Application of indirect algorithms to reference interval harmonization in Canada

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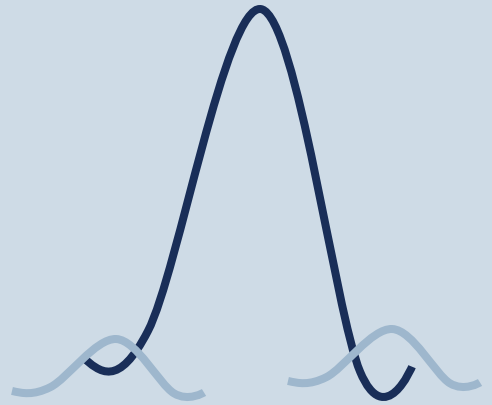
CSCC Working Group on Reference Interval Harmonization (hRI-WG)

IFCC Webinar – Principles and practice of indirect methods for RI establishment
November 21, 2023



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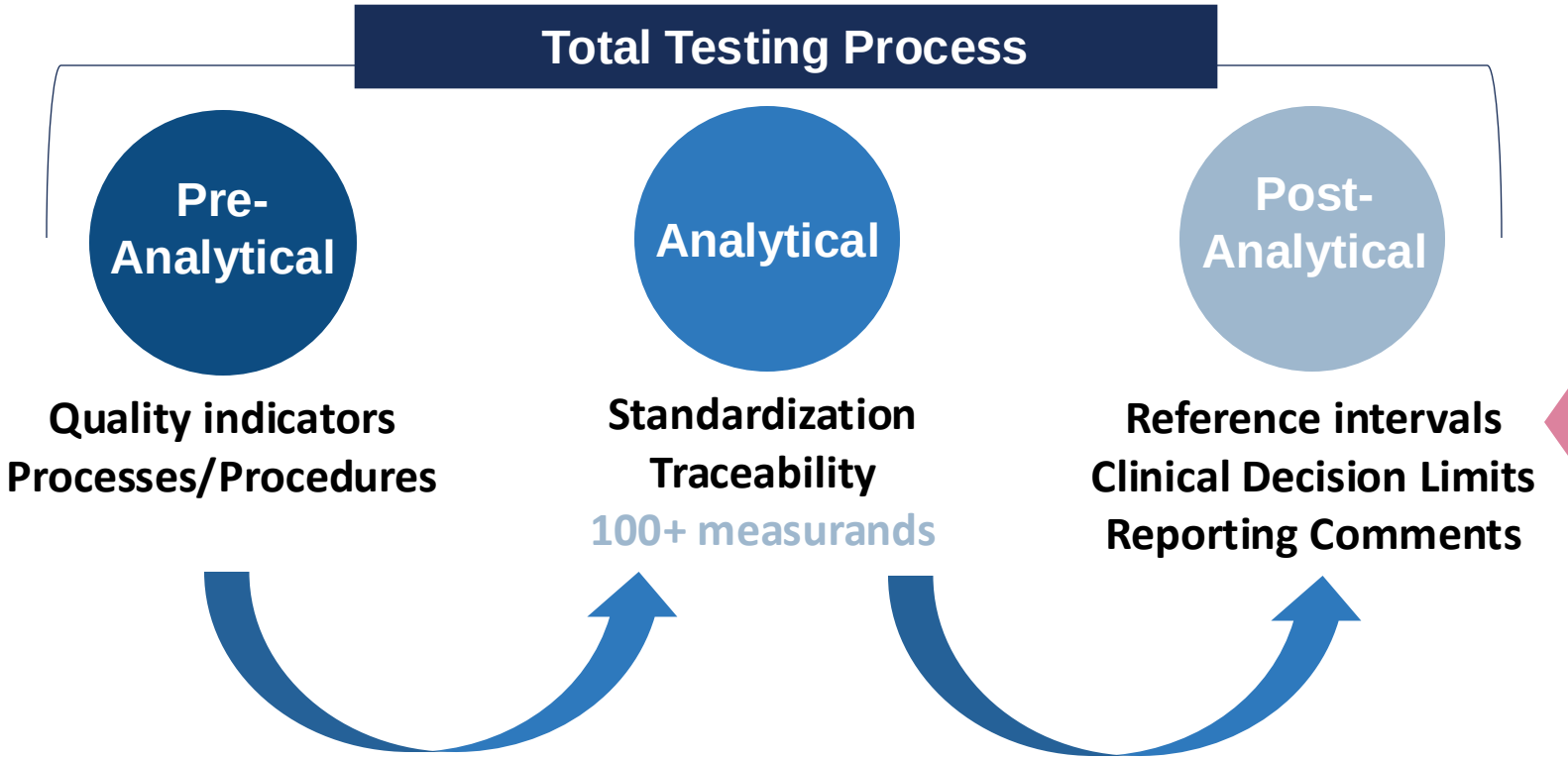
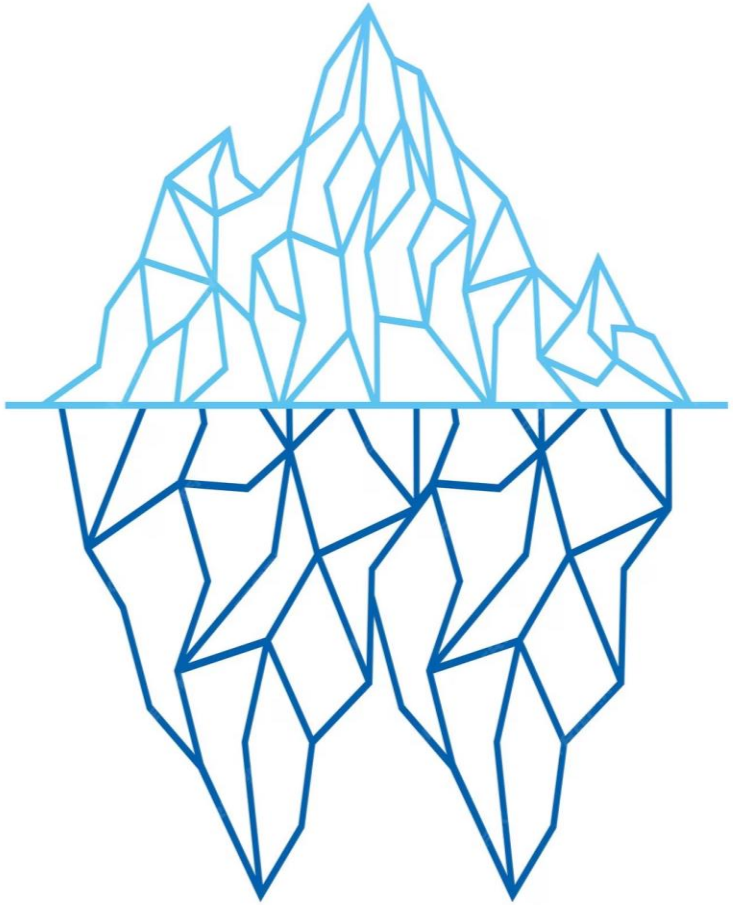
Importance of Harmonization in Laboratory Medicine

