HARMONIZED LIPID REPORTING ACROSS CANADA:
CSCC WORKING GROUP RECOMMENDATIONS

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On behalf of the CSCC Working Group on Reference Interval Harmonization

January 21, 2021

PRESENTATION OUTLINE

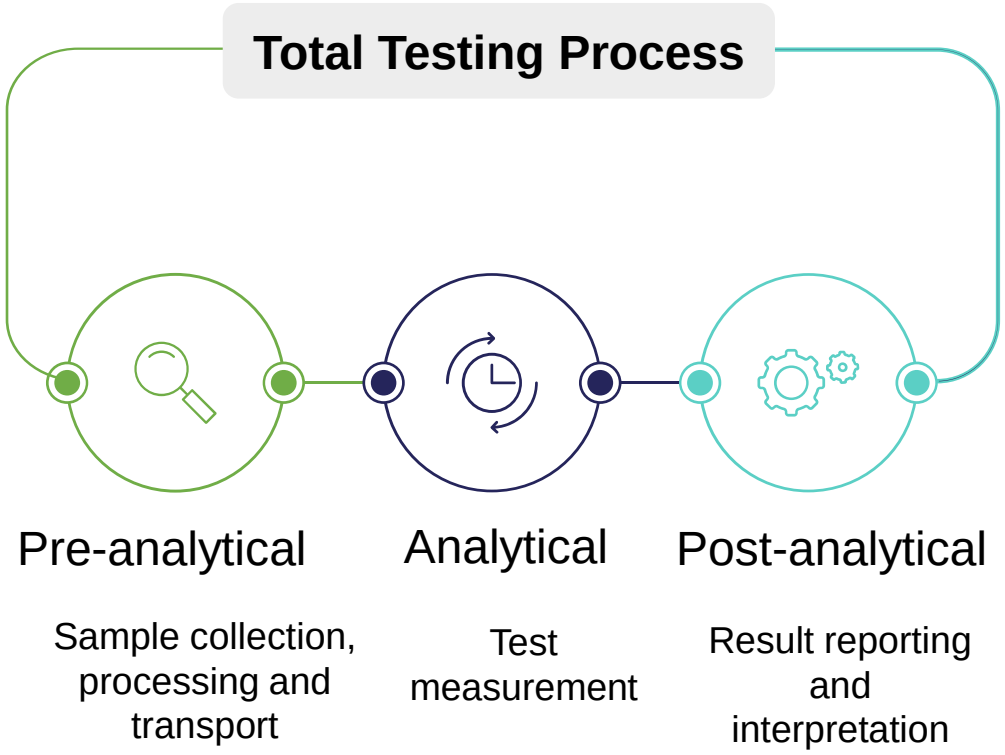
Objectives

- Harmonization of Postanalytical Test Result Reporting Across Canada (CSCC hRI)
- Review the current status of lipid reporting for adults and pediatrics across Canada
- Assess the current lipid guidelines for cardiovascular risk stratification
- Discuss a harmonized approach to lipid reporting and interpretation in clinical laboratories across Canada

Harmonization in Laboratory Medicine

- Harmonization is a fundamental aspect of ensuring the analytical and clinical quality of the ***total testing process***
- Growing expectation for standardized patient care across healthcare centers
- 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: *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

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CSCC hRI WG

Reference Interval Harmonization in Canada: *Current Gaps*

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

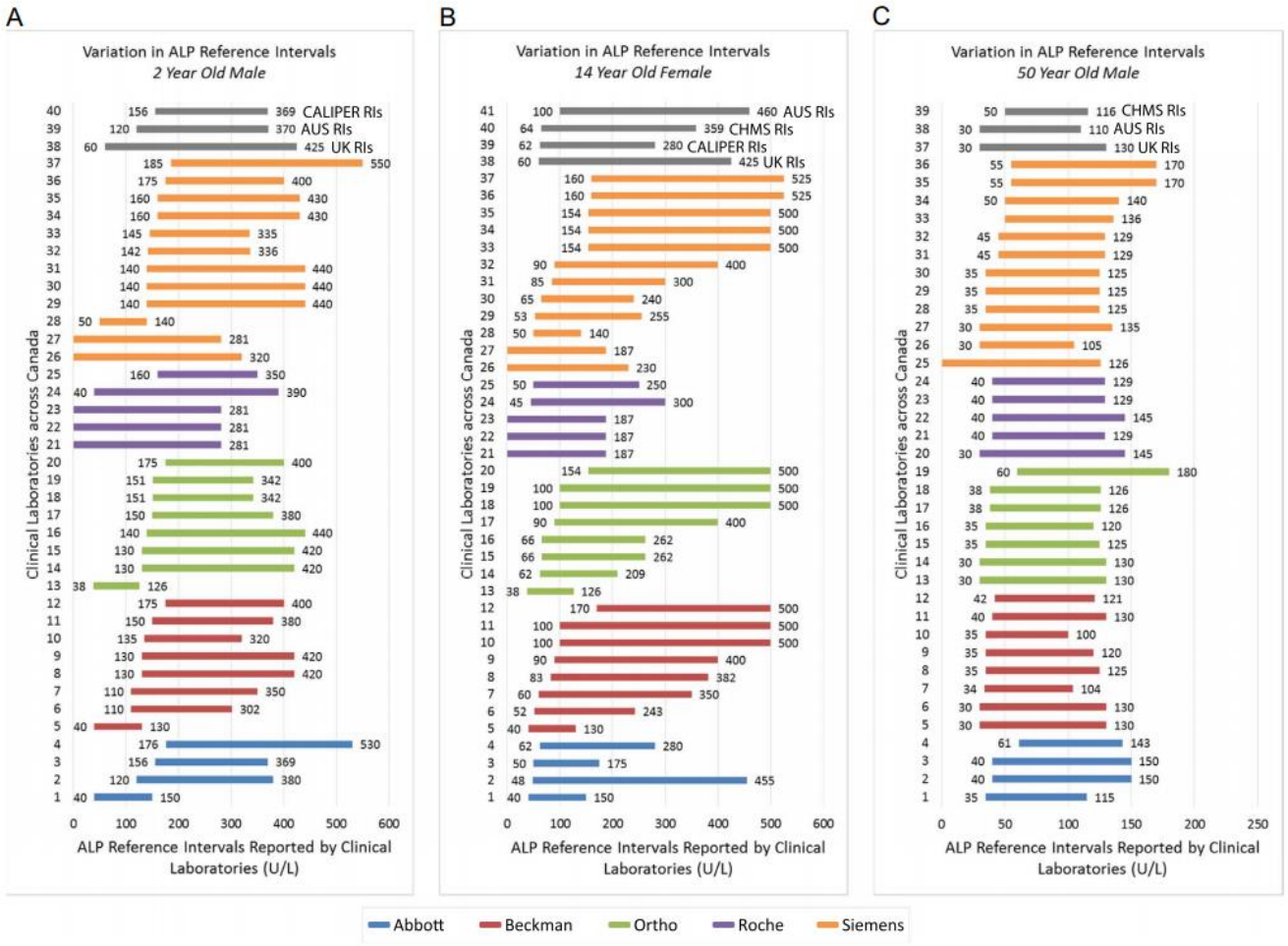
CSCC 2017 National Survey on Reference Intervals:

