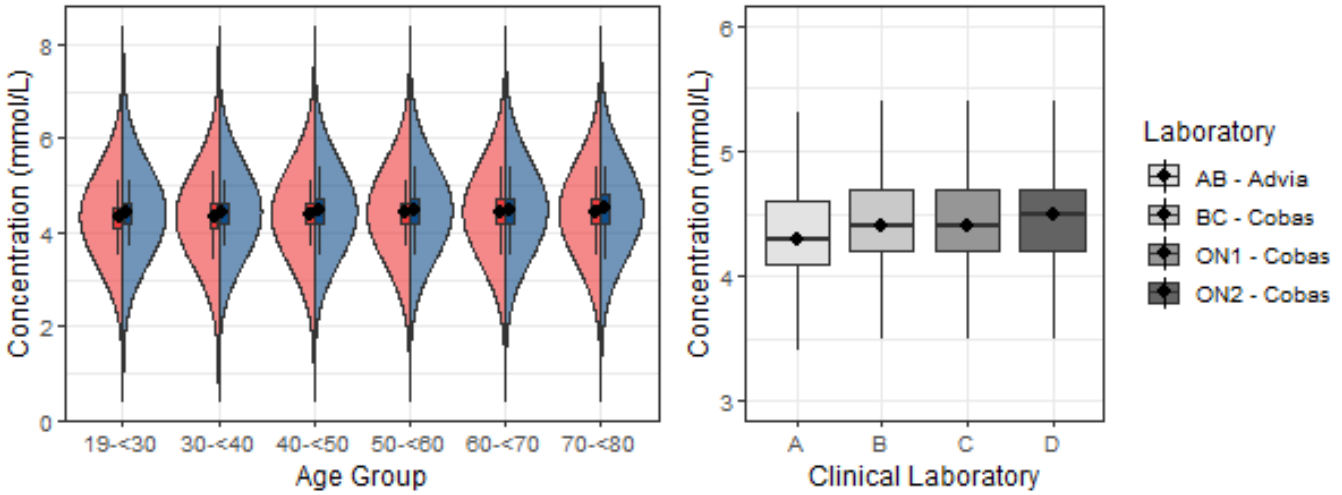
	Indirect Analysis of Provincial Data					Direct International Initiatives*					hRI
	Advia – AB	Cobas – BC	Cobas – ON1	Cobas – ON2	All	CHMS	AHRIA	AUSS	NORIP	ACOG	
N	118308	160655	58144	25097	362204						*19-79y:* **60-80 g/L**
LL *19-79y*	63 [63, 64]	61 [63, 64]	59 [59, 60]	61 [61, 62]	62 [61, 62]	65	60	62	62	60	
UL *19-79y*	81 [80, 81]	78 [77, 78]	77 [77, 78]	78 [77, 78]	79 [79, 79]	78	80	79	78	80	

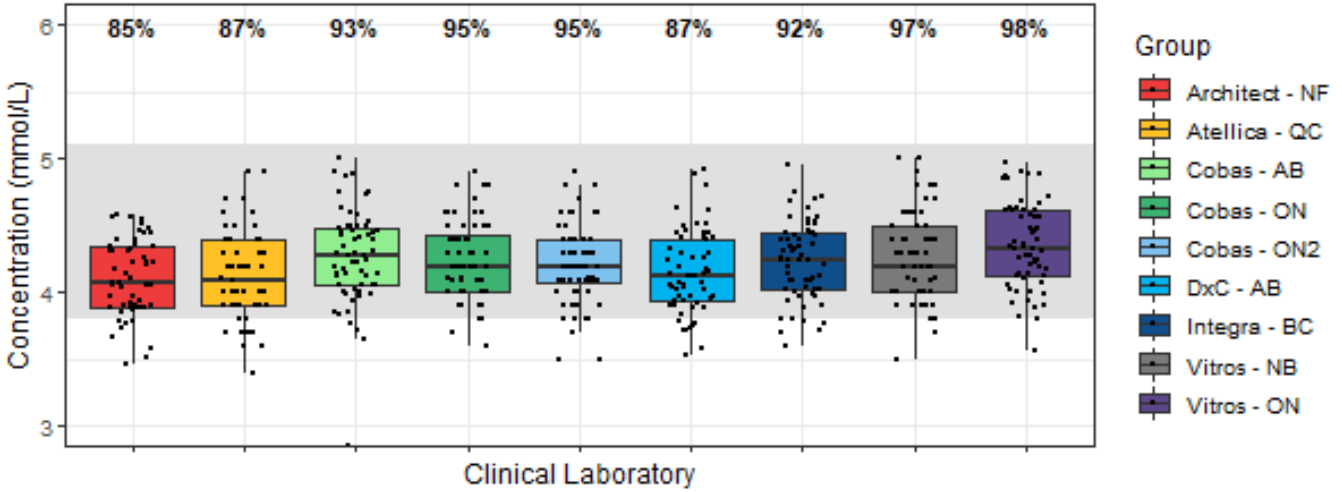
Result Summary:

- Approximately **300,000 results** evaluated
- No age/sex-specific differences observed
- Recommend hRI verified in all nine Canadian Laboratories participating in cross-Canada verification program (*serum and plasma*)

Potassium

Direct and Indirect Canadian Data Supports Harmonization





	Indirect Analysis of Provincial Data					Direct International Initiatives*					hRI
	Advia – AB	Cobas – BC	Cobas – ON1	Cobas – ON2	All	CHMS	AHRIA	AUSS	NORIP	UK	
N	773026	1583639	3930985	1512821	7800471						*19-79y:* **3.8-5.1 mmol/L**
LL *19-79y*	3.7 [3.70, 3.74]	3.8 [3.77, 3.84]	3.8 [3.77, 3.82]	4.1 [3.93, 4.13]	3.9 [3.89, 3.95]	3.8	3.5	3.7	3.6	3.5	
UL *19-79y*	5.1 [4.96, 5.07]	5.1 [4.97, 5.11]	5.1 [4.99, 5.10]	4.7 [4.68, 4.92]	4.9 [4.86, 4.92]	4.9	5.2	4.9	4.6	5.3	

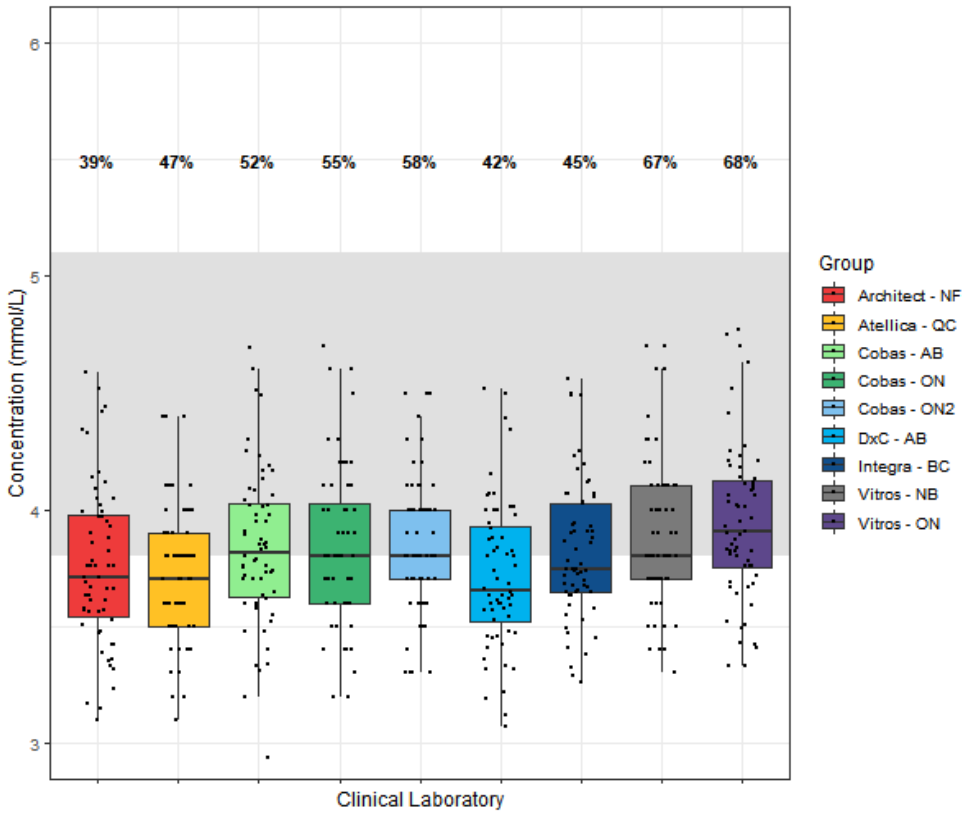
Result Summary:

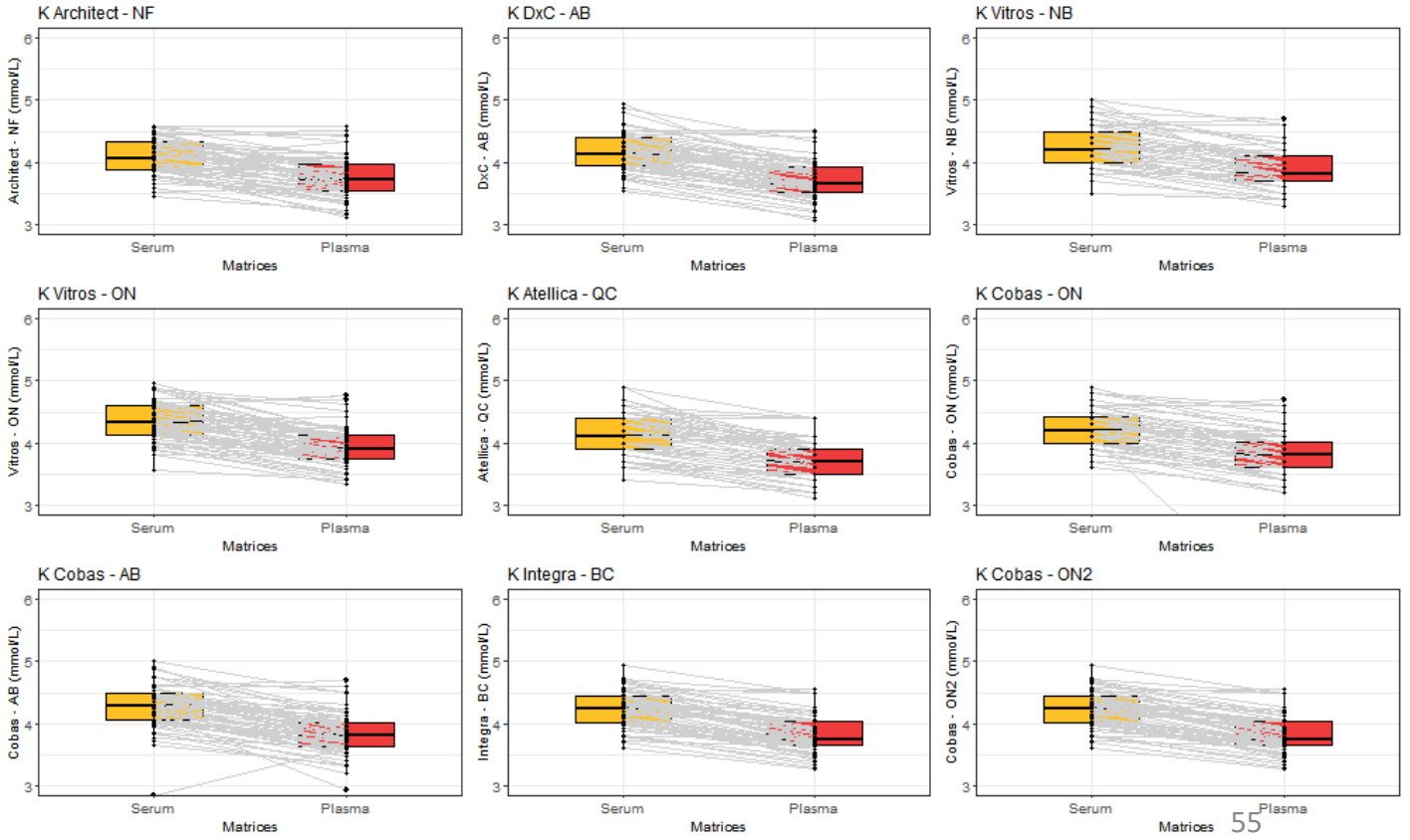
- Approximately **7.8 million results** evaluated
- No age/sex-specific differences observed
- Recommend hRI verified in all nine Canadian Laboratories participating in cross-Canada verification program in ***serum only***