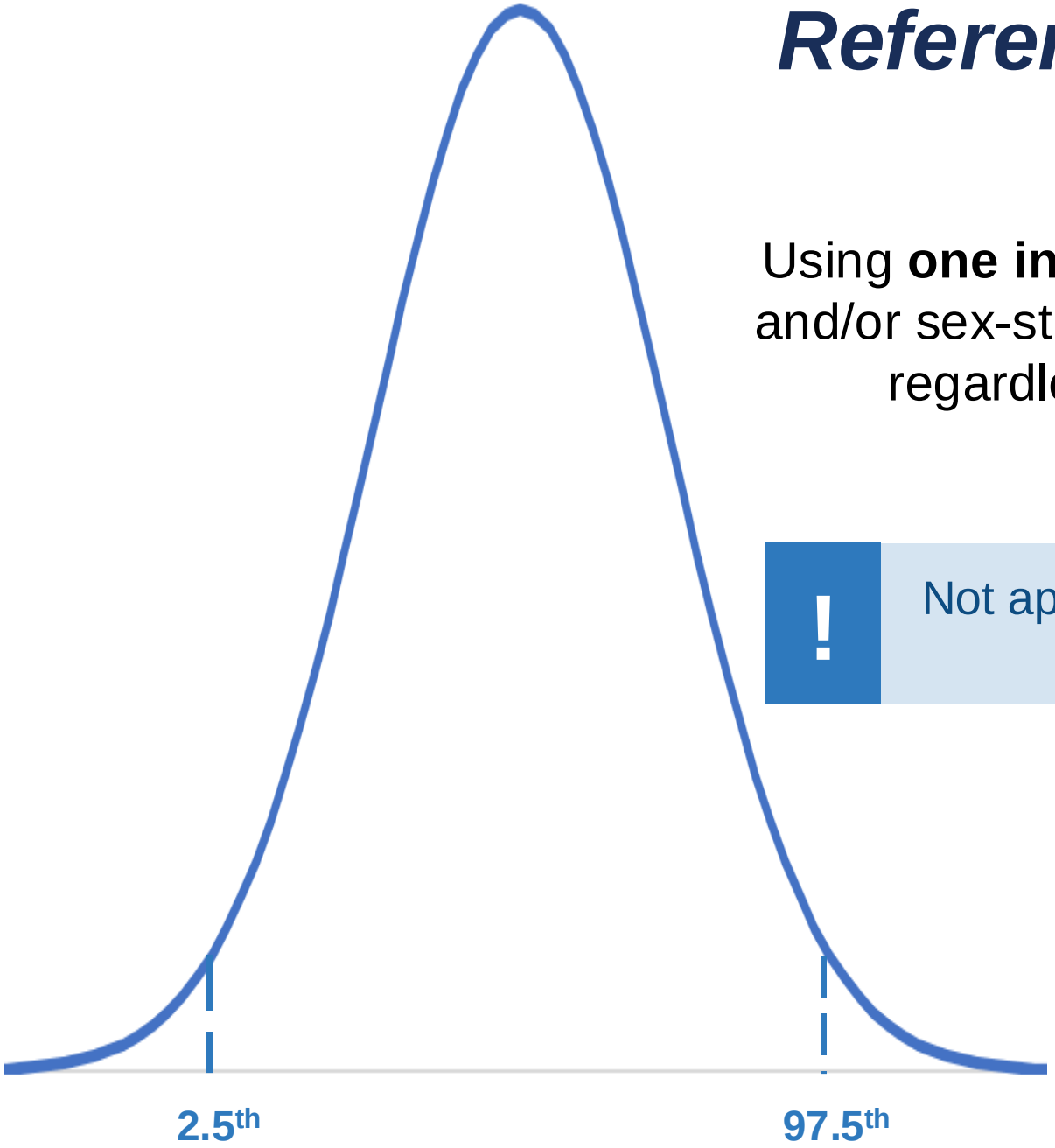
Harmonization: the equivalence of test results and interpretation among different routine measurement procedures over time and space according to defined analytical and clinical quality specifications





Plebani M. CCLM. 2013 Apr 1;51(4):741-51.

Reference Interval Harmonization:



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

! Not appropriate for measurands that demonstrate significant bias across assays

Driving Forces for Reference Interval Harmonization

Often assumed test results (or their interpretation) are **interchangeable**, regardless of the laboratory

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

Significant and unwarranted variation in RIs (same analytical methodology)

risk of misinterpreting results

(lack of appropriate follow-up, unnecessary investigations, and/or inappropriate resource utilization, clinical confusion)

Reference Interval Harmonization Efforts Globally

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CALIPER

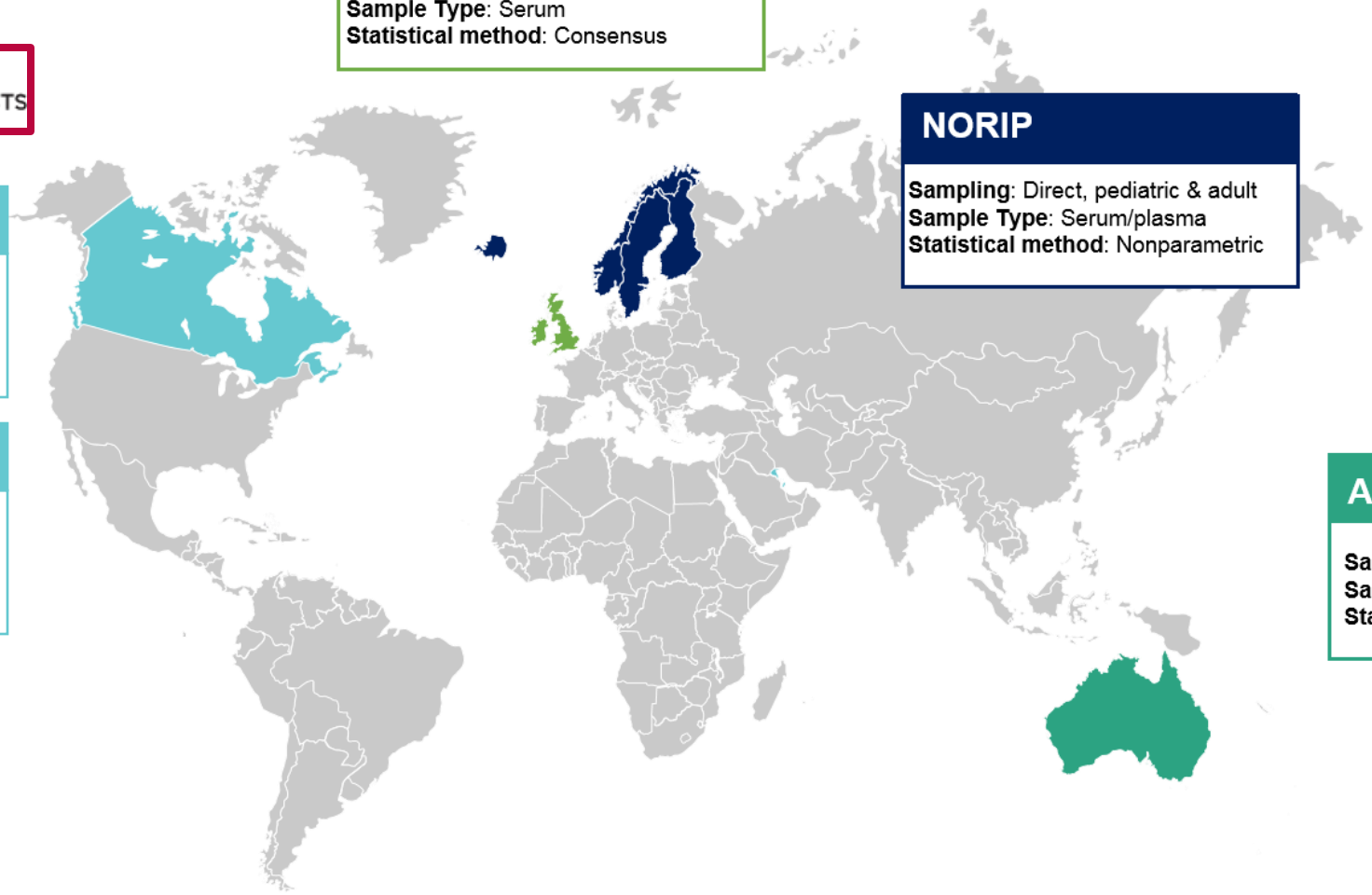
Sampling: direct, pediatric
Sample type: multiple
Statistical method: nonparametric

CSCC hRI-WG

Sampling: big data, adult
Sample type: serum/plasma
Statistical method: refineR

UK Pathology Harmony

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



NORIP

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

AHRIA & AHRIP

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

CSCC Working Group on Reference Interval Harmonization (hRI-WG)

