Rational use of Biochemistry testing

annual refresher course for family physicians

November 26 2018

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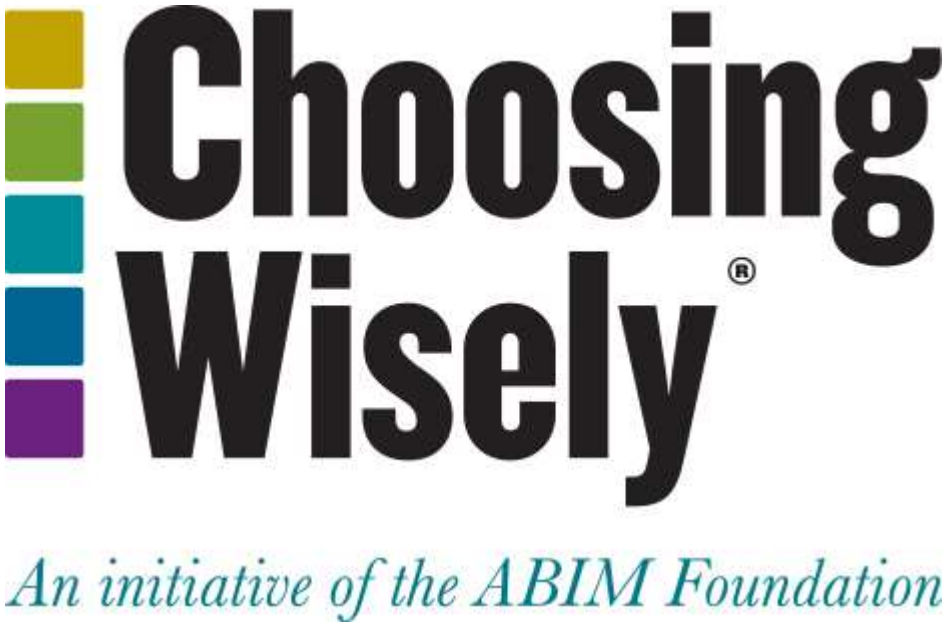
Declaration

- "I (we) declare that I have no conflicts of interest in the authorship of this contribution."

Learning objectives

- Organizations promoting rational use of biochemistry tests
- Identify the appropriate biochemistry tests recommended by the CTFPHC (now the CTFOTPHE) and the USPSTF for the periodic health exam (screening)
- Learn about the best tests for specific diagnoses



In 2012 the ABIM Foundation launched *Choosing Wisely*® with a goal of advancing a national dialogue on avoiding wasteful or unnecessary medical tests, treatments and procedures

Key Principles

- We need to order tests and prescribe medications based on best evidence. Unnecessary medications can cause unwanted side effects, and unnecessary testing can lead to further testing or possible harm.

- We have an obligation to our patients, profession and society to be responsible stewards of medical resources. If we are all committed to evidence-based prescribing and test ordering, we can reduce the great overuse of health care resources in the US, and make medical care more efficient and affordable

Mission

INESSS's mission is to promote clinical excellence and the efficient use of resources in the health and social services sector. At the heart of the mission, INESSS assesses, in particular, the clinical advantages and the costs of the technologies, medications and interventions used in health care and personal social services. It issues recommendations concerning their adoption, use and coverage by the public plan, and develops guides to clinical practice in order to ensure their optimal use.

Usage judicieux de 14 analyses biomédicales: Avril 2014

Les résultats des 14 analyses sont présentés dans les sections suivantes, soit d'abord les analyses en biochimie suivies des analyses en hématologie.

Liste d'analyses incluses biochimie:

- 1. Amylase et lipase sériques pour le diagnostic de la pancréatite aiguë
- 2. Aspartate aminotransférase (AST) pour la détection d'une atteinte hépatique
- 3. Bilirubine directe pour la détection d'une cholestase
- 4. Créatine kinase MB (CK-MB) pour le diagnostic de l'infarctus aigu du myocarde

Usage judicieux de 14 analyses biomédicales: Avril 2014

Résultats:

- 5. Électrophorèse des protéines sériques
- 6. Lactate déshydrogénase (LDH) dans le diagnostic de l'infarctus aigu du myocarde
- 7. Thyroxine Libre (T4L) pour le diagnostic d'une maladie thyroïdienne
- 8. Urée pour l'évaluation de la fonction rénale
- 9. Vitamine D 25-OH

Why order tests

- Screening
- Diagnosis
- To assess response to a specific treatment
- To determine prognosis

Periodic screening

Why develop periodic screening procedures?