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.

CSCC hRI WG: Path to Reference Interval Harmonization

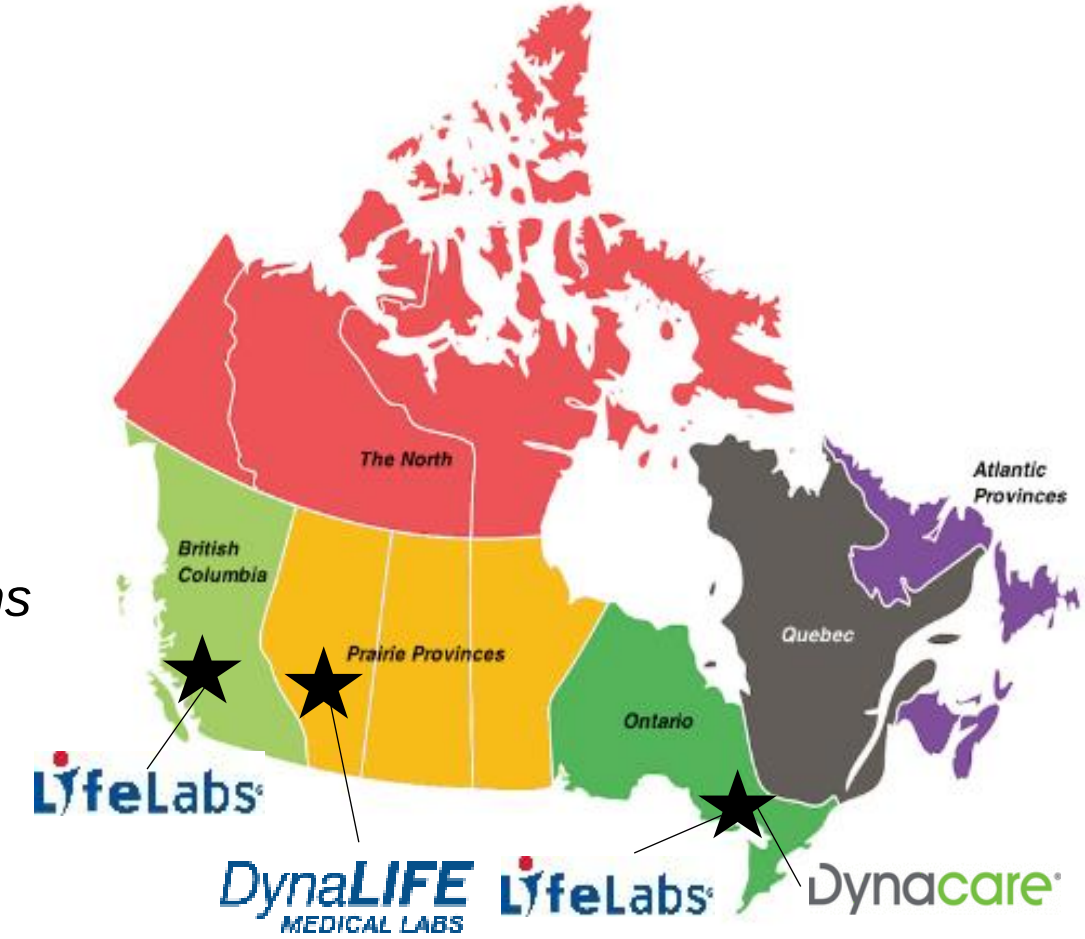
Selection of data contributing centres

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



CSCC hRI WG

CSCC hRI Plans/Progress

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 Dat

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

CSCC hRI WG

HARMONIZATION OF LIPID REPORTING ACROSS CANADA

Objectives

- Review the current status of lipid reporting for adults and pediatrics across Canada
- Assess the available lipid guidelines for cardiovascular risk stratification
- Discuss a harmonized approach to lipid reporting and interpretation in clinical laboratories across Canada