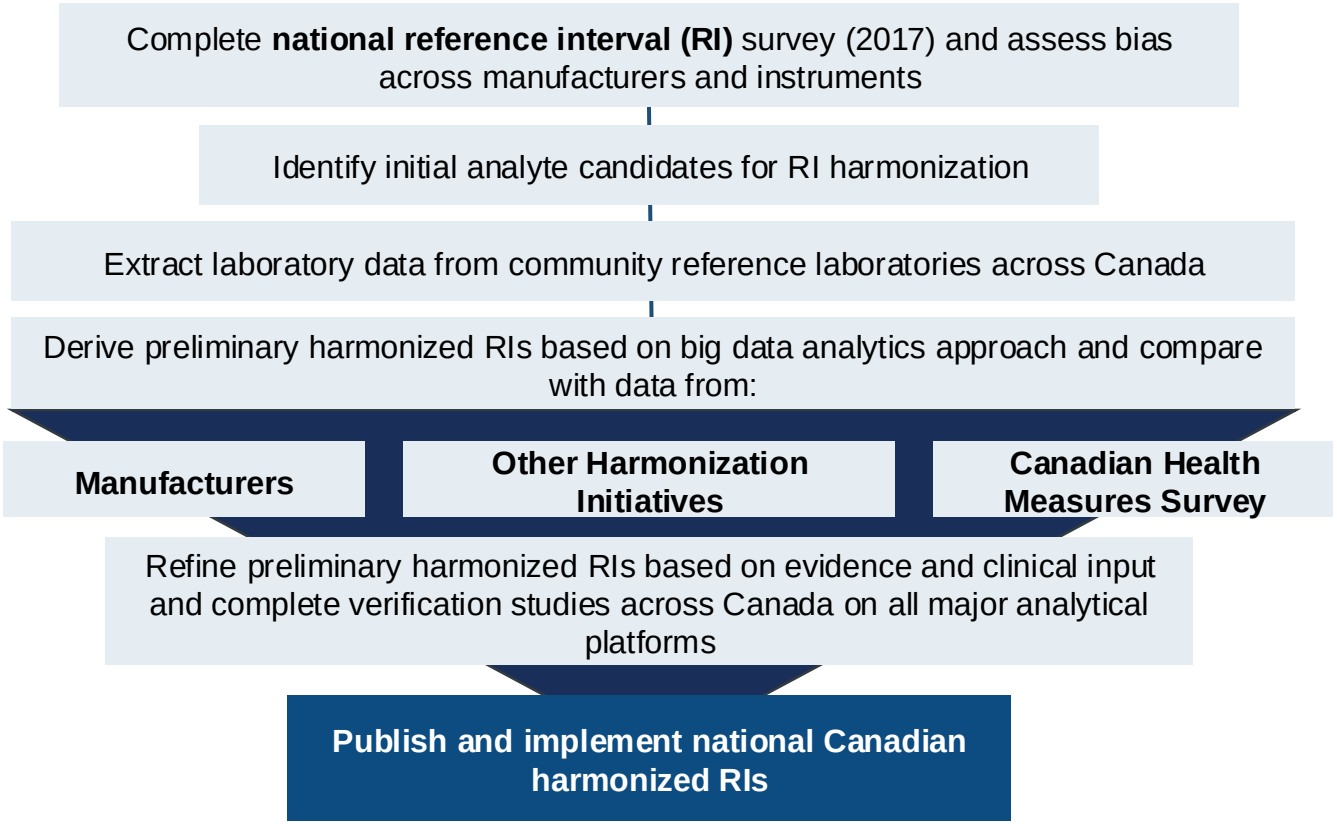
Main Objective: Establish evidence-based harmonized/common reference intervals (hRIs) and support their implementation in laboratories across Canada.

Co-Chairs

Khosrow Adeli
Christine Collier

WG Members

Dana Bailey
Cynthia Balion
Mary Kathryn Bohn
George Cembrowski
Vincent De Guire
Victoria Higgins
Benjamin Jung
Zahraa Mohammed-Ali
Karina Rodriguez Capote
David Seccombe
Jennifer Taher
Albert Tsui
Allison Venner
Nicole White-AlHabeeb



Status of RI Variation in Canadian Laboratories (hRI-WG Survey 2017)

Contents lists available at ScienceDirect

Clinical Biochemistry

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

Analytical

National Survey of Adult and Pediatric Reference Intervals in Clinical Laboratories across Canada: A Report of the CSCC Working Group on Reference Interval Harmonization

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[d] Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada
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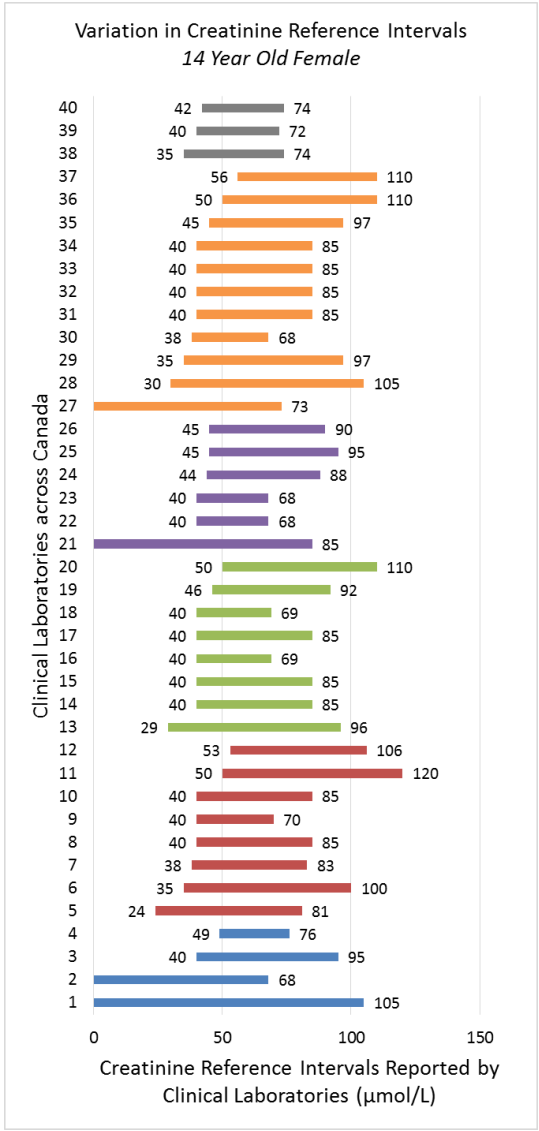
[f] Calgary Laboratory Services and Department of Pathology and Laboratory Medicine, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada
[g] Department of Pathology and Laboratory Medicine, The Ottawa Hospital, Eastern Ontario Regional Laboratories Association and University of Ottawa, Ottawa, ON, Canada

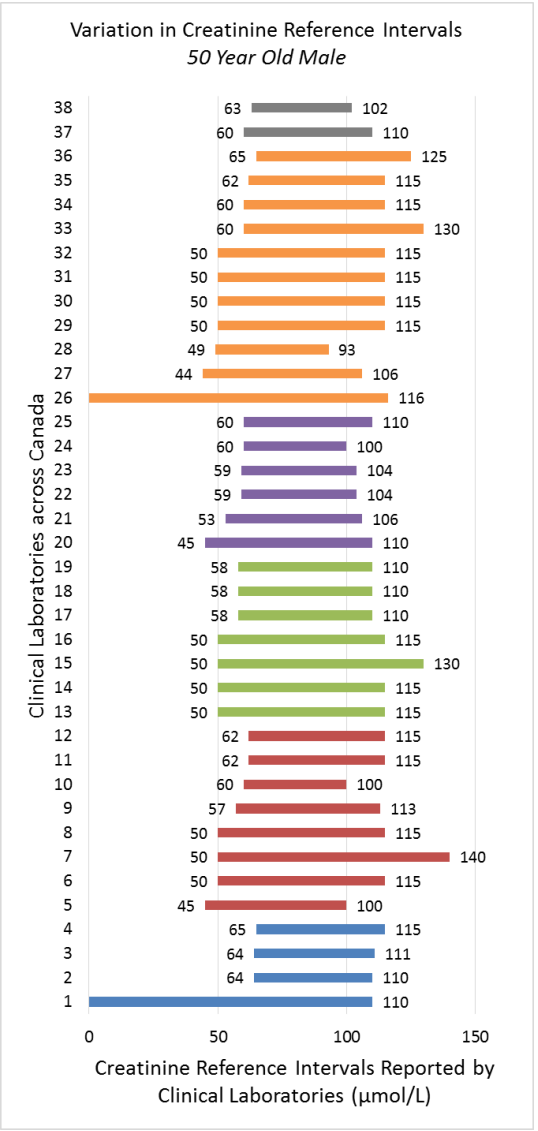
Design:

- 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





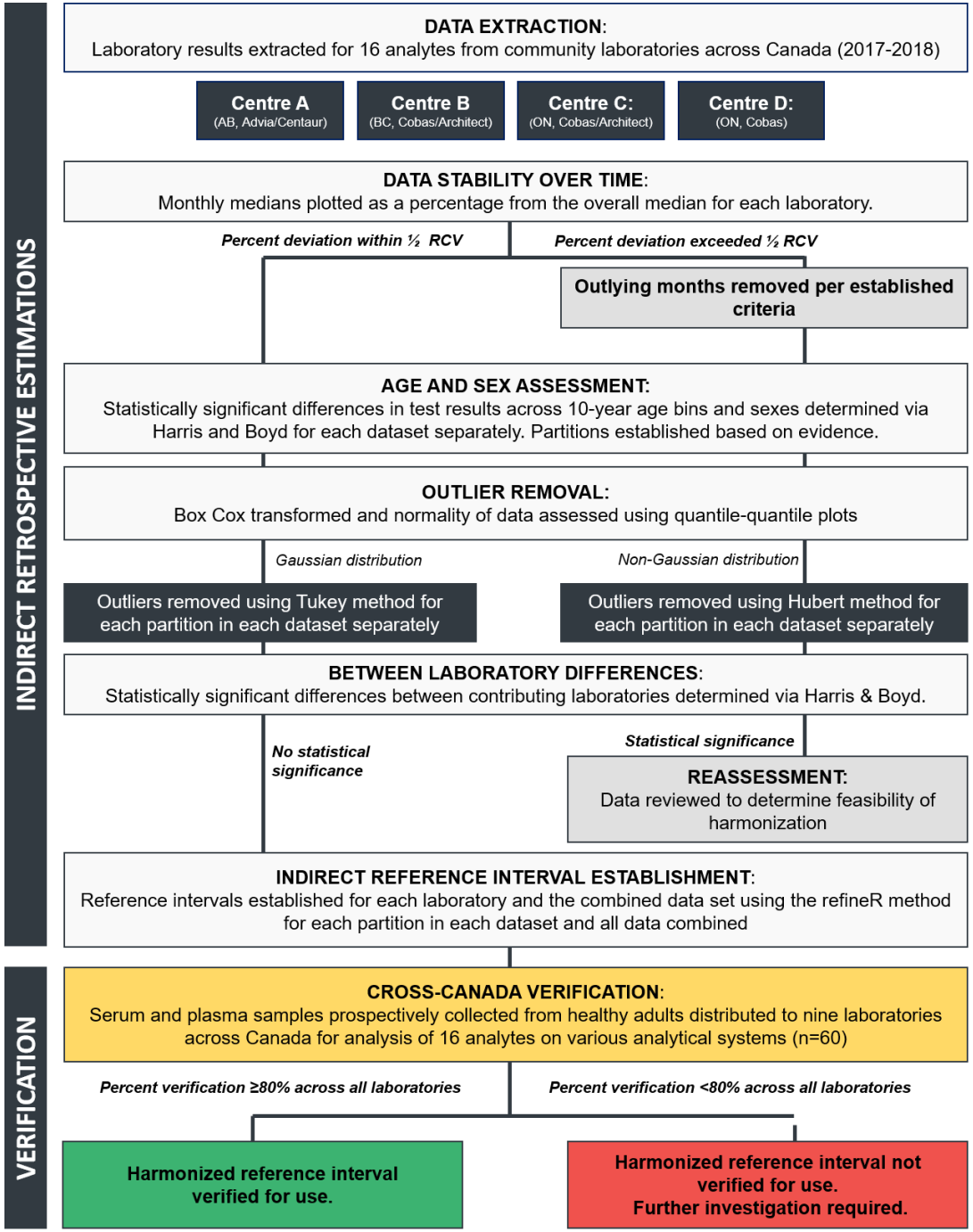
Can BIG data and indirect reference interval methods serve as tools for reference interval harmonization?

Clinical Chemistry 69:9
991–1008 (2023)

Informatics and Statistics

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

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



Big Data Driven Approach:

An initial panel of 16 analytes were selected as candidates for harmonization
(literature, EQA, IFU review)

- Alanine aminotransferase
- Alkaline phosphatase
- Albumin
- Bilirubin (total)
- Creatinine
- Calcium
- Chloride
- CO2 (total)
- Free T4
- LDH
- Magnesium
- Phosphate
- Potassium
- Sodium
- TSH
- Total Protein

Two years of data extracted from **4 community labs across Canada**

Centre A (Alberta, Advia/Cenatur)

Centre B (British Columbia, Cobas/Architect)

Centre C (Ontario, Cobas/Architect)

Centre D (Ontario, Cobas)

Up to 14 million data points!

Big Data Approach:

INDIRECT RETROSPECTIVE ESTIMATIONS

DATA EXTRACTION:
Laboratory results extracted for 16 analytes from community laboratories across Canada (2017-2018)

Centre A	Centre B	Centre C:	Centre D:
(AB, Advia/Centaur)	(BC, Cobas/Architect)	(ON, Cobas/Architect)	(ON, Cobas)

DATA STABILITY OVER TIME:
Monthly medians plotted as a percentage from the overall median for each laboratory.

Percent deviation within ½ RCV

Percent deviation exceeded ½ RCV

Outlying months removed per established criteria

AGE AND SEX ASSESSMENT:
Statistically significant differences in test results across 10-year age bins and sexes determined via Harris and Boyd for each dataset separately. Partitions established based on evidence.

OUTLIER REMOVAL:
Box Cox transformed and normality of data assessed using quantile-quantile plots

Gaussian distribution

Outliers removed using Tukey method for each partition in each dataset separately

Non-Gaussian distribution

Outliers removed using Hubert method for each partition in each dataset separately

BETWEEN LABORATORY DIFFERENCES:
Statistically significant differences between contributing laboratories determined via Harris & Boyd.

No statistical significance

Statistical significance

REASSESSMENT:
Data reviewed to determine feasibility of harmonization

INDIRECT REFERENCE INTERVAL ESTABLISHMENT:
Reference intervals established for each laboratory and the combined data set using the refineR method for each partition in each dataset and all data combined

VERIFICATION

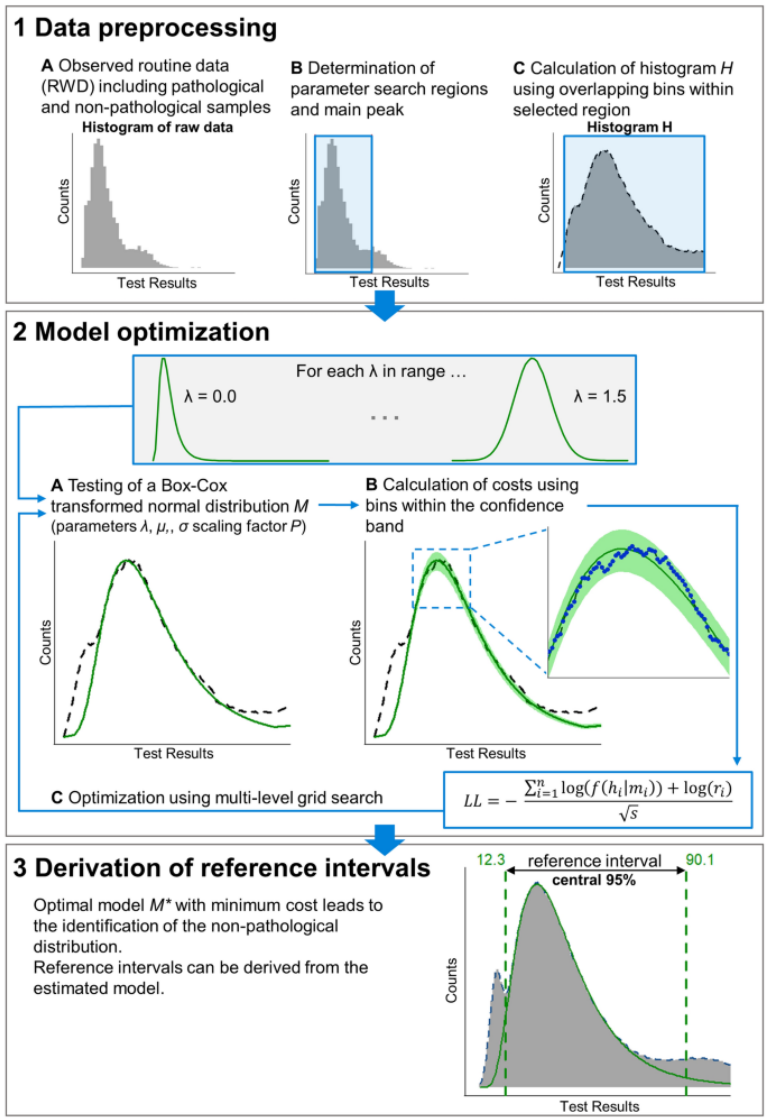
CROSS-CANADA VERIFICATION:
Serum and plasma samples prospectively collected from healthy adults distributed to nine laboratories across Canada for analysis of 16 analytes on various analytical systems (n=60)

Percent verification ≥80% across all laboratories

Percent verification <80% across all laboratories

Harmonized reference interval verified for use.

Harmonized reference interval not verified for use. Further investigation required.



Ammer et al. Scientific reports. 2021 Aug 6;11(1):16023.