- asymptomatic adults harbor organic disease
- screening can detect a disease at an early stage
- early detection can alter the course of the disease.

THE COLLEGE OF FAMILY PHYSICIANS OF CANADA

LE COLLÈGE DES MÉDECINS DE FAMILLE DU CANADA

Preventive Care Checklist Forms

Preventive Care Checklist

- Biochemistry tests
  males and females age 21-64:
  Hemoccult multiphase q1-2 years (age ≥50)

  Fasting Blood Glucose of A1C if at risk

  Fasting Lipid Profile (≥40 yr or sooner if at risk males) or Fasting Lipid Profile (≥50 yr or postmenopausal or sooner if at risk females)

Preventive Care Checklist

- Biochemistry tests:

  males and females age >65:

  Hemoccult multiphase q1-2 years (age 65-74)

  Fasting Blood Glucose or A1C if at risk

  Fasting Lipid Profile q1-5 years (up to 75)

CTF recommendations

- Do’s= A & B recommendations
- Don'ts= D & E recommendations

CTF
D & E recommendations

Diabetes Mellitus	Blood glucose fasting	General population
Ovarian cancer	CA125	pre and post menopausal
Pancreatic cancer	CA 19-9	General population
Prostate cancer	PSA	Males> 50
UTI	Urine dipstick/culture	Elderly ambulatory males,
		elderly


U.S. Preventive Services
TASK FORCE

Type 2 Diabetes Mellitus: Screening
Release Date: October 2015

Population	Recommendation	Grade
Adults aged 40 to 70 years who are overweight or obese	The USPSTF recommends screening for abnormal blood glucose as part of cardiovascular risk assessment in adults aged 40 to 70 years who are overweight or obese. Clinicians should offer or refer patients with abnormal blood glucose to intensive behavioral counseling interventions to promote a healthful diet and physical activity.	B

Prostate Cancer: Screening Release Date: May 2012

Population	Recommendation	Grade
Men, Screening with PSA	The U.S. Preventive Services Task Force (USPSTF) recommends against prostate-specific antigen (PSA)-based screening for prostate cancer.	D

Colorectal Cancer: Screening Release Date: June 2016

Population	Recommendation	Grade A
Adults aged 50 to 75 years	The USPSTF recommends screening for colorectal cancer starting at age 50 years and continuing until age 75 years. The risks and benefits of different screening methods vary.	

Thyroid Dysfunction: Screening
Release Date: March 2015

Population	Recommendation	Grade
Nonpregnant, asymptomatic adults	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for thyroid dysfunction in nonpregnant, asymptomatic adults.	I

Not screening tests!

Tumor markers such as PSA, CEA, CA 125, CA 19-9:

1. are not useful as a screening assay for cancer detection in the normal population
2. results can not be interpreted as absolute evidence of the presence or absence of cancer
3. serum markers are not specific for malignancy and values may vary by method
4. useful for evaluating patients' response to therapy
5. predicting recurrence

