Harmonized Lipid Reporting Recommendations:

An update from the CSCC Working Group on Reference Interval Harmonization

---

2018 OSCC ANNUAL SCIENTIFIC MEETING

VICTORIA HIGGINS

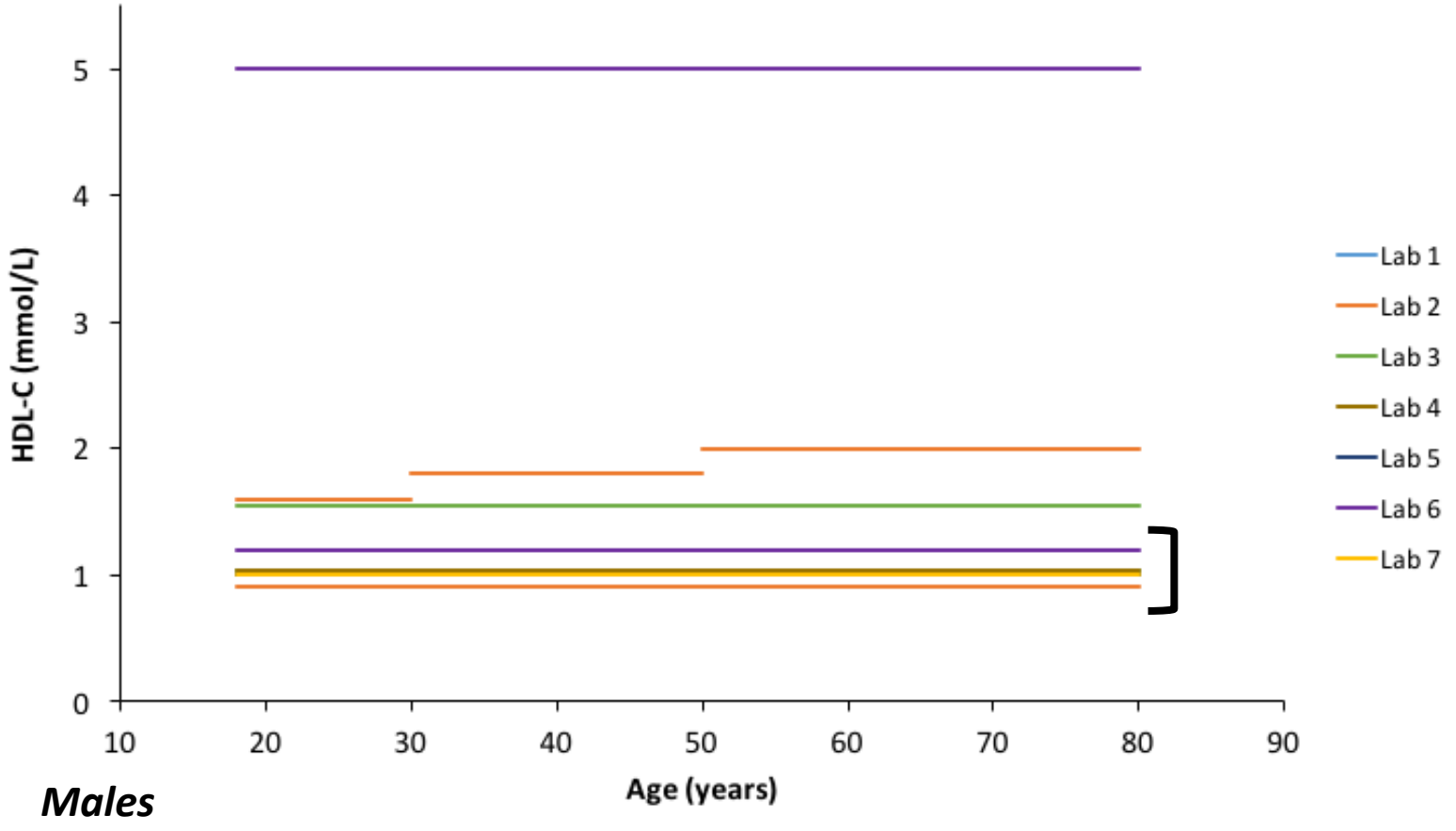
CANADIAN SOCIETY OF CLINICAL CHEMISTS LA SOCIÉTÉ CANADIENNE DES CLINICO-CHIMISTES

I, VICTORIA HIGGINS, DECLARE THAT NEITHER I NOR ANY MEMBER OF MY IMMEDIATE FAMILY HAS A FINANCIAL INTEREST IN A COMPANY AS DEFINED IN THE CSCC/CACB POLICIES ON CONFLICT OF INTEREST.