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(AB, Advia/Centaur)	(BC, Cobas/Architect)	(ON, Cobas/Architect)	(ON, Cobas)

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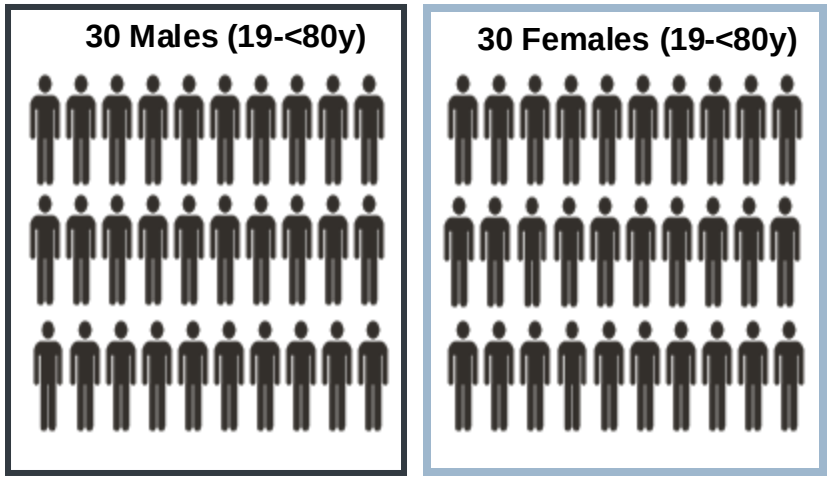
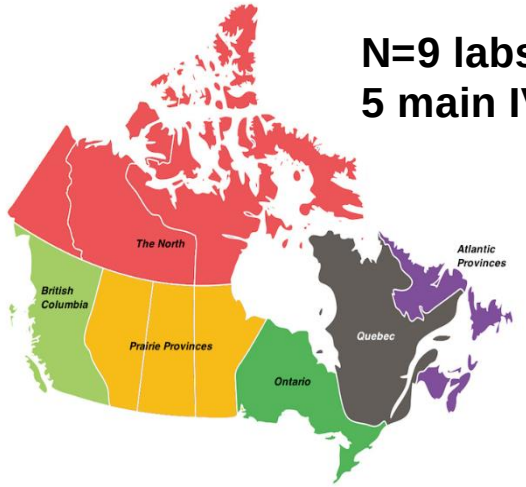
Big Data Approach:

+ verification



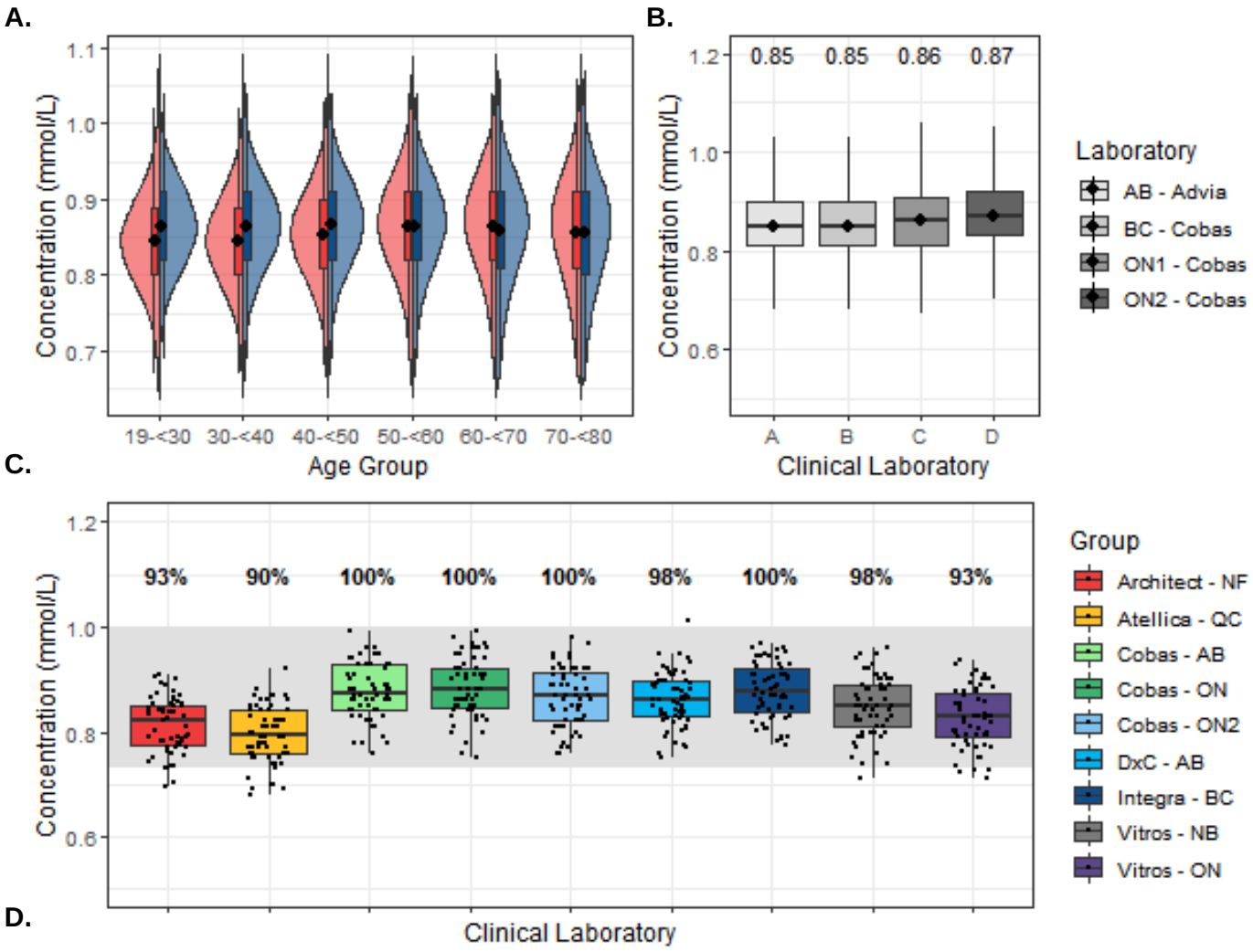
Healthy Canadians recruited from Toronto (ON) and Edmonton (AB) Canada



N=9 labs
5 main IVD

Magnesium

Direct and Indirect Canadian Data Supports Harmonization

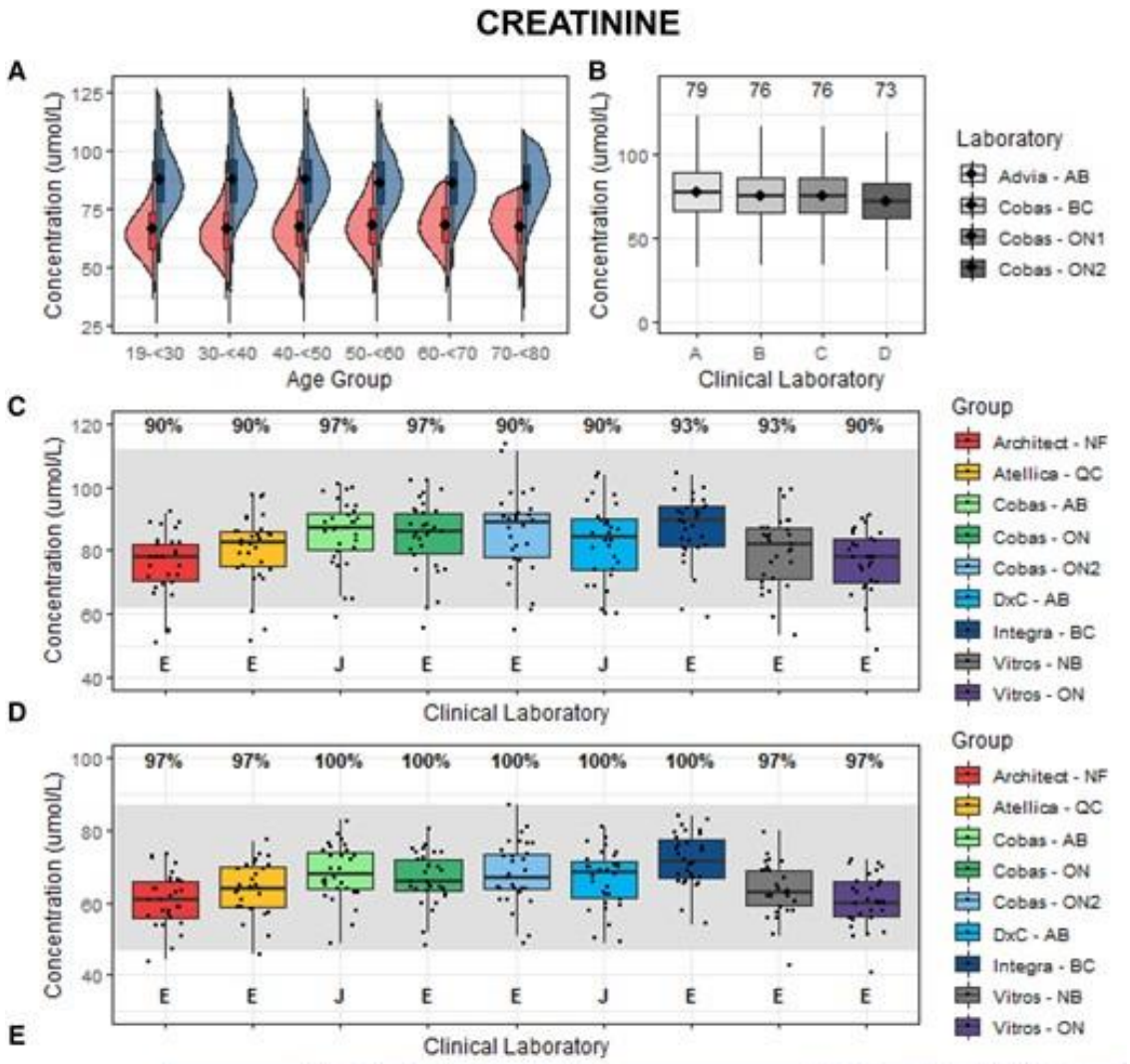


D.