CA-125

- CA -125

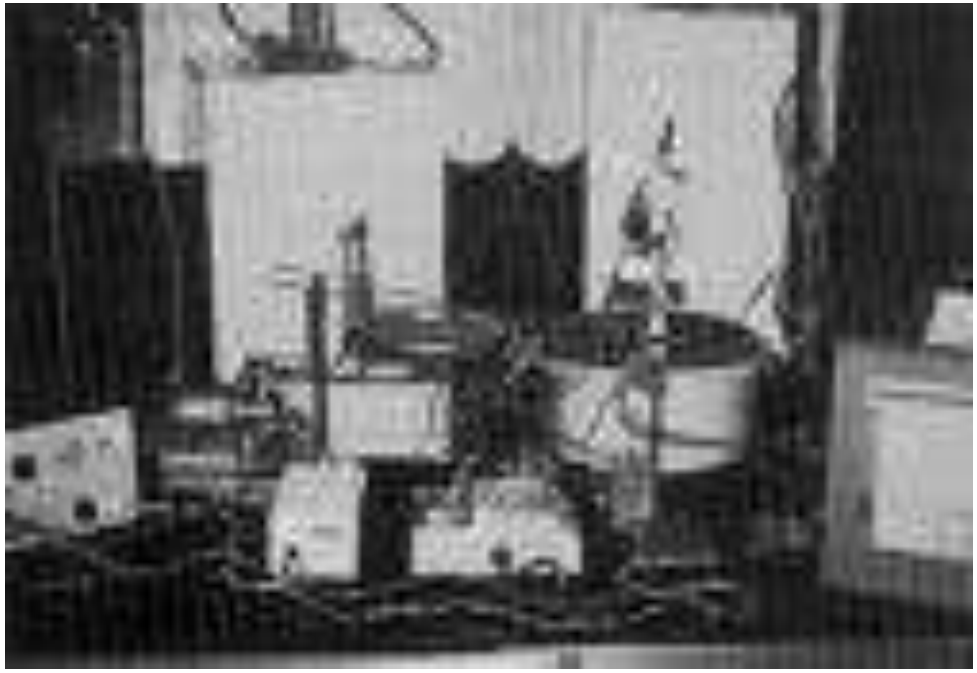
  there is a low incidence of ovarian cancer in the general population (age-adjusted incidence of 17 per 100,000 women).

  In women at average risk, the positive predictive value of an abnormal screening test is, at best, approximately 2% (i.e., 98% of women with positive test results will not have ovarian cancer).

Using tests for diagnosis

- Common diagnostic tests in *unselected* ambulatory patients such as: liver enzymes, amylase, tumor markers, protein electrophoresis are not indicated for screening and should be used for specific diagnosis
- A consequence of automation and social changes.

Sequential multiple analyzer or SMA



Common diagnostic tests

- Biochemical profiles are not routinely indicated for screening asymptomatic adults.
- Probability that a healthy person will have normal results for 1 test= 95%

  6 tests=74%

  20 tests=36%

What is the question?

Does my patient have pancreatitis?

- Order lipase if not available pancreatic amylase is the best choice.
- These tests are to be used in asymptomatic individuals.

Amylase

- Mysterious increase in pancreatic amylase

B I O C H I M I E / B I O C H E M I S T R Y

ANALYSE(S) / TEST(S)	RESULTAT(S) / RESULT(S)	ALARMES / FLAG(S)	UNITES / UNITS	VAL.DE REF. / REF.RANGE

BIOCHIMIE GÉNÉRALE /GENERAL BIOCHEMISTRY

SPECIMEN GLD COLLECTED 14/04/28 13:37 BY CS1 RECEIVED 14/04/28 13:55 BY ROB

CRÉATININE	67		umol/L	44-123
AMYLASE PANCRÉATIQUE	**1046**	**H**	U/L	4-60

Increased pancreatic amylase in an asymptomatic patient suggests the presence of macr
bound to an antibody). An amylase clearance is recommended to eliminate this possibil
clearance of this patient is 0.09% (reference range: > 2.0%), which consistent with m

CHIMIE URINAIRE (MICTION) / URINE RANDOM

SPECIMEN 130 COLLECTED 14/04/29 15:00 BY SL RECEIVED 14/04/29 15:01 BY SL

URINE CREAT.	9.21	mmol/L	NONE
AMYLASE	143	U/L	NONE

I M M U N O L O G I E / I M M U N O L O G Y

ANALYSE(S) / TEST(S)	RESULTAT(S) / RESULT(S)	ALARMES / FLAG(S)	UNITES / UNITS	VAL.DE REF. / REF.RANGE

DEPISTAGE DE MICROALBUMINE / MICROALBUMIN SCREEN

SPECIMEN 130 COLLECTED 14/04/29 15:00 BY SL RECEIVED 14/04/29 15:01 BY SL

URINE CREAT.	9.21	mmol/L	NONE

Does my patient have liver disease?

Useful for diagnosing hepatocellular inflammation or obstruction as in patients with jaundice, with history of alcohol abuse or on certain therapeutic drugs.

- Enzymes of hepatocellular necrosis: AST and ALT
- Enzymes of cholestasis: Alk Phos and GGT

Does my patient have liver disease?