Laboratory Testing for Lipids

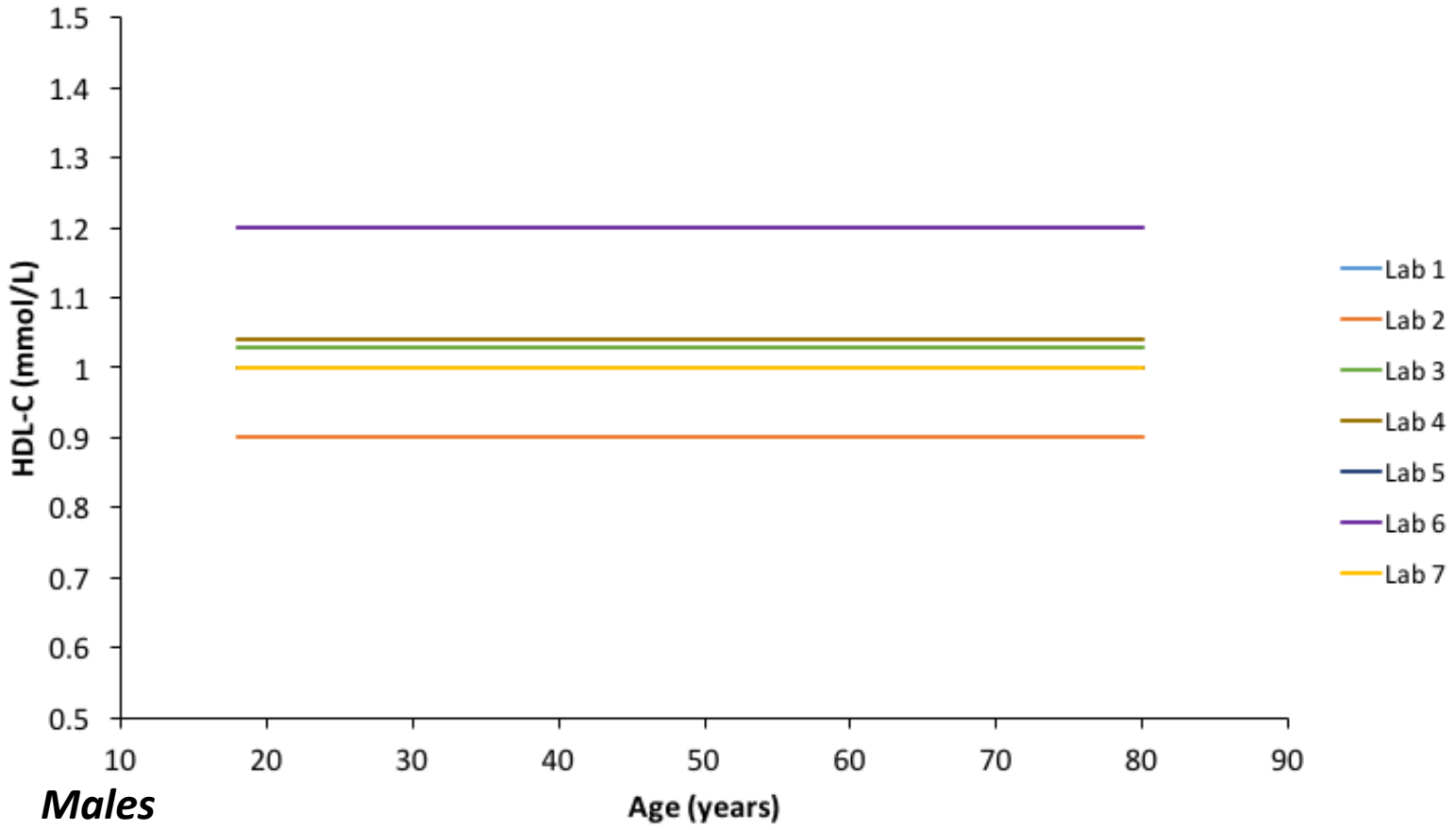
- Management of dyslipidemia and prevention of cardiovascular disease
- Traditional fasting lipid panel:
  - Total cholesterol
  - Triglycerides
  - Low-density lipoprotein cholesterol (LDL-C)
  - High-density lipoprotein cholesterol (HDL-C)
- Markers of total atherogenic lipoproteins
  - Non-HDL-C (cholesterol content)
    - Calculated as total cholesterol minus HDL-C
  - ApoB (particle number)