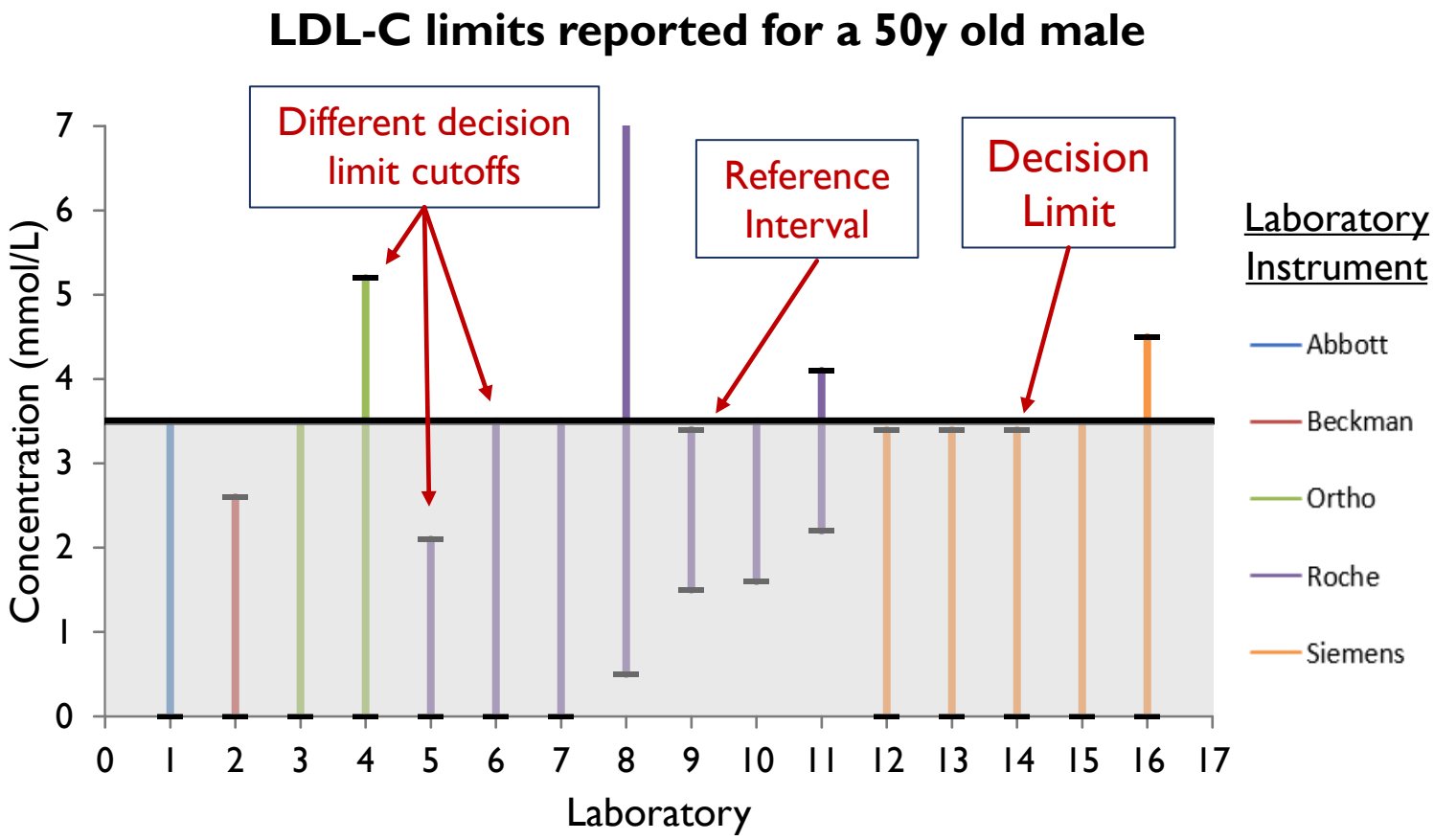
LIPID REPORTING SURVEY

Objective: Assess current lipid reporting practices across Canada to set a foundation for the development and implementation of harmonized lipid reporting

- CSCC hRI WG disseminated a survey to Canadian laboratories to assess current pediatric & adult lipic reporting practices across the country
- 24 respondents replied, representing 101 laboratories
- 5 main manufacturers represented
- All provinces/territories represented except PEI, Nunavut, Yukon, and Northwest Territories