- These are not LFTs
- Live enzymes answer the question is there liver disease.
- True liver function tests include: albumin, PT and bilirubin

Liver enzymes

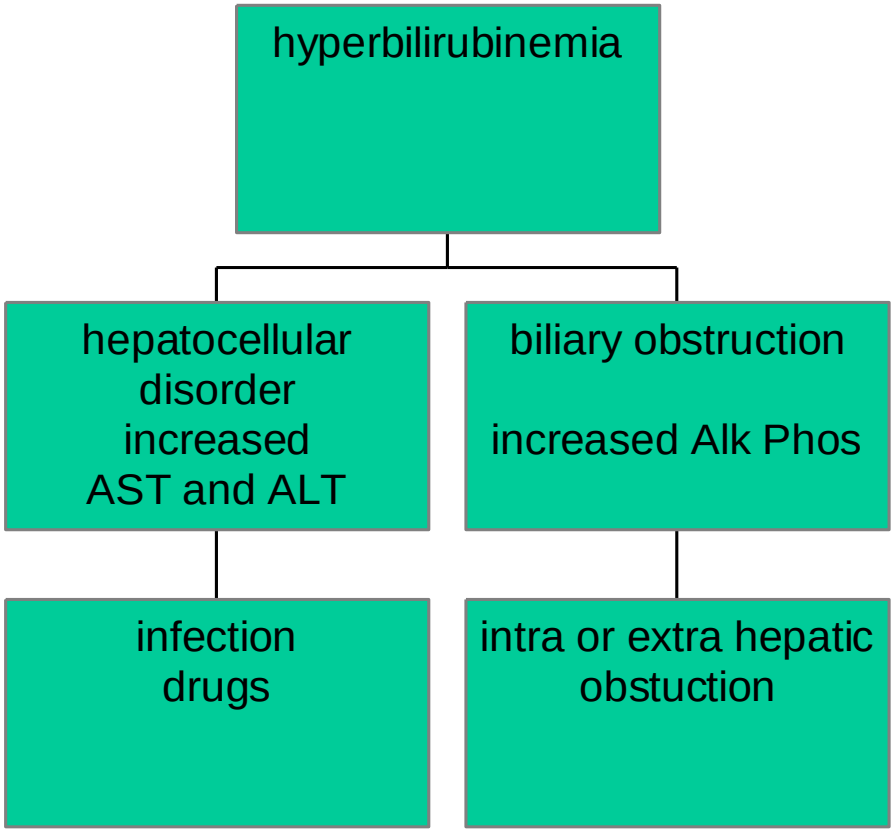


TABLE 1. CAUSES OF CHRONICALLY ELEVATED AMINOTRANSFERASE LEVELS.

Hepatic causes
Alcohol abuse
Medication
Chronic hepatitis B and C
Steatosis and nonalcoholic steatohepatitis
Autoimmune hepatitis
Hemochromatosis
Wilson's disease (in patients ≤40 years old)
Alpha$_1$-antitrypsin deficiency
Nonhepatic causes
Celiac sprue
Inherited disorders of muscle metabolism
Acquired muscle diseases
Strenuous exercise

TABLE 3. MEDICATIONS, HERBS, AND DRUGS OR SUBSTANCES OF ABUSE REPORTED TO CAUSE ELEVATIONS IN LIVER-ENZYME LEVELS.

Medications

Antibiotics
- Synthetic penicillins
- Ciprofloxacin
- Nitrofurantoin
- Ketoconazole and fluconazole
- Isoniazid

Antiepileptic drugs
- Phenytoin
- Carbamazepine

Inhibitors of hydroxymethylglutaryl–coenzyme A reductase
- Simvastatin
- Pravastatin
- Lovastatin
- Atorvastatin

Nonsteroidal antiinflammatory drugs

Sulfonylureas for hyperglycemia
- Glipizide

Herbs and homeopathic treatments

Chaparral

Chinese herbs
- Ji bu huan
- Ephedra (mahuang)

Gentian

Germander

Alchemilla (lady's mantle)

Senna

Shark cartilage

Scutellaria (skullcap)

Drugs and substances of abuse

Anabolic steroids

Cocaine

5-Methoxy-3,4-methylenedioxymethamphetamine (MDMA, "ecstasy")

Phencyclidine ("angel dust")

Glues and solvents
- Glues containing toluene
- Trichloroethylene, chloroform

TABLE 2. LABORATORY TESTS THAT MAY IDENTIFY THE CAUSE OF ELEVATED AMINOTRANSFERASE LEVELS IN A PATIENT WITH NO SYMPTOMS.