Potassium

Plasma vs Serum:

- Plasma potassium results were markedly lower as compared to paired sera
- Recommended hRI of **3.8-5.1 mmol/L** did not verify as per CSCC hRI WG criteria in plasma specimens
- A separate recommendation for plasma potassium is needed





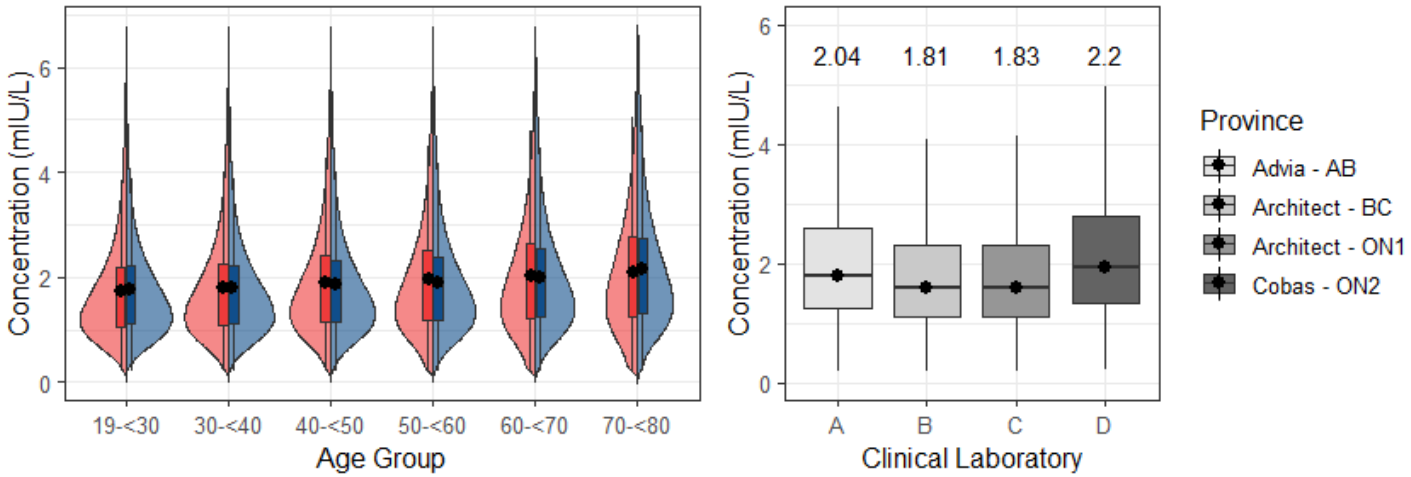
TSH

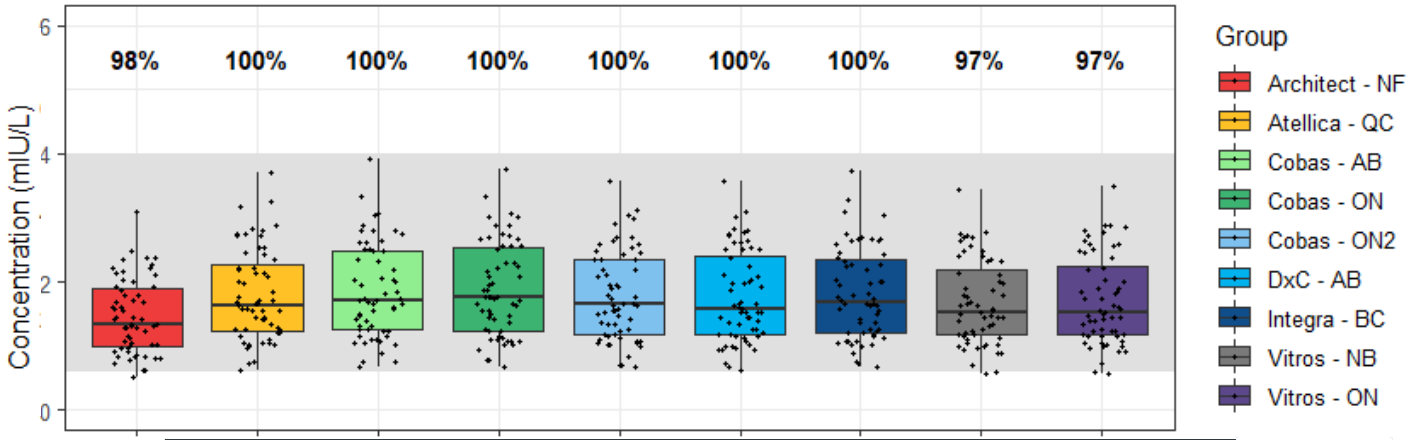
I

Direct and Indirect Canadian Data Supports Harmonization

Recommendation: 0.4-4.00 mIU/L

Thyroid 2014;24:1670-751. doi:10.1089/thy.2014.0028