Locations of Participating Laboratories

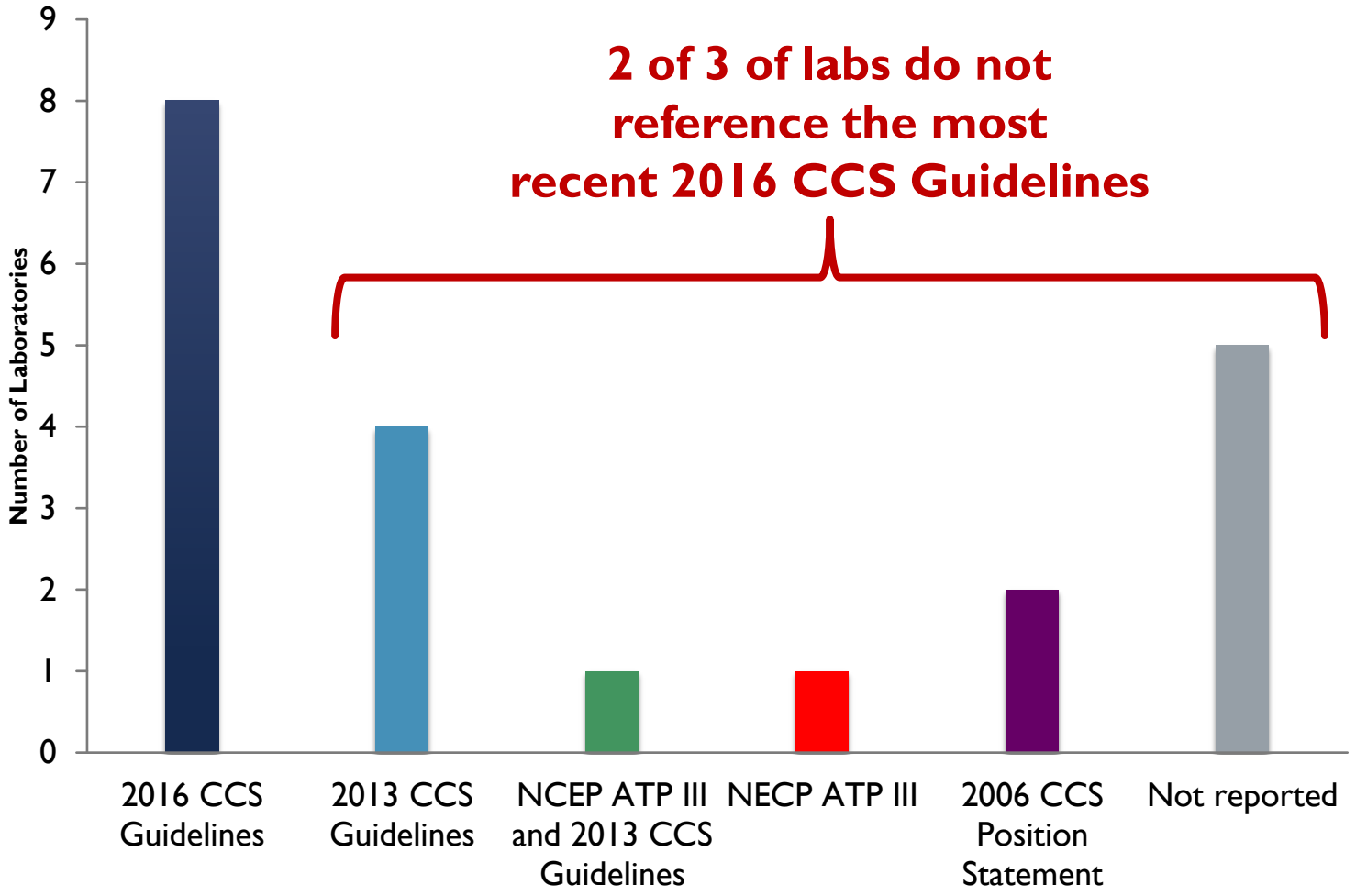
LIPID REPORTING SURVEY RESULTS



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

- Similar variability observed in reporting for total cholesterol, triglycerides, HDL-C, non-HDL-C, and apoB
- **Note:** standardization of cholesterol (CRMLN) ensures results agree across platforms and between laboratories (variation in limits is not justified!)