	Indirect Analysis of Provincial Data					Direct International Initiatives*			
	Advia – AB	Cobas – BC	Cobas – ON1	Cobas – ON2	All	AHRIA	AUSSIE	NORIP	UK
N	203541	124417	423031	157662	908651				
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*)



E

	Indirect Analysis of Provincial Data					Direct International Initiatives*			
	Advia – AB	Cobas – BC	Cobas – ON1	Cobas – ON2	All	CHMS	AHRIA	AUSS	NORIP
N	2003708	1894066	7077203	1933991	12908968				
LL 19-79y M	60 [60, 64]	63 [62, 63]	63 [62, 63]	60 [60, 62]	62 [62, 62]	62	60	65	60
UL 19-79y M	117 [117, 120]	111 [110, 113]	113 [112, 113]	103 [101, 111]	112 [112, 114]	106	110	103	100
LL 19-79y F	48 [46, 48]	47 [47, 48]	47 [47, 48]	46 [45, 46]	47 [47, 47]	53	45	54	50
UL 19-79y F	97 [90, 100]	87 [87, 89]	89 [88, 89]	87 [84, 88]	87 [87, 89]	88	90	83	90

Creatinine

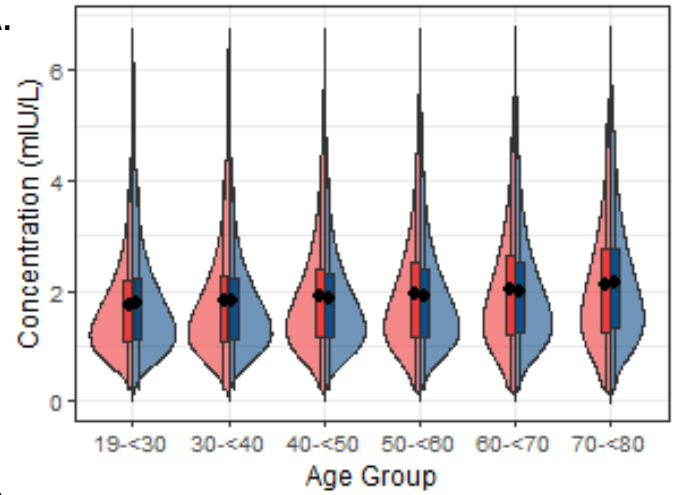
Direct and Indirect Canadian Data Supports Harmonization

Result Summary:

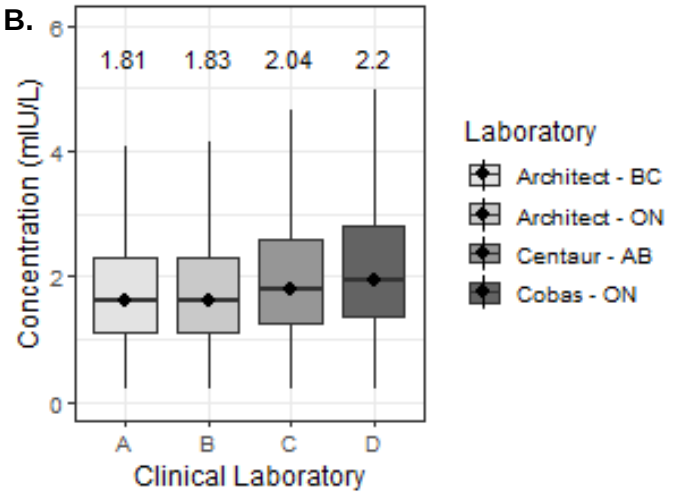
- Approximately **13 million results** evaluated
- Sex-specific differences observed
- Recommended hRI verified in all nine Canadian Laboratories participating in cross-Canada verification program (*serum and plasma*)
- **eGFR** was calculated based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (2009) equation and individuals with an eGFR of <60 (mL/min/1.73m^2) were excluded from analysis

THYROID STIMULATING HORMONE

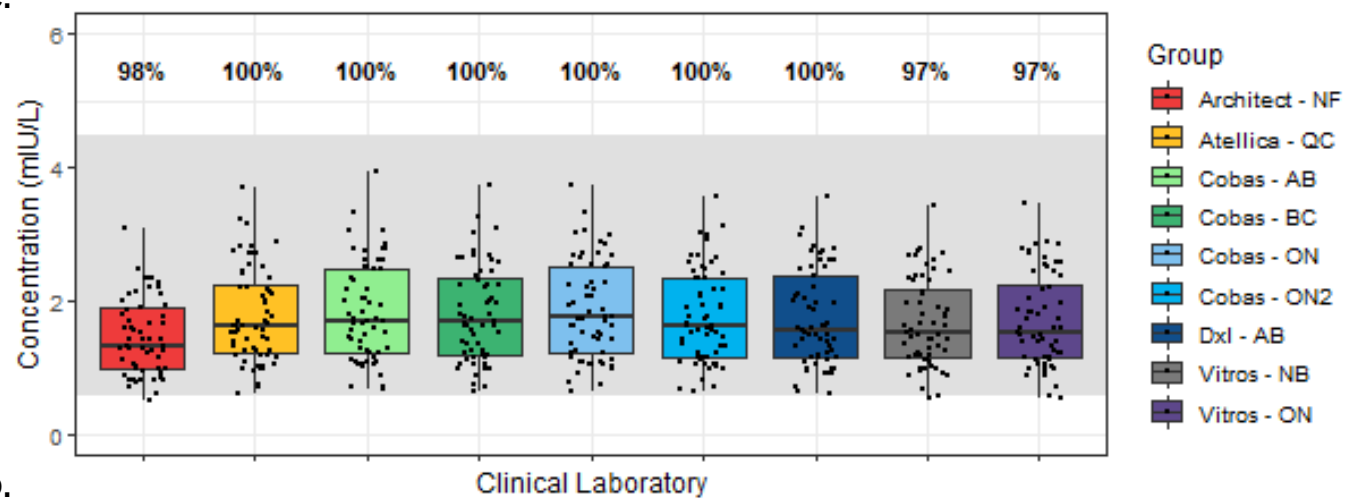
A.



B.



C.



D.

	Indirect Analysis of Provincial Data					Direct International Initiatives*			
	Centaur AB	Architect BC	Architect ON	Cobas ON	All	ATA	AUSS	NHANES	NORIP
N	1121045	1648061	4207623	1688546	8665275				
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

TSH

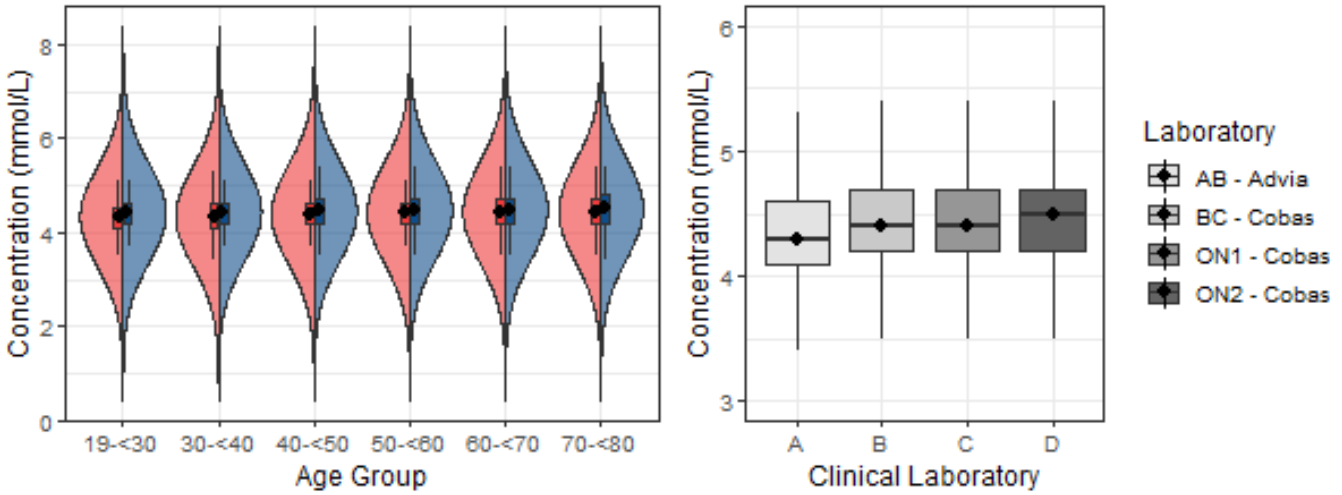
Direct and Indirect Canadian Data Supports Harmonization