Lipid Reporting in Canada: Survey Results



Males

Lipid Reporting in Canada: Survey Results



Males

Lipid Reporting in Canada: Survey Results

Variability in lipid reporting observed:

- Sex-specific HDL-C limits
- LDL-C limits (3.5 vs. 2.0 mmol/L)
- Non-fasting lipid testing
  - Specific non-fasting TG limits
- Source of limits
  - Historical, Guidelines (CCS, NCEP)
  - Pediatric: Pediatric Reference Intervals (AACC Press), CALIPER reference intervals, NHLBI guidelines

Reference Intervals or Decision Limits?

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

Decision Limits: Threshold values, in which values exceeding or falling below the threshold indicate 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

Reference Intervals or Decision Limits?

Lipid Parameter	Upper Reference Limit Flagging Rate	Decision Limit Flagging Rate
Triglycerides	3.86%	39.0%
Total Cholesterol	2.05%	21.7%
LDL-C	3.30%	18.3%
HDL-C	11.4% (LRL)	37.2%

Upper Reference Limits from Canadian Health Measures Survey (CHMS)

**Flagging rates based on Alberta DynaLife data (n = 451232-463881)*

Adult Lipid Reporting

What is the evidence?

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

- Who to screen
- Risk assessment
- Treatment initiation
- Treatment targets

2016 CCS Guidelines

What do they say about lipid reporting?

FRS Risk Level	Treatment Initiation	Treatment Target	
		Primary	Alternate
Low (FRS < 10%)	LDL-C ≥ 5.0 mmol/L (familial hypercholesterolemia)	>50% reduction in LDL-C	
Intermediate (FRS 10%-19%)	LDL-C ≥ 3.5 mmol/L ***or*** apoB ≥ 1.2 g/L ***or*** non-HDL-C ≥ 4.3 mmol/L	LDL-C <2.0 mmol/L or >50% reduction	apoB <0.8 g/L ***or*** non-HDL-C <2.6 mmol/L
High (FRS ≥ 20%)	Consider treatment in all patients		

FRS, Modified Framingham Risk Score

No recommendations provided for total cholesterol, HDL-C, or triglycerides

NCEP Adult Treatment Panel III

Total Cholesterol

- Optimal total cholesterol <5.2 mmol/L
  - Framingham study showed increased CHD incidence when total cholesterol >5.2 mmol/L

HDL-C

- Men: Independent of TG, patients with HDL-C <1.0 mmol/L were insulin resistant
- Women: HDL-C <1.3 mmol/L indicated lower insulin sensitivity

Triglycerides

- Optimal triglycerides <1.7 mmol/L
  - Literature review of prospective studies identified triglycerides > 1.7 mmol/L strongly associated with CHD

Recommended Adult (> 18 yrs) Lipid Report

Analyte	Decision Limit	Result Comment
Total Cholesterol	<5.20 mmol/L	Refer to 2016 CCS Guidelines FRS (http://www.cvdriskchecksecure.com/framingham-risk-score)
HDL-C	Males >1.00 mmol/L; Females > 1.30 mmol/L	**Low Risk:** Tx advised: LDL-C ≥5.0 mmol/L; Tx target: ≥50% reduction LDL-C **Intermediate Risk:** Tx advised: LDL-C ≥3.5 mmol/L OR Non-HDL-C ≥4.3 mmol/L OR ApoB ≥1.2 g/L OR ≥1 risk factor Tx 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:** Treat all; Tx 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
LDL-C	<3.5 mmol/L	
Triglycerides	<1.7 mmol/L	Non-fasting TG <2.0 mmol/L acceptable TG >1.5 mmol/L, use non-HDL-C or ApoB Tx target TG >4.5 mmol/L, measure fasted
Non-HDL-C	<4.3 mmol/L	
Hours fasting	Record (h)	

