

# Harmonized Lipid Reporting in Canada: One Step Closer

Nicole White-Al Habeeb CSCC Annual Meeting Roundtable 5 June 2019

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#### Nicole White-Al Habeeb

• I have no financial relationships to disclose.

• I will not discuss off label use and/or investigational use in my presentation.

# Outline

- Harmonized Reference Interval (hRI) Working Group
- Variation of lipid reporting across Canada
- Development and implementation
- Common Lipid Report Adults and Pediatrics

# CSCC Reference Interval Harmonization (hRI) Working Group

Goal: To develop evidence-based harmonized reference interval recommendations and support their implementation in laboratories across the country

Objective 1: Review adult and pediatric RIs currently in use in clinical laboratories across Canada

Objective 2: Assess the available evidence on RIs obtained in a priori studies of healthy populations

Objective 3: Develop appropriate recommendations and guidelines on the use of harmonized RIs across Canada

# Variation in RIs across Canada

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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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- > 37 laboratories reported RIs for 7 analytes (ALT, ALP, calcium, creatinine, FT4, hemoglobin, sodium)
- 40 laboratories measured 6 analytes (all except hemoglobin) in commutable reference samples
- High variation in reported RIs, even between laboratories using the same instrumentation, and was higher in pediatrics
- RI variation was greater than test result variation for the majority of analytes

#### **Create focus groups:**

- 1. Electrolytes (sodium, potassium, chloride, total CO2, magnesium)
- 2. Renal function (creatinine, calcium, phosphorus)
- 3. Hepatic function (ALT, ALP, albumin, total protein, total bilirubin, LDH)
- 4. Endocrinology (glucose, HbA1c, TSH, FT4, FT3)
- 5. Lipids (total cholesterol, LDL-C, HDL-C, triglycerides, apoB, non-HDL-C)

# Lipid Reporting Survey Results CSCC hRI Working Group

- The CSCC Harmonized Reference Interval (hRI) Working Group disseminated a survey to Canadian laboratories in November 2018 to assess current adult and pediatric lipid reporting practices across Canada.
- Respondents from 27 laboratories completed the survey

### Locations of Participating Laboratories



There was representation from all provinces with the exception of PEI, Nunavut, Yukon and Northwest Territories.

### Instrument Manufacturers

Instrument Manufacturers 35 30% 30 22% 25 19% 19% 20 Eredneucy 15 11% 10 5 0 Abbott Ortho Beckman Roche Siemens

Total Responses = 27

# Adult Lipid Reporting Survey Summary

# Significant variability in adult LDL-C reporting across Canadian labs

LDL-C upper and lower limits reported for a 50 yr male across 16 labs



\*Grey shaded area: hRI recommended upper flagging limit (3.5 mmol/L)

- <u>16 respondents reported LDL-C limits</u>
  - 12 labs Decision Limits
    - 5 different cutoffs
  - 3 labs Reference Intervals (RIs)
    3 different RIs
  - 1 lab reported lower limits only
- 11 respondents had no reported limits

#### Variability in LDL-C reporting in:

- The use of decision limits vs reference ranges
- Decision limit cutoffs

NOTE: similar variability was in reporting for non-HDL-C, HDL-C, triglycerides, total cholesterol and apoB

### Significant variability in interpretative comments

#### Laboratory 21

Ref: McPherson R et al. Can J Cardiol. 2006

- 96% (23/24) laboratories reported interpretative comments (adults)
- Significant variability in the amount of information included in interpretative comments and the reference

#### Laboratory 29

: RISK LEVEL	: INITIATE THERAPY	: TARGETS
:HIGH	Consider in all	NON-HDL-C <=2.6 MMo1/L
:(FRS >=207)	:	tor
:	:	:LDL-C* <=2 MMo1/L or
:	1	<pre>:&gt;=50% reduction</pre>
: INTERMEDIATE	:Non-HDL-C >=4.3mmo1/L	Non-HDL <=2.6 MMo1/L
CFRS 107-207	) (or	tor
:	:LDL-C* >=3.5mmo1/L	:LDL-C* <=2 MMo1/L or
:	1	<pre>:&gt;=50% reduction</pre>
:LOW	:LDL-C* >=5mmo1/L	:LDL-C* >=50% reduction
CFRS <1020	:or	:
:	:Familial	:
:	:Hypercholesterolemia	:

Please see 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of CVD (Can J Cardiol 2016; 32:1263-1282) for further information. Interpretation is based on calculated Framingham Risk Score (FRS). 2 of 3 labs surveyed in Canada are NOT referencing the most recent CCS Guidelines