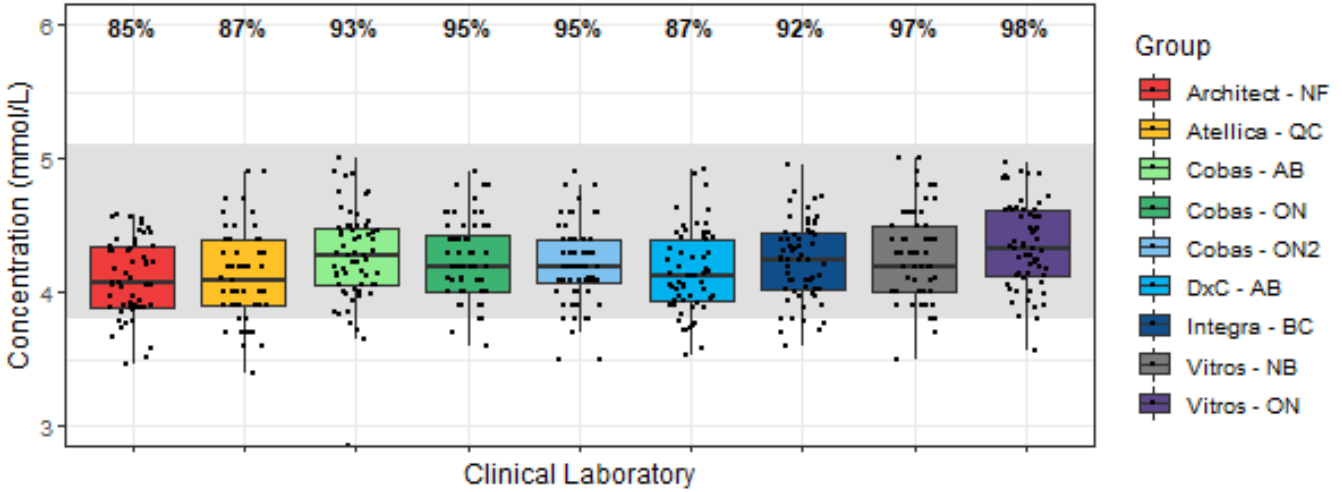
Result Summary:

- Approximately **8.6 million 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*)
- Estimated TSH upper limit was higher relative to ATA guidance of 4.00 mIU/L, although concordant with lower confidence intervals

Potassium

Direct and Indirect Canadian Data Supports Harmonization





	Indirect Analysis of Provincial Data					Direct International Initiatives*				
	Advia – AB	Cobas – BC	Cobas – ON1	Cobas – ON2	All	CHMS	AHRIA	AUSS	NORIP	UK
N	773026	1583639	3930985	1512821	7800471					
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

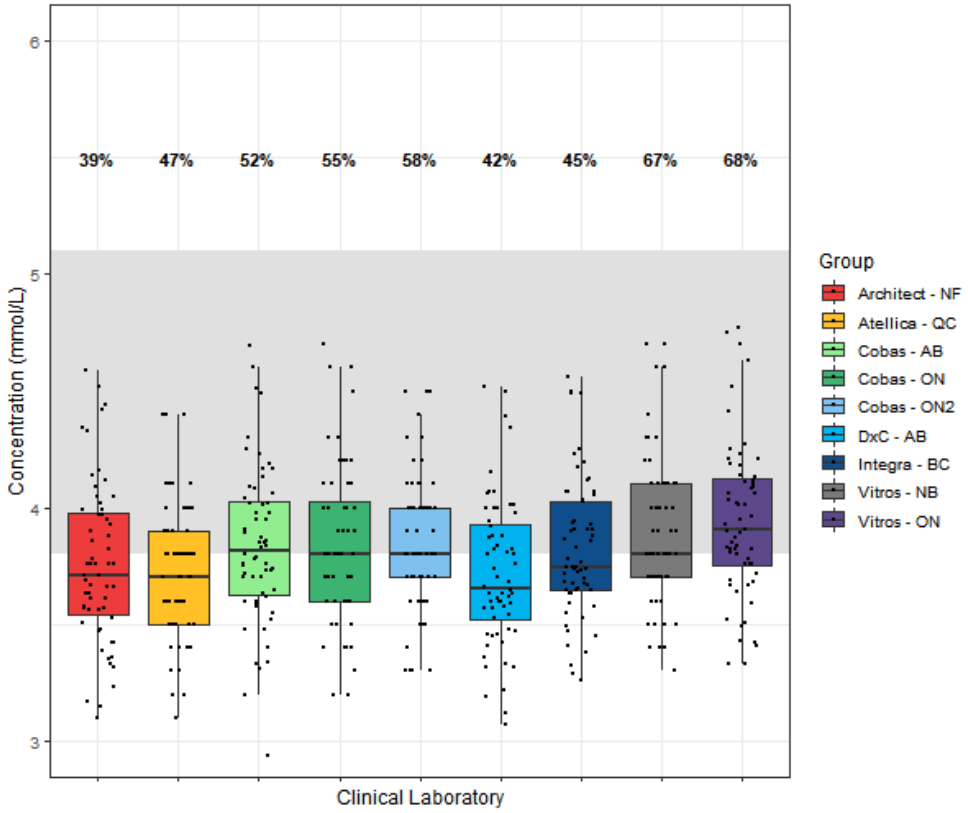
Result Summary:

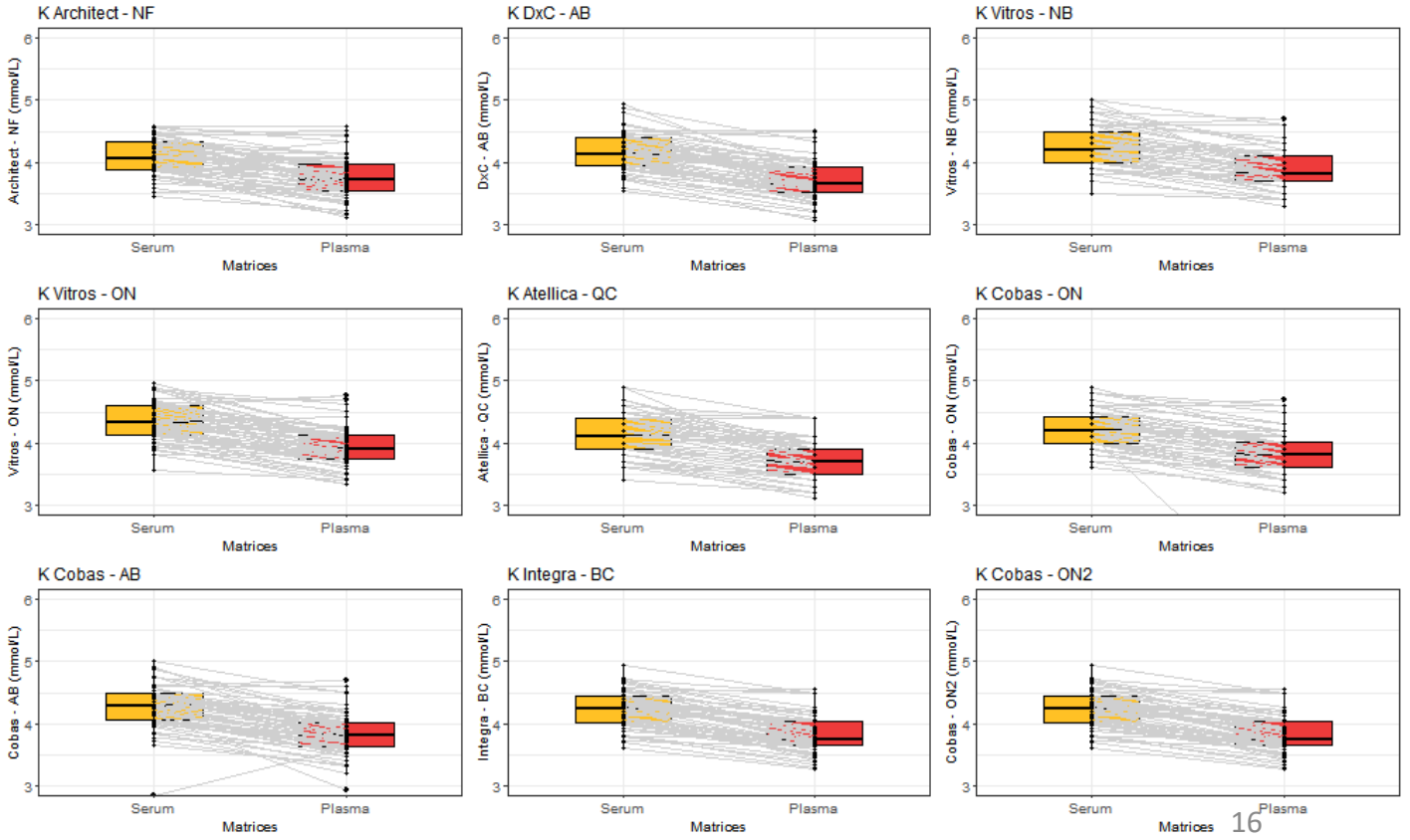
- Approximately **7.8 million results** evaluated
- No age/sex-specific differences observed
- Recommend hRI verified in all nine Canadian Laboratories participating in cross-Canada verification program in ***serum only***