LIPID REPORTING SURVEY RESULTS



LIPID REPORTING SURVEY RESULTS

Significant variability in adult interpretive comments

Laboratory 21

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

Laboratory 28

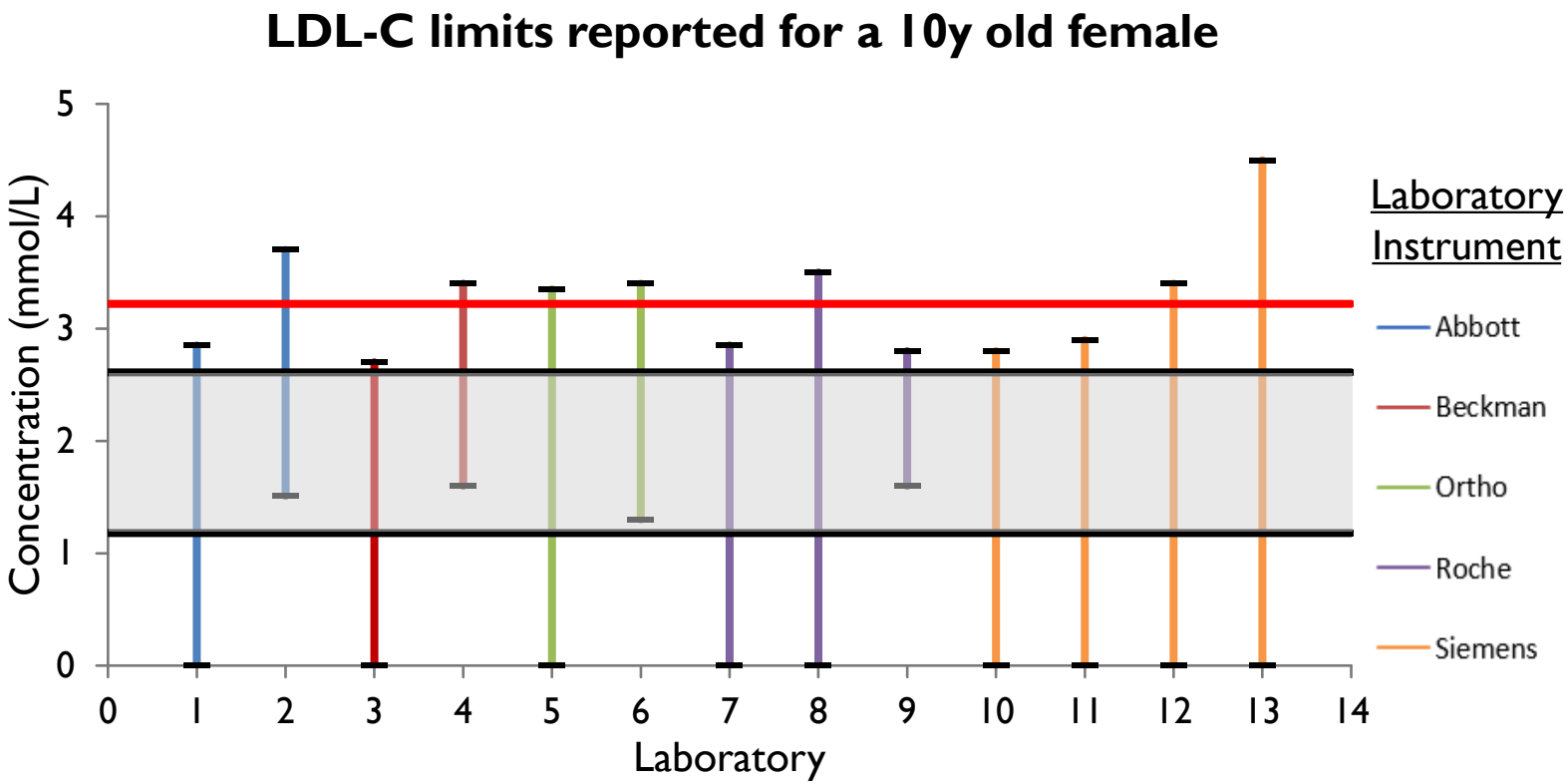
INTERPRETATIVE GUIDELINES FOR LIPID RESULTS

RISK LEVEL	INITIATE THERAPY	TARGETS
HIGH (FRS >=20%)	Consider in all	NON-HDL-C <=2.6 mmol/L or LDL-C* <=2 mmol/L or >=50% reduction
INTERMEDIATE (FRS 10%-20%)	Non-HDL-C >=4.3mmol/L or LDL-C* >=3.5mmol/L	Non-HDL <=2.6 mmol/L or LDL-C* <=2 mmol/L or >=50% reduction
LOW (FRS <10%)	LDL-C* >=5mmol/L or Familial Hypercholesterolemia	LDL-C* >=50% reduction

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).

Significant variability in the amount of information included and the reference for interpretative comments

LIPID REPORTING SURVEY RESULTS - PEDIATRICS



- Similar variability observed in reporting for total cholesterol, triglycerides, HDL-C, non-HDL-C, and apoB

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

LIPID REPORTING SURVEY RESULTS

Paediatric interpretative comments based on pediatric NHLBI Guidelines provide no age and sex stratification

Laboratory 6

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

	Acceptable	Borderline	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.

LIPID REPORTING SURVEY SUMMARY

- Significant differences exist in lipid reporting across Canada
  - Decision limits vs. reference intervals
  - Decision limit cutoffs
  - Interpretative comments

- Provincial harmonization in place for two provinces including Alberta and Newfoundland and Labrador
- However, most labs are not using the most recent CCS guidelines

It is essential to harmonize lipid reporting across Canada to ensure appropriate and uniform implementation of lipid and cardiovascular guidelines

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2016 CCS LIPID GUIDELINES

Canadian Journal of Cardiology 32 (2016) 1263–1282

Society Guidelines

2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult

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SCREENING

WHO TO SCREEN

Men ≥40 years of age; women ≥40 years of age (or postmenopausal)

Consider earlier in ethnic groups at increased risk such as South Asian or First Nations individuals

All patients with the following conditions regardless of age:

- Clinical evidence of atherosclerosis
- Abdominal aortic aneurysm
- Diabetes
- Arterial hypertension
- Current cigarette smoking
- Stigmata of dyslipidemia (arcus cornea, xanthelasma or xanthoma)
- Family history of premature CVD*
- Family history of dyslipidemia
- Chronic kidney disease
- Obesity (BMI ≥30 kg/m^2)
- Inflammatory bowel disease
- HIV infection
- Erectile dysfuntion
- Chronic obstructive pulmonary disease
- Hypertensive diseases of pregnancy

HOW TO SCREEN

For all:

- History and physical examination
- Standard lipid panel (TC, LDL-C, HDL-C, TG)
- Non-HDL-C (will be calculated from profile)
- Glucose
- eGFR

Optional:

- ApoB
- Urine albumin:creatinine ratio (if eGFR <60 mL/min/1.73m^2, hypertension or diabetes)

NON-FASTING LIPID TESTING IS ACCEPTABLE

Canadian Journal of Cardiology 2016 32, 1263-1282

FASTING VS NON-FASTING LIPID PROFILES

- Non-fasting lipids more representative of the normal state
- Increases convenience for patients
- Improve patient compliance
- Eliminates testing difficulty for patients who have trouble with prolonged fasting
- Samples received in lab throughout the day