# Pediatric Lipid Reporting Survey Summary



\*Grey shaded area: hRI recommended lower (2.5<sup>th</sup>) and upper (75<sup>th</sup>) flagging limits (1.18-2.61 mmol/L) Red line: Alternative high (95<sup>th</sup>) limit (3.22 mmol/L)

- <u>13 respondents reported LDL-C</u> <u>limits</u>
  - 9 labs Decision Limits
    - 4 different cutoffs
  - 4 labs Reference Intervals (RIs) - 4 different RIs

#### Variability in LDL-C reporting in:

- The use of decision limits vs reference ranges
- Decision limit cutoffs

NOTE: similar variability was in reporting for non-HDL-C, HDL-C, triglycerides, total cholesterol and apoB

### Pediatric Interpretative Comment Example

	< 75%	75-95%	>95%			
Interpretation of pediatric lipid levels (mmol/L)						
	Acceptable	Borderline	High			
<b>Total Cholesterol</b>	<4.40	4.40 - 5.16	≥5.17			
LDL-C	<2.85	2.85 - 3.34	≥3.35			
Non-HDL-C	<3.1	3.1 - 3.6	≥3.7			
TG (0-9 years)	<0.85	0.85 - 1.11	≥1.12			
TC (10 10 years)	<1.02	1.02 - 1.46	>1 /17			
10 (10-19 years)	\$1.02	1.02 - 1.40	21.47			
10 (10-19 years)	Acceptable	Borderline	Low			
HDL-C	<1.02 Acceptable >1.17	<b>Borderline</b> 1.05 - 1.17	Low ≤1.04			
HDL-C Calculations: Non-HD LDL-C LDL-C	<1.02 Acceptable >1.17 DL-C = Total Chol - HI C = Total Chol - HI C calculation is in	Borderline 1.05 - 1.17 HDL-C DL-C - (TG/2.2) avalid if TG excee	Low ≤1.04			

Laboratory 6

16

#### What is the origin of pediatric interpretive comments?

Laboratory No.	Source of Interpretative comments	Age and sex- stratified
2	Total Cholesterol has warning for results > 75 <sup>th</sup> percentile - may indicate lifestyle treatment	No
6	2011 US Nat. Heart Lung and Blood Inst expert panel guidelines	No
29	Pediatrics. 2011 Dec; 128(Suppl 5): S213–S256 <sup>1</sup>	No

1. For each reported lipid, comments are appended to indicate "acceptable, less than 75th percentile", "borderline high range, 75th to 95th percentile" and "high range, greater than 95th percentile" depending on the concentration, Tables 9-1 and 9-2 in Pediatrics. 2011 Dec; 128(Suppl 5): S213–S256.

# Interest in Lipid Reporting Harmonization Survey Summary

### Interest in Harmonization



The survey asked if laboratories are interested in implementing harmonized lipid reporting? 47% responded "Yes"

47% responded "Unsure" – NOTE: most of these labs are already involved in provincial or regional lipid harmonization initiatives

Alberta, Manitoba and Newfoundland have established provincial harmonized lipid reporting

# Survey Results

- Significant differences exist in adult and pediatric lipid reporting across Canada however provincial lipid harmonization is established in 3 provinces
- Variability in how fasting status is documented
- Few labs used non-fasting cutoffs

Labs are interested in implementing common lipid reporting in Canada!



# Action plan to implement harmonized lipid reporting across Canada



# Proposed Common Adult Lipid Report

#### **Flagging Decision Limits**

Analyte	Flagging Decision Limit
Total Cholesterol	>5.20 mmol/L
HDL-C	(M) <1.00 mmol/L
	(F) <1.30 mmol/L
LDL-C	≥3.5 mmol/L
Triglycerides	>1.7 mmol/L (fasting) > 2.0 mmol/L (non fasting)
Non-HDL-C	≥4.3 mmol/L
АроВ	≥1.2 g/L
Hours fasting	Record hours fasted (h)

#### **Interpretative Comments**

Risk Level	Initiate Treatment	Primary Target	Alternate Target
High (FRS ≥ 20%)	Consider treatment in all patients	<2.0 mmol/L or >50% decrease in LDL-C	
Intermediate (FRS 10%- 19%)	Consider treatment if: LDL-C $\geq$ 3.5 mmol/L or Non-HDL-C $\geq$ 4.3 mmol/L or apoB $\geq$ 1.2 g/L or $\geq$ 1 risk factor	<2.0 mmol/L or >50% decrease in LDL-C	Non-HDL-C <2.6 mmol/L ApoB <0.8 g/L
Low (FRS < 10%)	Consider treatment if: 1) LDL-C ≥ 5.0 mmol/L 2) Familial hypercholesterolemia	>50% decrease in LDL-C	

Refer to 2016 CCS Guidelines

If TG >1.5 mmol/L, use non-HDL-C or apoB treatment target (rather than LDL-C) If TG > 4.5 mmol/L, LDL-C will be canceled. Repeat testing in the fasted state.