TEST	DIAGNOSIS
Initial tests	
Test for hepatitis C antibody in serum	Presence of hepatitis C antibody indicates chronic hepatitis C
Test for hepatitis B surface antigen, surface antibody, and core antibody in serum	Presence of hepatitis B surface antigen and core antibody indicates chronic hepatitis B
Measurement of serum iron and total iron-binding capacity	Iron overload suggests hemochromatosis
Measurement of serum ceruloplasmin	Decreased ceruloplasmin levels suggest Wilson's disease (if patient is ≤40 years old)
Serum protein electrophoresis	Increase in polyclonal immunoglobulins suggests autoimmune hepatitis
Serum protein electrophoresis	Marked decrease in α-globulin bands suggests alpha$_1$-antitrypsin deficiency
Additional tests*	
Reverse-transcriptase polymerase chain reaction for hepatitis C virus RNA	Presence of viral RNA indicates chronic hepatitis C
Alpha$_1$-antitrypsin phenotyping	Presence of the ZZ phenotype indicates alpha$_1$-antitrypsin deficiency
Tests for antiendomysial and antigliadin antibodies in serum	Presence of antibodies indicates celiac sprue
Measurement of creatine kinase and aldolase	Elevated enzyme levels indicate disorders of striated muscle

*If the results of the initial set of tests are normal, these additional tests may pinpoint the cause.

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B I O C H I M I E / B I O C H E M I S T R Y

ANALYSE(S) TEST(S)	RESULTAT(S) RESULT(S)	ALARMES FLAG(S)	UNITES UNITS	VAL.DE REF. REF.RANGE
INDICES SÉRIQUES / SERUM INDICES				
SPECIMEN GLD COLLECTED 05/01/27 12:20 BY RSS RECEIVED 05/01/27 12:33 BY ROB				
HÉMOLYSE / HEMOLYSIS	0			0-2
ICTERE / ICTERUS	**3**	**H**		0-2
LIPÉMIE / LIPEMIA	0			0-2
BIOCHIMIE GÉNÉRALE /GENERAL BIOCHEMISTRY				
SPECIMEN GLD COLLECTED 05/01/27 12:20 BY RSS RECEIVED 05/01/27 12:33 BY ROB				
BILIRUBINE TOTALE	**51.4**	**H**	umol/L	3.6-25.2
DIRECT BILIRUBINE	**28.9**	**H**	umol/L	0.0-4.0
ALKALINE PHOSPHATASE	**176**	**H**	IU/L	13-113
ALT	**1303**	**H**	IU/L	5-60
AST	**357**	**H**	IU/L	10-42

Légende/legend: L:Bas/Low H:Haut/High P:Critique/Panic AB:Anormal/Abnormal

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EMERGENCY

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M I C R O B I O L O G I E / V I R O L O G I E /

ANALYSE(S) TEST(S)	RESULTAT(S) RESULT(S)	ALARMES FLAG(S)	UNITES UNITS	VAL.DE REF. REF.RANGE
SÉROLOGIE / SEROLOGY				
SPECIMEN EL1 COLLECTED 05/01/23 11:54 BY DP RECEIVED 05/01/23 12:38 BY KA				
HEP.B SURFACE ANTIGEN	NEGATIVE			
SEROLOGIE VIROLOGIE / SEROLOGY (VIROLOGY)				
SPECIMEN EL1 COLLECTED 05/01/23 11:54 BY DP RECEIVED 05/01/23 12:38 BY KA				
HEPATITIS A IgM	17.49		COI	

Valeurs de référence/Normal Ranges
<1.1 COI: Absence d'anticorps IgM pour l'hépatite A
Absence of Hepatitis A IgM Antibody

****

Légende/legend: L:Bas/Low H:Haut/High P:Critique/Panic AB:Anormal/Abnormal

What is my patient's renal function?

Do I wish to evaluate renal filtration or the glomerulus as a selective sieve?

- eGFR: The test estimates the volume of blood that is filtered by the kidneys over a given period of time. There is consensus that an eGFR represents the best routinely available measurement of kidney function.

Renal function

- Calculation of an eGFR is currently based on the MDRD equation.