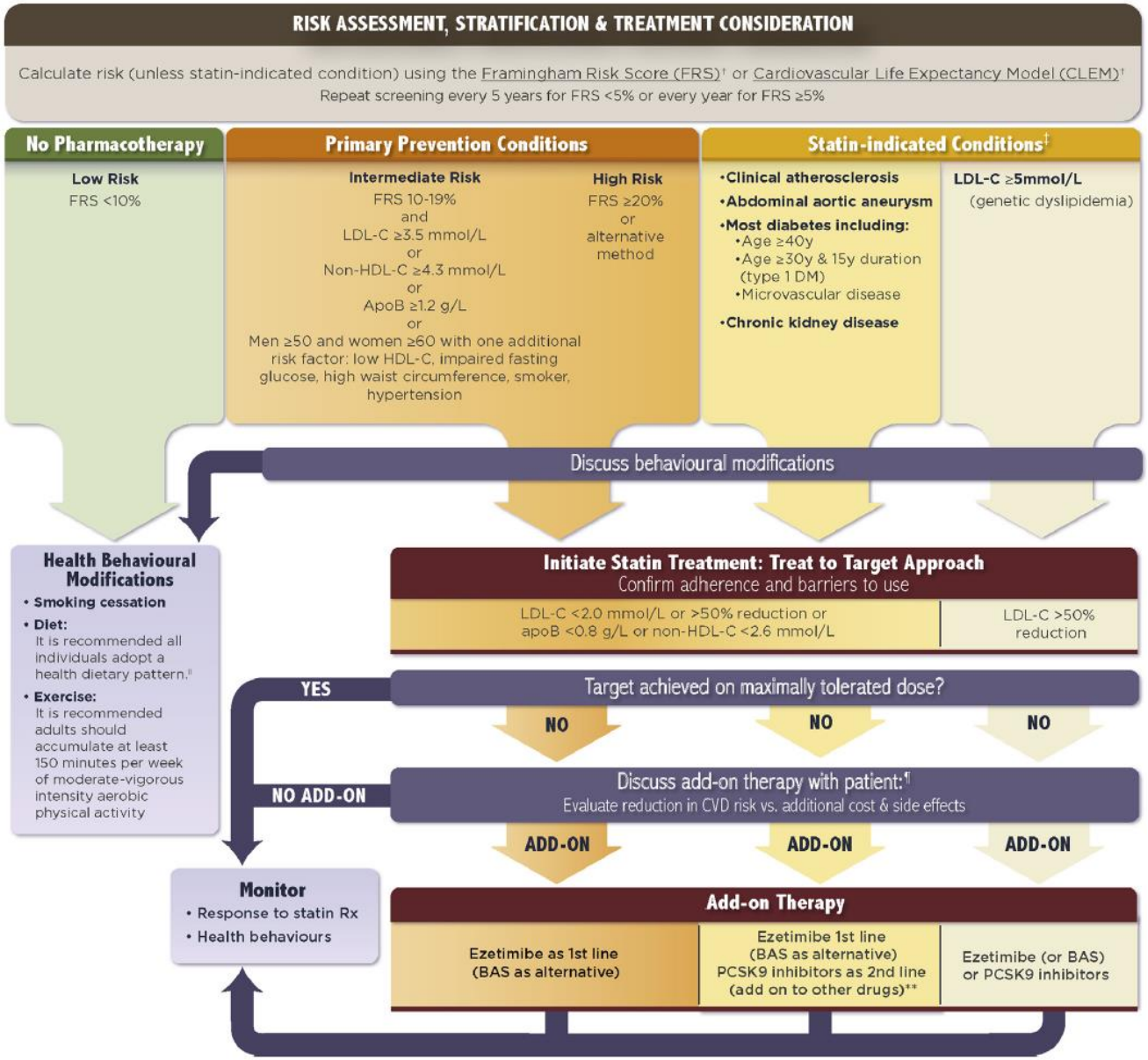
CLINICAL GUIDELINES: *FASTING OR NON-FASTING?*

- Danish Society for Clinical Biochemistry (2009)
- UK National Institute of Excellent (NICE, 2014)
- Canadian Cardiovascular Society Guidelines (2016)
- European Atherosclerosis Society and the European Federation of Clinical Chemistry and Laboratory Medicine (EAS/EFLM, 2016)
- 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

Non-fasting Recommended

2016 CCS LIPID GUIDELINES

RISK ASSESSMENT, STRATIFICATION, & TREATMENT



Canadian Journal of Cardiology 2016 32, 1263-1282

PEDIATRIC GUIDELINES

National Heart, Lung, and Blood Institute

No Canadian lipid guidelines specific for pediatrics

National Heart, Lung and Blood Institute. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. 2011

2011 NHLBI PEDIATRIC GUIDELINES

Lipid Parameter	Acceptable Limit	High Limit	Source
Total Cholesterol, mmol/L	<4.40	≥5.15	Lipid Research Clinics (LRC) Prevalence Study (1970-1976), ages 0-19 years
LDL-C, mmol/L	<2.85	≥3.35	
Triglycerides, mmol/L	0-<10y: <0.85 10-<18y: <1.00	0-<10y: ≥1.15 10-<18y: ≥1.45	
HDL-C, mmol/L	>1.15	<1.05	
Non-HDL-C, mmol/L	<3.10	≥3.75	Bogalusa Heart Study (1992-1994), ages 5-17 years
ApoB, g/L	<0.9	≥1.0	NHANES III (1988-1994), ages 4-18 years

Acceptable limit: 75th percentile (25th for HDL-C)
High limit: 95th percentile (10th percentile for HDL-C (low))

National Heart, Lung and Blood Institute. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. 2011

WOULD CALIPER BE MORE SUITABLE?

- Pediatric reference interval database for over 180 biomarkers
- Collected blood samples from over 12,000 healthy children and adolescents

Advantages:

- Derived from a Canadian population
- Specific for age and sex
- Defined lower limit
- Updated methodology
- Non-fasting blood samples

CALIPER

'ARM' us with the knowledge to help others

REFERENCE INTERVALS VS. DECISION LIMITS

RIs and DLs are often listed in the same column on reports, which can confuse the basis of terminology and the distinction between the two

Reference Intervals: The range of laboratory test results expected in a healthy reference population (commonly defined as the 2.5th and 97.5th percentiles)

Decision Limits: Threshold values, in which values exceeding or falling below the threshold indicating the patient is at a significantly higher risk of a clinical outcome or satisfies criteria for diagnosis of a specific disease

"When decision limits determined by national or worldwide consensus exist, these limits, rather than reference intervals should be reported" – CLSI EP28-A3c

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SHOULD WE FLAG ON …

Treatment Initiation

Analyte	Decision Limit	Flagging Rate
LDL-C	<3.5 mmol/L	**21.7%**
Non-HDL-C	<4.3 mmol/L	**22.5%**
ApoB	<1.2 g/L	

Intermediate-Risk Patients

OR

Treatment Target

Analyte	Decision Limit	Flagging Rate
LDL-C	<2.0 mmol/L	**78.9%**
Non-HDL-C	<2.6 mmol/L	**80.4%**
ApoB	<0.8 g/L	

Intermediate- and High-Risk Patients on Treatment

?