ApoB	<1.2 g/L	Refer to 2016 CCS Guidelines FRS (http://www.cvdriskchecksecure.com/framingham-risk-score) **If ≥1.2 g/L** Tx advised: FRS Intermediate or High; Tx target: ApoB ≤0.8 g/L **If <1.2 g/L** Tx target: ApoB ≤0.8 g/L

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 Patients on Treatment

**Flagging rates based on Alberta DynaLife 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)

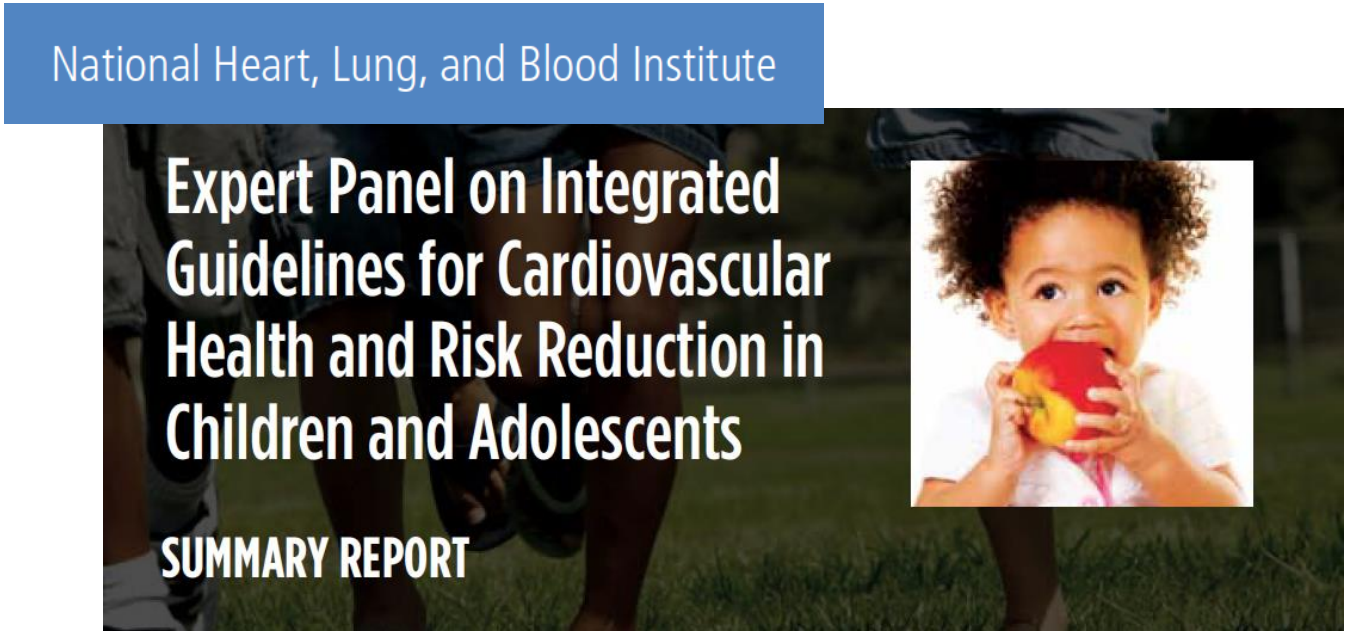
OR

Treatment Target

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

Pediatric Lipid Decision Limits

What is the evidence?