# Origin of Recommended Adult Lipid Decision Limits

#### **Total Cholesterol**

- Increased CHD incidence at serum cholesterol > 5.20 mmol/L (Framingham Study)

#### LDL-C, ApoB and non-HDL-C

- Primary prevention studies included subjects without vascular disease who on average were in the FRS IR group, but also include some HR and LR subjects
- Studies (AFCAPS/TexCAPS, WOSCOPS, ASCOTE, JUPITER) showed statin therapy reduced CVD events for subjects with
  - LDL-C≥ 3.5 mmol/L or non-HDL-C ≥4.3 mmol/L or ApoB≥1.2 g/L or men ≥50 yrs and women ≥60 yrs and ≥1 CVD risk factor

#### Triglycerides

- NCEP ATP III panel reviewed studies and found when TG > 1.7 mmol/L, substantially increased CHD risk

#### HDL-C

 Population studies show continuous rise in CHD risk as HDL-C levels decline; no threshold relationship defined and therefore any categorical definition of low HCL-C is arbitrary. NCEP ATP III recommended a categorical low HDL-C defined as <1.03 mmol/L</li>

# Do you agree with the recommended FLAGGING DECISION LIMITS in the proposed harmonized lipid report?

#### Total cholesterol > 5.20 mmol/L

- 1. Should not flag TC, as it does not support clinical decision making.
- 2. 5.2 mmol/L cut-off will contribute to 'flag fatigue'. NICE guidelines use 6.7 mmol/L.

#### HDL-C (male) < 1.00 mmol/L HDL-C (female) < 1.30 mmol/L

- 1. Should not flag HDL-C, so physicians are not tempted to use unhelpful therapies
- 2. Only flag HDL-C when value below limit of reporting
  - Should refer severe HDL-C deficiency
- 3. Messaging needs to be related to risk, not treatment decisions

#### TG (fasting) > 1.70 mmol/L TG (non-fasting) > 2.00 mmol/L

- 1. No need to flag TG, as cut-offs are not provided in CCS guidelines
- 2. Only need to flag TG > 10 mmol/L (risk of pancreatitis)



Data from the Canadian Health Measures Survey

# Would you prefer flagging the following parameters in accordance with treatment initiation or treatment targets?

Target to Initiate Treatment	Treatment Target to Achieve
LDL-C ≥ 3.5 mmol/L	LDL-C < 2.0 mmol/L
Non-HDL-C $\geq$ 4.3 mmol/L	Non-HDL-C < 2.6 mmol/L
Apo B ≥ 1.2 g/L	Apo B < 0.8 g/L

- 1. Treatment targets are patient-specific and too complex for LIS reporting
- 2. Treatment target preferred, but must still show:
  - Treatment targets for low risk individuals
  - Treatment initiation values

# Pediatric Common Lipid Report Recommendations

# Origin of Recommended Pediatric Lipid Decision Limits for NHLBI

#### Total Cholesterol, LDL-C, HDL-C, Triglycerides

- Lipid Research Clinics (LRC) Prevalence Study (1970-1976) of US and Canadian children and adolescents (0-19 years)
- Borderline and high cut-points calculated as 75<sup>th</sup> and 95<sup>th</sup> percentiles, respectively
  Non-HDL-C
- Equivalent to LDL-C recommended cut-points for CAD risk assessment
  - 2,843 serum samples from 5-17 year olds in Bogalusa Heart Study (1992-1994)
  - Regression analysis performed to determine non-HDL-C based on LDL-C