More recently, a modified equation has been endorsed by KDIGO, by the Canadian Society of Nephrology (CSN), and the Ontario Renal Network (ORN). The CKD-EPI equation is considered to be more accurate than the MDRD equation for calculating eGFR, particularly for patients with an eGFR in the 60-120 mL/min/1.73 m2 range, for females, and for younger patient populations.

Renal function

- The CKD-EPI equation uses a more sophisticated calculation for the eGFR, but includes the same factors as MDRD equation; those are age, gender, serum creatinine, and ethnicity. No additional patient information needs to be provided by clinicians.

Note: For patients who do not have muscle mass typical of their demographic group, a 24-hour urine creatinine clearance may be used to improve diagnostic accuracy

Renal function

Why not creatinine alone?

- In assessment of renal function, plasma creatinine remains normal down to a GFR of about 30 mL/min.

- Creatinine is therefore not a sensitive marker of renal function.

Who should be tested for CKD?

- Patients with diabetes mellitus
- Patients with hypertension
- Patients with heart failure
- Patients with atherosclerotic coronary, cerebrovascular or peripheral vascular disease
- Patients with unexplained anemia
- Patients with a family history of ESRD
- First nations peoples

Renal function

What about urea?

- The principal clinical utility of serum urea, which lies in its measurement in conjunction with that of serum creatinine and subsequent calculation of the urea nitrogen-to-creatinine ratio. This can be used as a crude discriminator between prerenal and postrenal azotemia.
- As part of the work up of patients with stage 3 CKD to evaluate the need for nutritional status assessment.
- To determine timely inititiation of dialysis

Mrs White

- 81 year old female with a serum creatinine of 90 µmol/L (normal).
- **EQUATION:VALUE:**
  52 (mL/min/1.73 m2) CKD-EPI CREATININE (2009)

eGFR : 30-59 ml/min/1.73m^2 = a moderate decrease in renal function.

Mr. Weider

- 26 year old african american body builder with a creatinine of 90 µmol/L (normal).

- **EQUATION:VALUE:**
  117(mL/min/1.73 m2) **CKD-EPI CREATININE (2009)**

PATIENT PRIVE / PRIVATE
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RAMQ#: AMZA49051210

à suivre - continued

BIOCHIMIE / BIOCHEMISTRY

ANALYSE(S) / TEST(S)	RESULTAT(S) / RESULT(S)	ALARMES / FLAG(S)	UNITES / UNITS	VAL.DE REF. / REF.RANGE	T.M. / M.T.
Débit de filt. glomérulaire / Glomerular Filt. Rate					
TFGe / eGFR	29		ml/min/1.73sm		Remis

Stade de la maladie rénale chronique selon le NKF
Stage of Chronic Kidney Disease according to NFK

Dommage rénal avec FG normale ou élevée Kidney damage with normal or increased GFR	>= 90
Dommage rénal avec FG un peu diminuée Kidney damage with mild decrease in GFR	60-89
Baisse de FG modérée Moderate decrease in GFR	30-59
Baisse de FG importante Severe decrease in GFR	15-29
Défaillance rénale / Kidney failure	<15

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suite à la prochaine page - continued on next page

Renal function

- Glomerular permeability: in diseases such as diabetes there may develop an increased glomerular permeability with progressively increasing excretion of higher molecular weight proteins as permeability increases (e.g., albumin, IgG).

Normally we excrete up to 30mg/24hr of albumin but we can use the ACR (albumin/creatinine) to screen for diabetic nephropathy instead of a 24 hr urine collection.

Testing for CKD

- A random urine sample can identify kidney injury. Urine albumin or protein excretion should be quantified with an albumin to creatinine ratio (ACR) or a protein to creatinine ratio (PCR).
- 24 hour urine collections are not routinely required to assess creatinine clearance or protein excretion as they are cumbersome and often inaccurate.