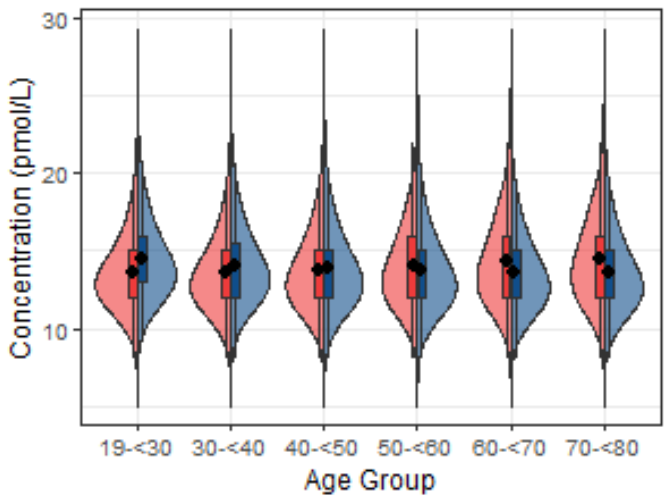
	Indirect Analysis of Provincial Data					Direct International Initiatives*				hRI
	Centaur – AB	Arch – BC	Arch – ON	Cobas – ON	All	ATA	AUSS	NHANES	NORIP	
N	1121045	1648061	4207623	1688546	8665275					*19-79y:* **0.60-4.00 mIU/L**
LL *19-79y*	0.67 [0.63, 0.68]	0.59 [0.58, 0.60]	0.60 [0.56, 0.60]	0.70 [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, 4.59]	4.45 [4.04, 4.53]	5.45 [5.13, 5.60]	4.48 [4.02, 4.85]	4.0	3.40	3.60	4.12	

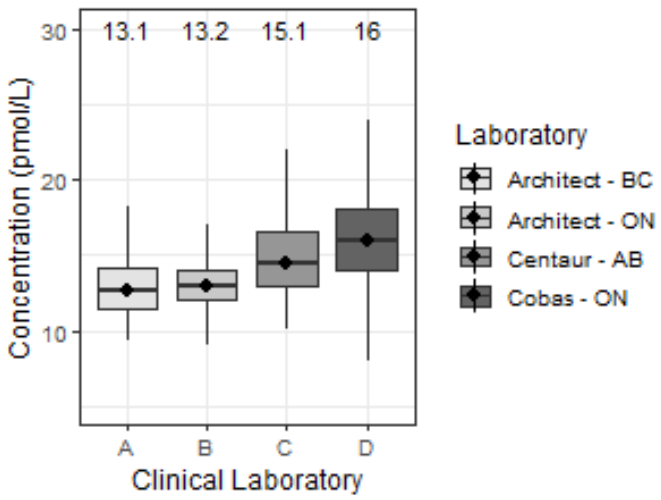
Result Summary:

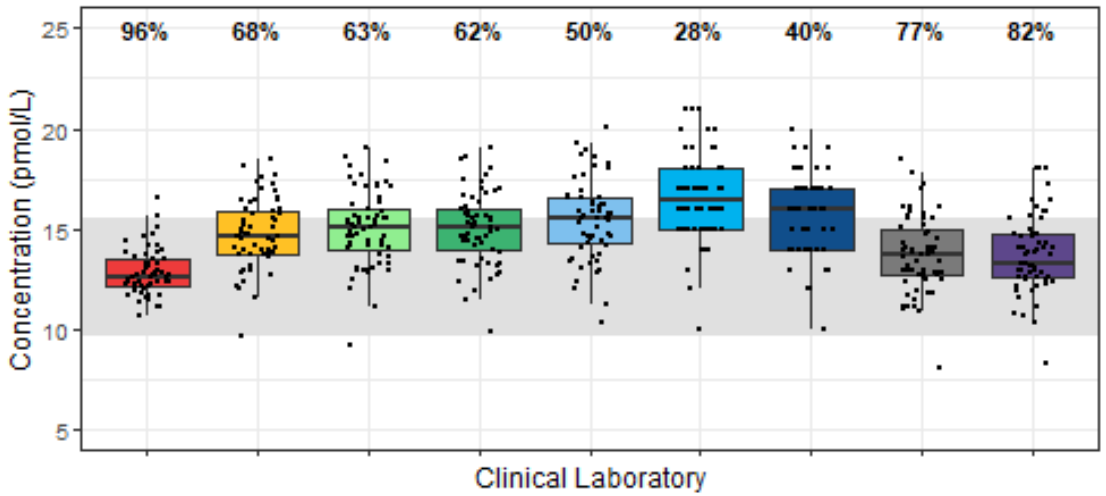
- Approximately **9 million results** evaluated
- No age/sex-specific differences observed
- Upper reference limits ranged from **4.05-5.26 mIU/L** across provincial community laboratories
- Recommended hRI verified in all nine Canadian Laboratories participating in cross-Canada verification program (*serum and plasma*)
- Results suggest excellent concordance between laboratories and acceptable analytical standardization of TSH for RI harmonization

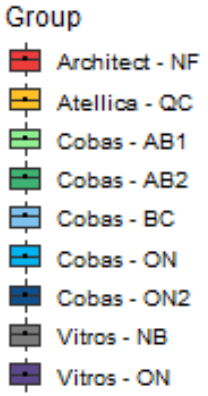
Free T4

Direct and Indirect Canadian Data do NOT Support Harmonization









	Indirect Analysis of Provincial Data					Direct International Initiatives*			hRI
	Advia – AB	Centaur –BC	Architect – ON1	Cobas – ON2	All*	AUSSIE	NORIP	ATA	
N	124713	196029	972585	376870	1664797				*19-79y:* **None**
LL *19-79y*	10.4 [10.2, 10.5]	9.2 [9.1, 9.6]	9.4 [9.4, 9.8]	12.6 [11.9, 14.0]	9.7	10.7	10.9	None	
UL *19-79y*	19.2 [18.1, 19.4]	15.4 [15.1, 16.4]	15.2 [15.1, 16.0]	18.4 [17.2, 18.9]	15.5	17	16.9	None	

Result Summary:

- Approximately **1.6 million results** evaluated
- No age/sex-specific differences observed
- Upper reference limits ranged from **16.8-20.5 pmol/L** across provincial community laboratories
- Data suggests hRIs are not appropriate for free T4 test interpretation and manufacturer-specific results RIs are needed

CSCC hRI WG: Key Takeaways

- A **novel big data analytics** approach was undertaken to define preliminary hRIs for 16 analytes:
  - (1) extraction of data from community reference laboratories across Canada
  - (2) assessment of outliers
  - (3) statistical evaluation of age, sex, and center-specific differences
  - (4) derivation of preliminary hRIs using the refineR method
  - (5) comparison of established hRIs to direct data in the healthy Canadian population.

- Robustness of these data was assessed through a **Cross-Canada Verification Study where results supported implementation of these recommendations**

- Showcases the power of big data and new statistical techniques to assist in addressing gaps in clinical service

Future work?

CSCC hRI WG: Next Steps

Finalize & Publish!

CSCC hRI WG: Next Steps

A

Knowledge-translation toolbox

Website

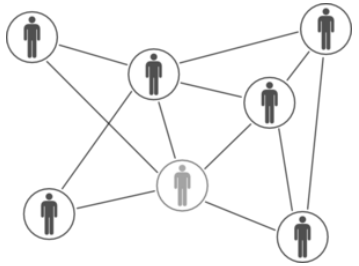
Instructional Video

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

Repeat for other analytes of interest!

Acknowledgments

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