Potassium: Matrices Effects

Plasma vs Serum:

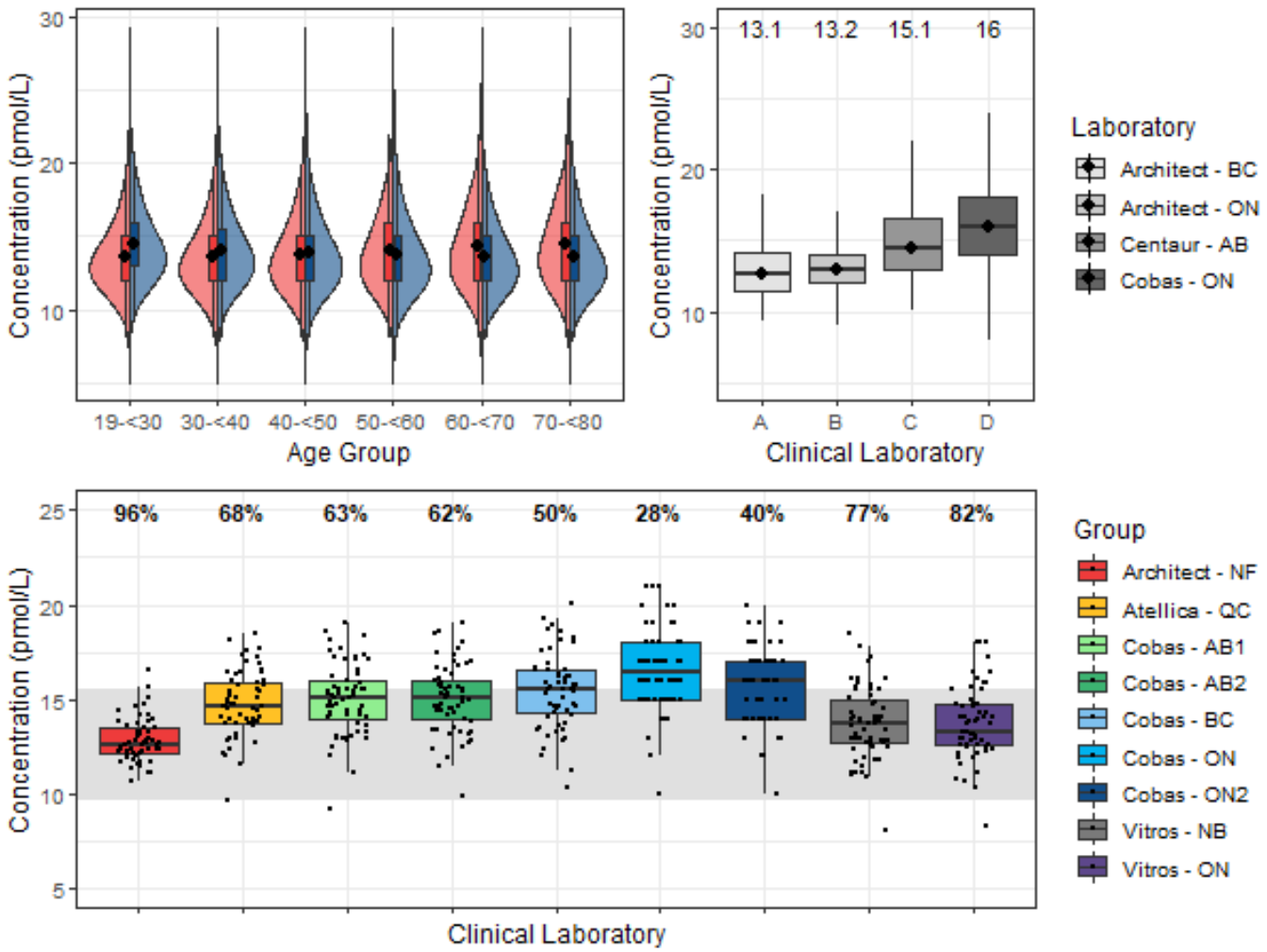
- Plasma potassium results were markedly lower as compared to paired sera
- Established hRI did not verify as per CSCC hRI WG criteria in plasma specimens
- A separate recommendation for plasma potassium is needed





Free T4

Direct and Indirect Canadian Data do NOT Support Harmonization



	Indirect Analysis of Provincial Data					Direct International Initiatives*		
	Advia – AB	Centaur – BC	Architect – ON1	Cobas – ON2	All*	AUSSIE	NORIP	ATA
N	124713	196029	972585	376870	1664797			
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

Key Takeaways

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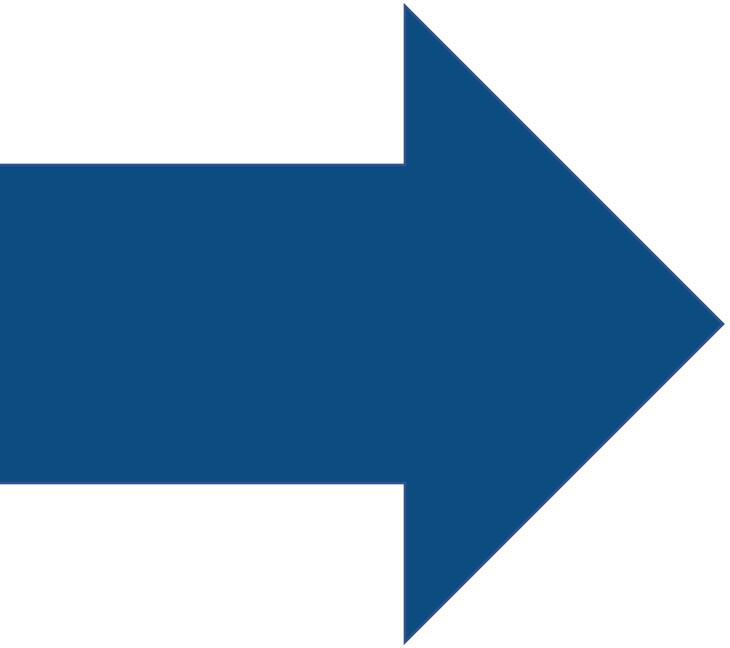
Informatics and Statistics

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

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

Implementation (consultation, practice guidelines etc.)

- Via a **big data analytics approach**, we assessed indirect datasets of unprecedented sample size providing a solid evidence-base for harmonization assessment
- Harmonized RIs were calculated for all assays, except free thyroxine
- **11 hRIs met proposed verification criterion for** ALP, ALT albumin (BCG), creatinine, chloride, LDH, magnesium, phosphate, potassium (serum), total protein (serum), and thyroid stimulation hormone
- Further investigation is needed for select analytes (albumin (BCP), calcium, total CO2, total bilirubin, sodium)



Data-driven approach can be harnessed to support RI harmonization in other populations:

1) extract community laboratory data in their population covering relevant analytical methods
2) evaluate age-, sex-, and laboratory specific differences
3) derive hRIs using the refineR method and compare to any available direct population data
4) verify derived hRIs using prospectively collected specimens representative of their population

Applying this approach on a global scale lends itself to the evaluation of population-specific differences and feasibility of global RI harmonization

Acknowledgments

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