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RAMQ#: CHEL36121616

à suivre - continued

IMMUNOLOGIE / IMMUNOLOGY

ANALYSE(S) / TEST(S)	RESULTAT(S) / RESULT(S)	ALARMES / FLAG(S)	UNITES / UNITS	VAL.DE REF. / REF.RANGE	T.M. / M.T.
SPECIMEN GLD COLLECTED 09/12/08 07:51 BY N-MM1 RECEIVED 09/12/08 10:28 BY ROB					
PROTÉINE RÉACTIVE-C	LESS THAN 1.00		mg/L	0.00-8.00	Remis
DEPISTAGE DE MICROALBUMINE / MICROALBUMIN SCREEN					
SPECIMEN 130 COLLECTED 09/12/08 07:51 BY N-MM1 RECEIVED 09/12/08 10:51 BY ROB					
ALBUMIN RANDOM	14.40		mg/L	0.00-20.00	Remis
URINE CREAT.	16.66		mmol/L	NONE	Remis
ALB/CREAT RATIO	0.9			0.0-2.0	Remis

If ratio is high, Please confirm with 2 out of 3 measurements over 3 months.

suite à la prochaine page - continued on next page

Specific diseases


Canadian
Diabetes
Association

CDA CPG 2018

Screening for type 2 diabetes:

- using a fasting plasma glucose (FPG) and/or glycated hemoglobin (A1C) should be performed every 3 years in individuals ≥40 years of age or in individuals at high risk using a risk calculator.

CDA CPG 2018

Diagnosis of DM:

- A fasting plasma glucose level of ≥7.0 mmol/L or
- a 2-hour plasma glucose value in a 75 g oral glucose tolerance test of ≥11.1 mmol/L or
- **a glycated hemoglobin (A1C) value of ≥6.5% (no fasting needed)**

CDA CPG 2018

Therapy in most individuals with type 1 or type 2 diabetes should be targeted to achieve:

- an A1C ≤7.0% in order to reduce the risk of microvascular and, if implemented early in the course of disease, macrovascular complications.

In order to achieve an A1C ≤7.0%, people with diabetes should aim for:

- FPG or preprandial PG target of 4.0–7.0 mmol/L and a 2-hour PPG target of 5.0–10.0 mmol/L

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RAMQ#: CHEL36121616

à suivre - continued

BIOCHIMIE / BIOCHEMISTRY

ANALYSE(S) / TEST(S)	RESULTAT(S) / RESULT(S)	ALARMES / FLAG(S)	UNITES / UNITS	VAL.DE REF. / REF.RANGE	T.M. / M.T.
ALT	16		IU/L	5-60	Remis
AST	27		IU/L	10-42	Remis
ALBUMINE/ALBUMIN	43		g/L	32-46	Remis
FRUCTOSAMINE	241		umol/L	150-285	Remis
CALCIUM IONIZED	**1.07**	**L**	mmol/L	1.12-1.32	JGL
CA IONIZED PH CORR.7.4	1.02		mmol/L		JGL

SPECIMEN L1C COLLECTED 09/12/08 07:51 BY N-MM1 RECEIVED 09/12/08 10:30 BY ROB

HEMOGLOBIN A1C	0.061				I/AUT

EFFECTIF(VE):09/09/2009

OBJECTIF DE TRAITMENT: <=0.07
TARGET FOR GLYCEMIC CONTROL: <=0.07

SPECIMEN GLD COLLECTED 09/12/08 07:51 BY N-MM1 RECEIVED 09/12/08 10:28 BY ROB

APOLIPOPROTEIN B	**1.48**	**H**	g/L	0.00-0.90	Remis

GAZ SANGUINS / BLOOD GAS

SPECIMEN BGS COLLECTED 09/12/08 07:51 BY N-MM1 RECEIVED 09/12/08 10:19 BY JGL

pH	**7.29**	**L**		7.35-7.45	JGL

suite à la prochaine page - continued on next page

CDA CPG 2018

Screening for **CKD**:

In adults, screening for CKD in diabetes:

- Random urine ACR and a serum creatinine converted into an eGFR.

- Screening should commence at diagnosis of diabetes in individuals with type 2 diabetes and 5 years after diagnosis in adults with type 1 diabetes and repeated yearly thereafter.

CDA CPG 2018

- A diagnosis of CKD should be made in patients with a random urine ACR ≥2.0 mg/mmol and/or
- an eGFR<60 mL/min on at least 2 of 3 samples over a 3-month period.