**Flagging rates based on DynaLIFE (Edmonton, Alberta) data (n = 451232-463881)*

SHOULD WE FLAG ON …

Treatment Initiation

- Lower flagging rates (lower false positive rate)
  - Not flagging everyone!
- Values should be flagged when physicians need to be alerted (patients on treatment already monitored)

OR

Treatment Target

- Higher flagging rates (lower false negative rate)
  - Won't miss anyone!

RECOMMENDED HARMONIZED ADULT LIPID REPORT

Analyte	Decision Limit	Result Comment
Total Cholesterol	<5.2 mmol/L	Treatment thresholds and targets based on the 2016 CCS Guidelines For patients ≥40 years, estimate risk using the modified Framingham Risk Score (FRS): **Low Risk (FRS < 10%)** Treatment advised if LDL-C ≥ 5.0 mmol/L Treatment target: ≥ 50% reduction LDL-C **Intermediate Risk (FRS 10 - 19%)** Treatment advised if LDL-C ≥ 3.5 mmol/L OR Non-HDL-C ≥4.3 mmol/L OR ApoB ≥ 1.2 g/L OR Men≥50 and women≥60 yrs with ≥1 additional CV risk factor Treatment targets: LDL-C ≤ 2.0 mmol/L OR decrease by ≥50% OR Non-HDL-C ≤2.6 mmol/L OR ApoB ≤ 0.8 g/L **High Risk (FRS ≥20% or presence of high-risk features)** Treatment advised in all patients Treatment targets: LDL-C ≤2.0 mmol/L OR decrease by ≥50% OR Non-HDL-C ≤ 2.6 mmol/L OR ApoB ≤ 0.8 g/L If non-fasting, triglycerides <2.0 mmol/L acceptable If triglycerides >1.5 mmol/L, recommend using non-HDL-C or ApoB as treatment target of choice If triglycerides >4.5 mmol/L, LDL-C cannot be reported & recommend measuring lipids and lipoproteins fasted
HDL-C	>1.0 mmol/L	
LDL-C	<3.5 mmol/L	
Triglycerides	<1.7 mmol/L	
Non-HDL-C	<4.3 mmol/L	
Fasting (hours)	Record (h)	
ApoB	<1.2 g/L	Treatment thresholds and targets based on the 2016 CCS Guidelines If apoB ≥1.2 g/L: Treatment advised if Framingham Risk Score is Intermediate or High. Treatment target for ApoB ≤ 0.8 g/L If apoB <1.2 g/L: Treatment target for ApoB ≤ 0.8 g/L

CALIPER REFERENCE INTERVALS

Analyte	Age Range (years)	Reference Intervals (mmol/L)	Flagging Rate	
			Lower Limit (2.5th)	Upper Limit (97.5th)
Total Cholesterol	1-<18	2.90-5.40	3.47%	7.46%
HDL-C	1-<4 4-<13 13-<18 M 13-<18 F	0.84-1.63 0.92-1.88 0.82-1.77 0.83-1.86	3.06%	5.83%
LDL-C	1-<10M 1-<10F 10-<18	1.22-3.14 1.52-3.32 1.18-3.40	3.03%	6.54%
Triglycerides	1-<18	0.50-2.23	5.43%	8.69%
Non-HDL-C	1-<10M 1-<10F 10-<18	1.79-3.68 2.07-4.28 1.68-4.04	4.51%	8.22%
ApoB	1-<6 6-<18	0.41-0.93 0.31-0.84		

**Flagging rates based on DynaLIFE (Edmonton, Alberta) data (n = 6670-6745)*

Lower Reference Limits

- Useful to identify pediatric lipid diseases (e.g., hypobetalipoproteinemia, abetalipoproteinemia)

Colantonio D, et al. Clin Chem 2012; Higgins V, et al. Clin Chim Acta 2018

SHOULD WE FLAG ON …

NHLBI Guidelines

Analyte	Flagging Rates	
	Acceptable (75^{th})	High/Low ($95^{th}/10^{th}$)
Total Cholesterol	35.9%	11.5%
HDL-C	32.9%	20.5%
LDL-C	19.3%	7.00%
Triglycerides	54.0%	28.0%
Non-HDL-C	34.0%	12.5%

25^{th} and 10^{th} percentile for HDL-C

OR

CALIPER Limits

Analyte	Flagging Rate	
	Acceptable (75^{th})	High/Low ($95^{th}/10^{th}$)
Total Cholesterol	29.3%	9.43%
HDL-C	28.5%	12.7%
LDL-C	29.5%	9.37%
Triglycerides	26.6%	11.0%
Non-HDL-C	30.3%	10.2%

25^{th} and 10^{th} percentile for HDL-C

?

*Flagging rates based on DynaLIFE (Edmonton, Alberta) data (n = 6670-6745)

SHOULD WE FLAG ON …

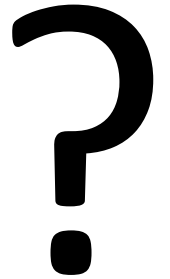
NHLBI Guidelines

- Guidelines published and used clinically in the US
- Decision limits established prior to the obesity epidemic

OR

CALIPER Limits

- Derived from a Canadian population
- Specific for age and sex
- Defined lower limit
- Updated methodology
- Non-fasting blood samples