- Dyslipidemia is associated with initiation and progression of atherosclerotic lesions in children and adolescents

2011 NHLBI Pediatric Guidelines

Lipid Parameter	Acceptable Limit	High Limit	Source
Total Cholesterol	75th percentile	95th percentile	Lipid Research Clinics (LRC) Prevalence Study (1970-1976), ages 0-19 years
LDL-C			
Triglycerides			
HDL-C	25th percentile	10th percentile (Low)	
Non-HDL-C	Equivalent to LDL-C limits		Bogalusa Heart Study (1992-1994), ages 5-17 years
ApoB	75th percentile	95th percentile	NHANES III (1988-1994), ages 4-18 years

Recommended Pediatric Lipid Report

Analyte	Age	Decision Limit	Result Comment
Total Cholesterol	<18 years	<4.40 mmol/L	Based on NHLBI 2011 for Children and Adolescents Acceptable and high/low limits relative to dyslipidemia and atherosclerosis risk: Total Cholesterol Acceptable < 4.40 mmol/L; High ≥ 5.15 mmol/L HDL-C Acceptable > 1.15 mmol/L; Low < 1.05 mmol/L LDL-C Acceptable < 2.85 mmol/L; High ≥ 3.35 mmol/L Triglycerides (0-<10 yrs) Acceptable < 0.85 mmol/L; High ≥ 1.15 mmol/L Triglycerides (10-<18 yrs) Acceptable < 1.00 mmol/L High ≥ 1.45 mmol/L Non-HDL-C Acceptable < 3.10 mmol/L; High ≥ 3.75 mmol/L
HDL-C	<18 years	>1.15 mmol/L	
LDL-C	<18 years	<2.85 mmol/L	
Triglycerides	<10 years	< 0.85 mmol/L	
	10-<18 years	< 1.00 mmol/L	
Non-HDL-C	<18 years	< 3.10 mmol/L	
Hours fasting	Record (h)		
ApoB	<18 years	<0.9 g/L	Based on NHLBI 2011 for Children and Adolescents Acceptable < 0.9 g/L; High **≥** 1.0 g/L

Flagging on acceptable limits: low risk associated with false positives

Would CALIPER Reference Intervals be more suitable?

- Pediatric reference interval database for over 170 biomarkers
- Collected blood samples from over 10,000 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

CALIPER Reference Intervals

Analyte	Age Range (years)	Reference Intervals (mmol/L)	Flagging Rate	
			Lower Limit	Upper Limit
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%

Lower Reference Limits

- Useful to identify pediatric lipid diseases (e.g. apoA1 deficiency, abetalipoproteinemia)

Upper Reference Limits

- Very low flagging rate when using 97.5th percentile

**Flagging rates based on Alberta DynaLife data (n = 6670-6745)*

Should we flag using…

NHLBI Guidelines

Analyte	Flagging Rates	
	Acceptable	High/Low
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%

OR

CALIPER Limits

Analyte	Flagging Rate	
	Acceptable	High/Low
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%