Canadian Journal of Cardiology
Journal canadien de cardiologie

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

HOW TO SCREEN

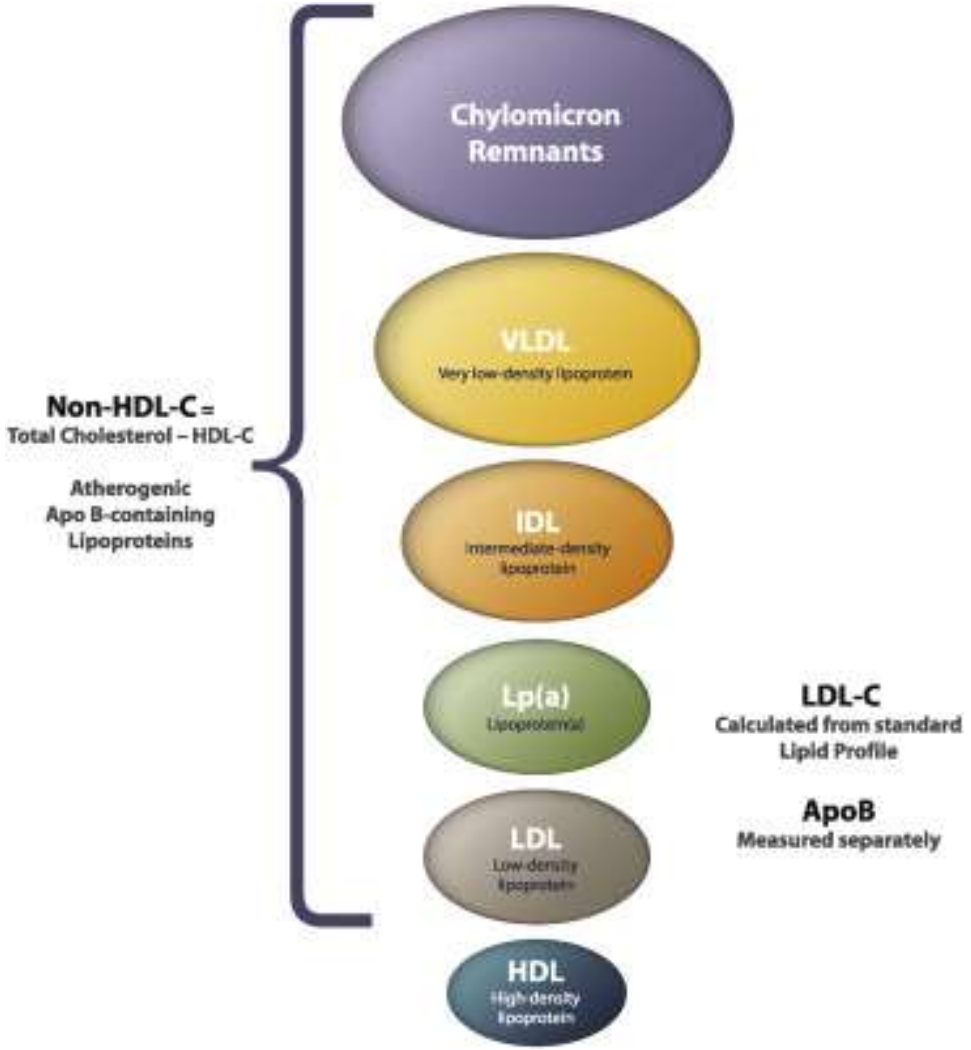
For all:

- 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



Friedewald equation

- **Friedewald** (1972) **Formula**:

LDL = TC - HDL - TG/2.17 (**mmol/L**).

If TG ≥ 4.5 mmo/L formula is precluded.

References

- **Clinical Practice Guidelines:**

  2013 Canadian Diabetes Association

  www.diabetes.ca
- **Canadian Task Force on the Periodic Health Exam**

References

- PDF] 2016 Update of the ***Canadian Cardiovascular Society Guidelines*** for **...**

References

- **McPherson & Pincus: Henry's Clinical Diagnosis and Management by Laboratory Methods, *21st ed.***; SI Units
- **Tietz** NW (ed): Clinical Guide to Laboratory Tests.
- http://www.mayomedicallaboratories.com/test-catalog

References

- *Clinical practice guidelines*
- Web-based calculators: http://www.ukidney.com/page32/page32.html
- http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm
- http://www.renal.org/eGFRcalc/GFR.pl
- Downloadable calculators and PDA formats: http://www.pcel.info/gfr/
- http://www.medcalc.com/