# Proposed Common Pediatric Lipid Reports

Flagging Decision Limits

Analyte	Age Range (years)	Lower Decision Limit (2.5 <sup>th</sup> percentile)	Borderline High (75 <sup>th</sup> percentile)	Analyte	Age Range (years)	High (95 <sup>th</sup> percentile)	Decision limits based on CALIPER reference data ( <i>Clin</i> <i>Chem 2012;58:854</i> -
Total Cholesterol	2-<18	2.90 mmol/L	4.54 mmol/L	Total Cholesterol	2-<18	5.25 mmol/L	868; Clin Chim Acta 2018;486:129-134)
LDL-C	2-<10 M	1.22 mmol/L	2.43 mmol/L	LDL-C	2-<10 M	3.04 mmol/L	
	2-<10 F	1.52 mmol/L	2.54 mmol/L		2-<10 F	3.16 mmol/L	
	10-<19	1.18 mmol/L	2.61 mmol/L		10-<19	3.22 mmol/L	
Triglycerides	2-<18	0.50 mmol/L	1.44 mmol/L	Triglycerides	2-<18	2.04 mmol/L	
Non-HDL-C	2-<10 M	1.79 mmol/L	3.01 mmol/L	Non-HDL-C	2-<10 M	3.62 mmol/L	
	2-<10 F	2.07 mmol/L	3.24 mmol/L		2-<10 F	3.98 mmol/L	
	10-<19	1.68 mmol/L	3.19 mmol/L		10-<19	3.88 mmol/L	
АроВ	2-<6	0.41 g/L	0.72 g/L	АроВ	2-<6	0.87 g/L	
	6-<18	0.31 g/L	0.63 g/L		6-<18	0.80 g/L	
HDL-C	2-<4	1.63 mmol/L	1.04 mmol/L	HDL-C	2-<4	0.93 mmol/L	
	4-<13	1.88 mmol/L	1.17 mmol/L		4-<13	1.05 mmol/L	
	13-<18 M	1.77 mmol/L	1.05 mmol/L		13-<18 M	0.93 mmol/L	
	13-<18 F	1.86 mmol/L	1.19 mmol/L		13-<18 F	1.02 mmol/L	

**Interpretative Comments** 

### Proposed Common Pediatric Lipid Reports

#### HRI Recommendations

Analyte	Age Range (years)	Lower Decision Limit (2.5 <sup>th</sup> percentile)	Borderline High (75 <sup>th</sup> percentile)
Total Cholesterol	2-<18	2.90 mmol/L	4.54 mmol/L
LDL-C	2-<10 M	1.22 mmol/L	2.43 mmol/L
	2-<10 F	1.52 mmol/L	2.54 mmol/L
	10-<19	1.18 mmol/L	2.61 mmol/L
Triglycerides	2-<18	0.50 mmol/L	1.44 mmol/L
Non-HDL-C	2-<10 M	1.79 mmol/L	3.01 mmol/L
	2-<10 F	2.07 mmol/L	3.24 mmol/L
	10-<19	1.68 mmol/L	3.19 mmol/L
АроВ	2-<6	0.41 g/L	0.72 g/L
	6-<18	0.31 g/L	0.63 g/L
HDL-C	2-<4	1.63 mmol/L	1.04 mmol/L
	4-<13	1.88 mmol/L	1.17 mmol/L
	13-<18 M	1.77 mmol/L	1.05 mmol/L
	13-<18 F	1.86 mmol/L	1.19 mmol/L

#### NHLBI

#### Interpretation of pediatric lipid levels (mmol/L)

	Acceptable	Borderline	High
Total Cholesterol	<4.40	4.40 - 5.16	≥5.17
LDL-C	<2.85	2.85 - 3.34	≥3.35
Non-HDL-C	<3.1	3.1 - 3.6	≥3.7
TG (0-9 years)	< 0.85	0.85 - 1.11	≥1.12
TG (10-19 years)	<1.02	1.02 - 1.46	≥1.47
	Accontable	Bordorlino	Low
	Acceptable	Bordennie	LOW
HDL-C	>1.17	1.05 - 1.17	≤1.04

Calculations: Non-HDL-C = Total Chol - HDL-C

LDL-C = Total Chol - HDL-C - (TG/2.2)

LDL-C calculation is invalid if TG exceeds 4.52 mmol/L

Reference: Daniels SR, et al. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: Full report, 2011. US National Heart Lung and Blood Institute.

#### Do you agree with reporting lower limits and flagging values below these limits?

#### Lower Limit: 2.5<sup>th</sup> percentile (CALIPER Reference Data)

- 1. Agree with these lower limits, if they are required
- 2. Flagging lower limit may result in unnecessary clinical evaluation. Should only be provided for those required (e.g. low LDL).

Do you agree with flagging results that exceed the borderline high limit and including the high limit in interpretive comments?

#### Borderline High Limit: 75<sup>th</sup> percentile (CALIPER Reference Data) High Limit: 95<sup>th</sup> percentile (CALIPER Reference Data)

- 1. Flagging on borderline high limits may result in too many flags
- 2. Agree with flagging borderline high limit, but must make it clear that these are not truly abnormal and the high limit must be clearly defined

#### Do you prefer CALIPER age- and sex-specific reference data or NHLBI guideline decision limits?

- 1. Age- and sex-specific limits are largely preferred
  - Suggest restricting age to >2 years to align with current screening recommendations
- 2. Reservation with CALIPER is the inclusion of overweight and obese subjects

# Summary

- Significant variability exists in lipid reporting across Canada
- Laboratories are interested in a harmonized lipid report
- Provincial harmonization in place for 3 provinces
- Proposed common adult and pediatric lipid reports are still a work in progress
- Clinical consultation valuable to ensure recommendations agree with clinical guidelines and practice

**ESCC** SECC

### Acknowledgements

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