**Flagging rates based on Alberta DynaLife data (n = 6670-6745)*

Should we flag using…

NHLBI Guidelines

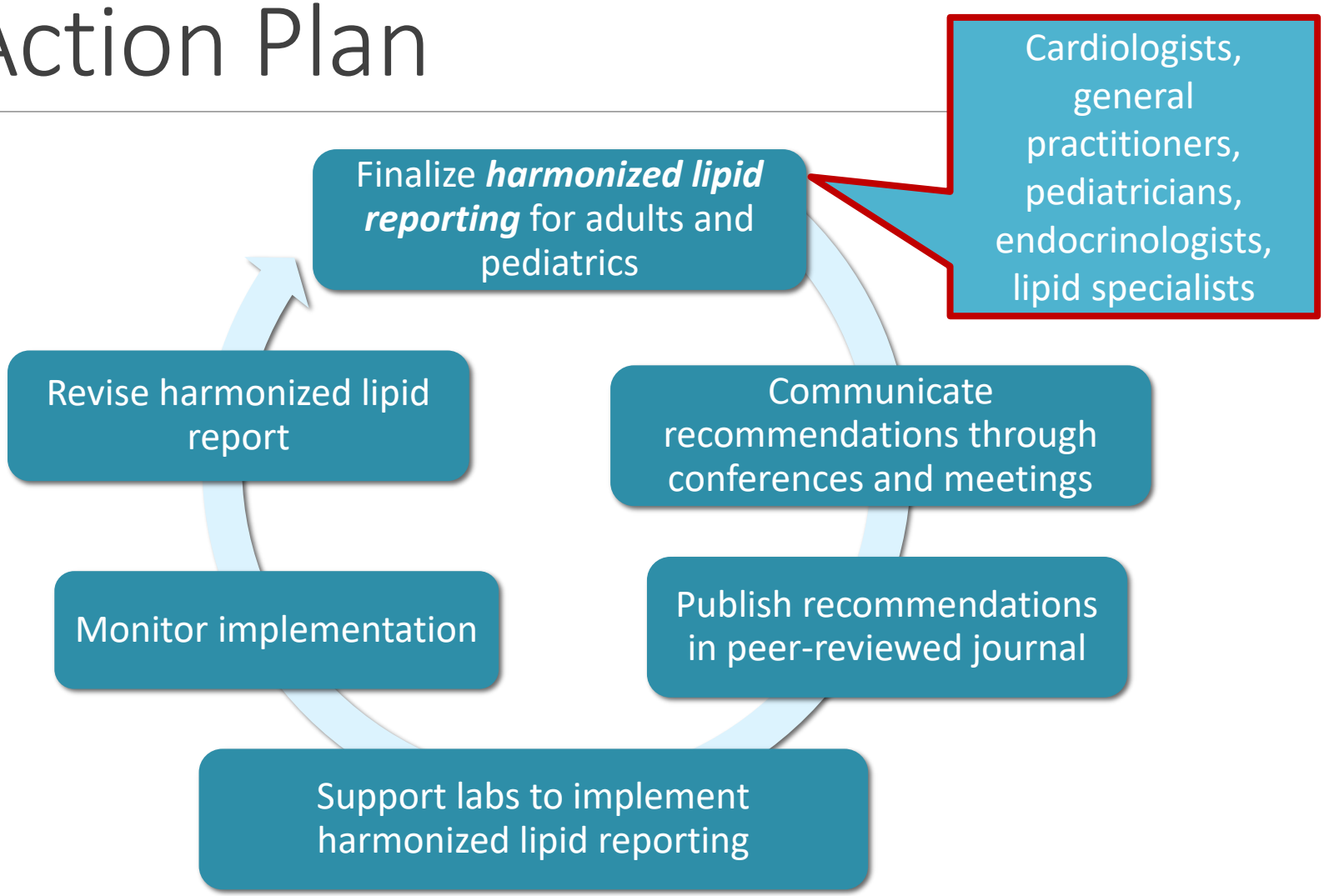
- Guidelines published and used clinically in the US
- Decision limits established prior to the obesity epidemic

OR

CALIPER Limits

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

Action Plan


Finalize ***harmonized lipid reporting*** for adults and pediatrics
Cardiologists, general practitioners, pediatricians, endocrinologists, lipid specialists
Communicate recommendations through conferences and meetings
Publish recommendations in peer-reviewed journal
Support labs to implement harmonized lipid reporting
Monitor implementation
Revise harmonized lipid report

Acknowledgements

Khosrow Adeli
Christine Collier
Nicole White-Al Habeeb
Dana Bailey
Allison Venner
Terrance Agbor
Shervin Asgari
Cynthia Balion
George Cembrowski
Jake Cosme
Jim Dalton
Angela Fung
Trefor Higgins
Joska Ivica
Felix Leung
Joseph Macri
Janet Simmons
Michelle Parker
Omair Sarfaraz
David Seccombe
Julie Shaw
Julia Stemp
Jennifer Taher
Dorothy Truong
Uvaraj Uddayasankar

Supplemental Slides

What is the evidence for adult decision limits?

Total Cholesterol

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

LDL-C, ApoB and non-HDL-C

Treatment Initiation

- 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
  - Included subjects without vascular disease who on average were in the FRS IR group, but also include some HR and LR subjects

Treatment Targets

- Treatment target LDL-C ≤2.0 mmol/L - Data from PROVE-IT, TNT, A to Z, IDEAL and SEARCH trials confirmed that lowering the LDL-C to a mean of 2.0 mmol/L or less is associated with the lowest risk of recurrent CVD events in secondary prevention patient populations

What is the evidence for adult decision limits?