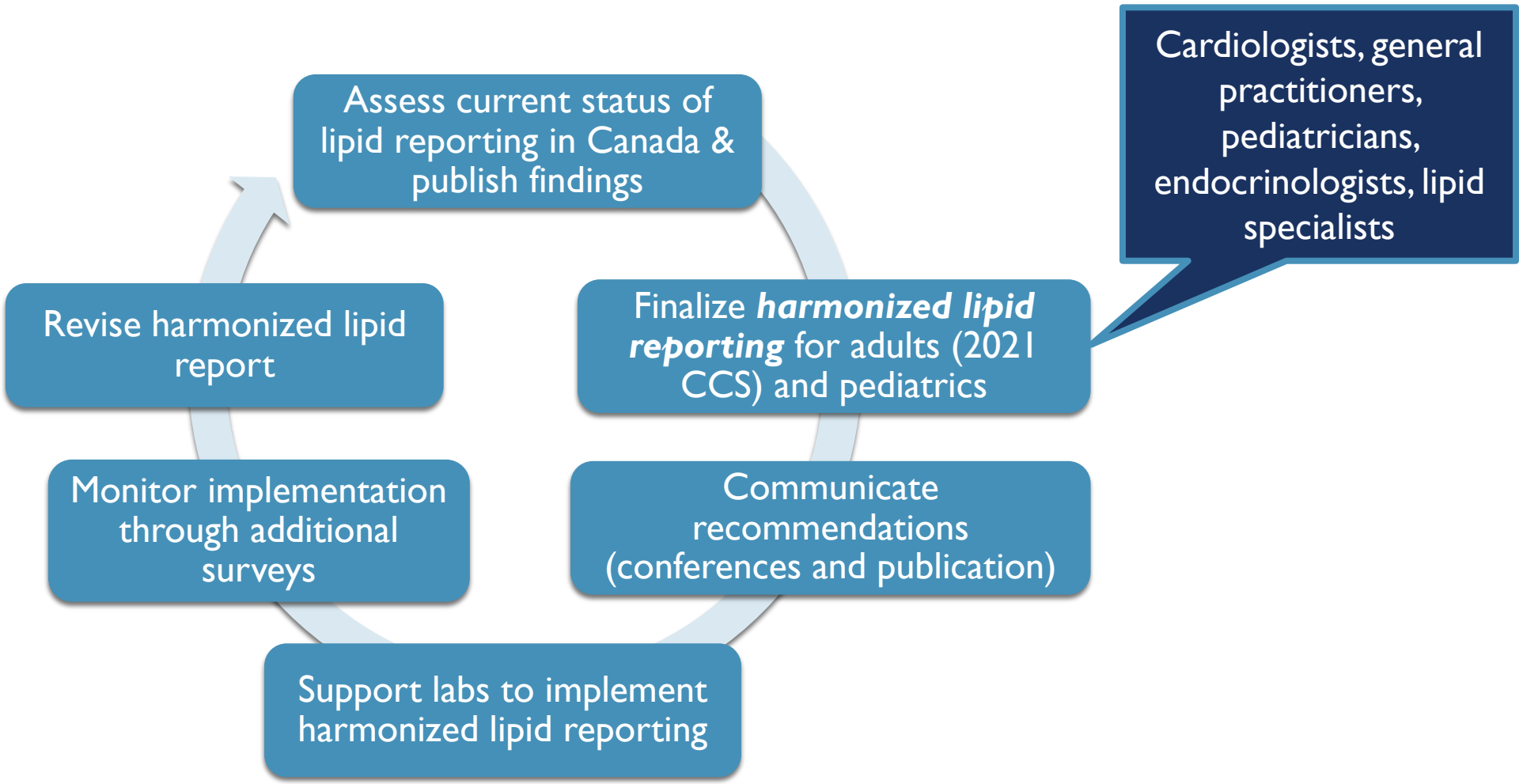
RECOMMENDED HARMONIZED PEDIATRIC LIPID REPORT

Analyte	Sex	Age	Decision Limit	Result Comment
Total Cholesterol	Both	<18 y	<4.54 mmol/L	Based on CALIPER data of healthy Canadian children & adolescents. Decision limit corresponds to 75th percentile for all parameters, except 25th percentile for HDL-C.
HDL-C	Both	4-<13 y	>1.17 mmol/L	
	Male	13-<18 y	>1.05 mmol/L	
	Female	13-<18 y	>1.19 mmol/L	
LDL-C	Male	1-<10 y	<2.43 mmol/L	
	Female	1-<10 y	<2.54 mmol/L	
	Both	10-<19 y	<2.61 mmol/L	
Triglycerides	Both	1-<18 y	<1.44 mmol/L	
Non-HDL-C	Male	1-<10y	<3.01 mmol/L	
	Female	1-<10y	<3.24 mmol/L	
	Both	10-<19y	<3.19 mmol/L	
Hours fasting	Record (h)			
ApoB	Both	1-<6 y	<0.72 g/L	Based on CALIPER data of healthy Canadian children & adolescents. Decision limit corresponds to 75th percentile.
		6-<18 y	<0.63 g/L	

CHALLENGES TO IMPLEMENTING HARMONIZED LIPID REPORTING

- LIS limitations
- Physicians' preference to exclude lengthy comments on report
- Harmonized provincial or regional recommendations already in place

ACTION PLAN


Assess current status of lipid reporting in Canada & publish findings
Finalize ***harmonized lipid reporting*** for adults (2021 CCS) and pediatrics
Communicate recommendations (conferences and publication)
Support labs to implement harmonized lipid reporting
Monitor implementation through additional surveys
Revise harmonized lipid report
Cardiologists, general practitioners, pediatricians, endocrinologists, lipid specialists

CONCLUDING REMARKS

- There is significant variability in adult and pediatric lipid reporting across Canada
- CCS Guidelines for management of dyslipidemia is the basis for the adult harmonized lipid report
- Pediatric harmonized lipid report is based on CALIPER data and NHLBI percentile cut-offs
- Harmonized pediatric & adult lipid reports will help improve patient care

ACKNOWLEDGEMENTS

Lipid Team

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