Triglycerides

- NCEP ATP III panel reviewed studies and found TG >1.7mmol/L substantially increased CHD risk
- In non-fasting patients TG >2.0 mmol/L, as TG increase ~20% in non-fasting vs. fasting individuals (European Atherosclerosis Society)

HDL-C

- Population studies show a continuous rise in CHD risk as HDL-C levels decline; no threshold relationship defined and therefore any categorical definition of low HDL-C is arbitrary. NCEP ATP III recommended a categorical low HDL-C defined as <1.03 mmol/L (40 mg/dL)
- Women typically have higher HDL-C
- Metabolic syndrome
  - Men: patients with HDL-C <1.0 mmol/L were insulin resistant independent of TG levels
  - Women: Sex-specific differences in untreated hypertensive patients - women with HDL-C <1.3 mmol/L had lower insulin sensitivity

2011 NHLBI Pediatric Guidelines

What do they say about lipid reporting?

- Universal screening for 9-11 year olds and 17-21 year olds

Lipid Parameter	Value Range	Treatment Initiation (after 6 months of diet and lifestyle intervention)	Treatment Target
LDL-C	3.4-4.0 mmol/L	Initiate statin treatment if 2 high-level risk factors ***or*** 1 high-level + 2 moderate-level risk factors ***or*** clinical CVD	LDL-C < 3.4 mmol/L
	4.1-4.9 mmol/L	Initiate statin treatment if positive family history ***or*** 1 high-level risk factor ***or*** ≥ 2 moderate-level risk factors	
	≥ 5.0 mmol/L	Initiate statin treatment	

Children <10 years should only be treated with medication if have severe primary hyperlipidemia or high-risk condition associated with serious medical morbidity.

Decision Limits Calculated using CALIPER Data

Analyte	Age Range	75th Percentile (Acceptable)	95th Percentile (High)
Total Cholesterol	0-14 d M	2.22	2.76
	0-14 d F	2.62	3.08
	15d-<1 yr	4.46	5.82
	1-<18 yrs	4.54	5.25
LDL-C	0-<1 yr	2.36	3.82
	1-<10 yrs M	2.43	3.04
	1-<10 yrs F	2.54	3.16
	10-<18 yrs	2.61	3.22
Triglycerides	0-14 d	2.04	2.66
	15d-<1 yr	1.08	2.87
	1-<18 yrs	1.44	2.04
Non-HDL-C	0-<1 yr	3.17	4.76
	1-<10 yrs M	3.01	3.62
	1-<10 yrs F	3.24	3.98
	10-<18 yrs	3.19	3.88
ApoB	0-14 d	0.48	0.61
	15d-<1 yr	0.76	1.10
	1-<6 yrs	0.72	0.87
	6-<18 yrs	0.63	0.80

Analyte	Age Range	25th Percentile (Acceptable)	10th Percentile (Low)
HDL-C	0-14 d M	0.58	0.49
	0-14 d F	0.89	0.60
	15d-<1 yr	1.04	0.93
	1-<4 yrs	1.17	1.05
	4-<13 yrs	1.05	0.93
	13-<18 yrs M	1.19	1.02
	13-<18 yrs F		

Should we flag on…

Acceptable Limits

Analyte	Decision Limit	Flagging Rate
Total Cholesterol	<4.40 mmol/L	35.9%
HDL-C	>1.15 mmol/L	32.9%
LDL-C	<2.85 mmol/L	19.3%
Triglycerides (<10 yrs)	< 0.85 mmol/L	54.0%
Triglycerides (10-18 yrs)	< 1.00 mmol/L	
Non-HDL-C	< 3.10 mmol/L	34.0%

OR

High/Low Limits

Analyte	Decision Limit	Flagging Rate
Total Cholesterol	<5.15 mmol/L	11.5%
HDL-C	>1.05 mmol/L	20.5%
LDL-C	<3.35 mmol/L	7.00%
Triglycerides (<10 yrs)	< 1.15 mmol/L	28.0%
Triglycerides (10-18 yrs)	< 1.45 mmol/L	
Non-HDL-C	< 3.75 mmol/L	12.5%

**Flagging rates based on Alberta DynaLife data (n = 6670-6745)*

Should we flag on…

Acceptable Limits

- Higher flagging rates (lower false negative rate)
  - Won't miss anyone!
- Low risk of false positive, as recommended treatment is most often diet and lifestyle modification

OR

High/Low Limits

- Lowing flagging rates (lower false positive rate)
  - Not flagging everyone!
- May miss children that would benefit from diet and lifestyle education