

*“Experience and Expectations:  
eGFR Reporting in Canada”*

British Columbia Society of  
Laboratory Science

October 16, 2008

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*The Forces of Change*

Chronic disease – (CVD, diabetes, renal disease)  
A costly problem that is getting bigger

Evidence - based medicine  
Proliferation of clinical guidelines

Increasing awareness of the costs associated with  
non-standardized testing

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*The Forces of Change*

Information (Internet) is shifting the base of power  
from the physician to the patient (patient centric  
medicine)

Technology is moving testing to the “point-of-  
care” – drug stores, mobile clinics

Empower the patient to take more responsibility  
for their own healthcare

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*Kidney Disease*

Cost of end-stage renal disease in the US \$16.7 billion annually (2000)

Projected to grow to \$39.3 billion annually by 2010

Solution: identify and treat kidney disease at an earlier stage to prevent progression to ERD

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*Kidney Disease*

< 10% of diabetic patients are even screened for kidney disease

< 20% of those with kidney disease even know they have it

76% of patients on first referral to nephrologists already have Stage 4 disease

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*Prevalence of Renal Insufficiency (US)*

GFR (ml/min)	Stage 3 59-30	Stage 4 29-15	Stage 5 < 15
Number of People	7.6 million	360,000	>300,000

*76% of patients on first referral to a nephrologist have stage 4 renal disease*

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*The Problem*

What creatinine level indicates kidney disease for a 65-year old diabetic, hypertensive white woman weighing 50 Kg?

77% Responded

Kidney disease is indicated when her creatinine exceeds 133 $\mu$ mol/L

Reality

At that level, she already has late Stage 3 disease (eGFR 37 ml/min/1.73m<sup>2</sup>)

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*Detection of CKD with Routine Reporting of eGFR*

Family practice OPD, patients 65 years +; 324 C-G calculation of GFR

Intervention – automatic reporting of eGFR to physicians by the laboratory

Pre-intervention 22.4% of patients recognized

Post-intervention 85.1% of patients were recognized (p>001)

*(Arch Intern Med 2004;164:1788-1792)*

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*Clinical Guidelines for Chronic Kidney Disease (NKF)*

GFR should be estimated from prediction equations

Serum creatinine alone should not be used to assess the level of kidney function

Clinical laboratories should report an estimate of GFR

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*Clinical Guidelines for Chronic Kidney Disease (NKF)*

Measurement of creatinine clearance using timed urine collections does not improve the estimation of GFR

(AM J Kidney Dis 37 (suppl 1):S182-S238, 2002)

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*Canadian Society of Nephrology*

Position Paper

CSN endorses the routine reporting of eGFR (Cockcroft Gault or MDRD)

CSN endorses standardization of serum creatinine measurement methodology to a gold standard to ensure reproducibility and consistency across laboratories and geographic locations

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*Rationale for Use and Reporting of eGFR*

GFR and creatinine clearance are poorly inferred from serum creatinine alone

Creatinine is more often measured than urinary albumin in practice

Measurement of kidney function (GFR or creatinine clearance) is essential once albuminuria is discovered

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*Rationale for Use and Reporting of eGFR*

MDRD equation does not require weight as a variable and is the most thoroughly validated equation for eGFR

The equation is superior to other methods of approximating GFR

Nephrologists routinely use an estimating equation for GFR

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*Classifying the Patient*

eGFR is a critical test - clinicians will take action based on the test value

The eGFR calculation is based upon the patient's age, gender and serum creatinine test result

Calibration error in creatinine measurements will systematically skew all eGFR test results

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**ACCURACY AND PRECISION**



Neither precise nor accurate      Precise but not accurate      Precise and accurate

Repeated tests of the same sample by the same laboratory or device.

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*Creatinine – CLIA Performance Goals*

Peer group mean +/- 15% or 23.4 umoles/L  
whichever is greater

Under CLIA – given a peer mean of 100 umoles/L  
labs will get a “pass” if they are within +/- 23.4%

Recommended performance limit for reporting of  
eGFR – ID-GC/MS Reference Value +/- 11.4 %

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“How variable are creatinine measurements  
between clinical laboratories in Canada?”

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*Creatinine Study (2003)*

22 human serum EQA samples  
Measured over two years by 432 laboratories  
9240 creatinine test results  
Creatinine targets set by ID-GC/MS

Least squares regression equation calculated  
over concentrations from 51.3 to 151.6 umol/L

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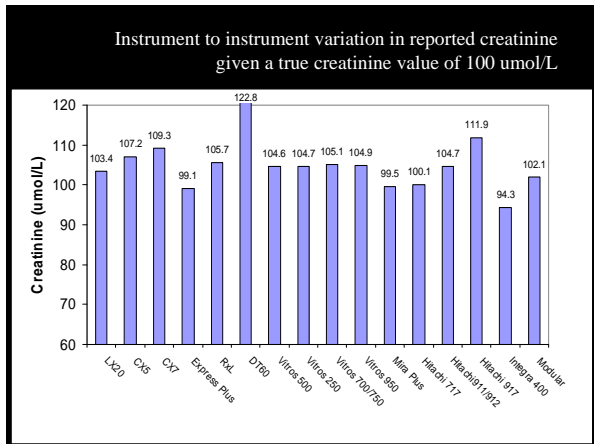
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*What would be the impact of this variability on the calculation of eGFR (MDRD algorithm) for a male patient, age 65 having a true creatinine value of 111  $\mu\text{mol/L}$  (eGFR = 62  $\text{ml/min}$ )?*

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*Impact on Classification of Patients*

False positive misclassification rate of 69%

75% of the labs in the study would have misclassified this patient

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## The BC Standardization Program (20040201)

### Objectives

Introduce the routine reporting of eGFR on a province-wide basis

Minimize the contribution of lab error in the reporting of eGFR

Standardize the reporting of eGFR on a province-wide basis

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## Clinical Practice Guideline

Dispels belief that little can be done to slow or prevent onset of ESRD

- 7 recommendations for investigation & management (at-risk and diagnosed)
- Care objectives to increase appropriate, evidence-based care
- Patient flow sheet
- Physician resource list

**GUIDELINES & PROTOCOLS**  
ADVISORY COMMITTEE

**Identification, Evaluation and Management of Patients with Chronic Kidney Disease**

**Scope**

The first part of this guideline provides recommendations for the investigation and management of adult patients at risk of, and those diagnosed with, chronic kidney disease (CKD). The second part of the guideline provides care objectives for patients with CKD, focusing on appropriate investigations of labs, and systems that should be in place to improve the standard of appropriate, evidence-based care to patients.

**Part 1: Introduction to scope and aims**

**Recommendation 1: Identify high-risk populations**

Identify patients at risk of kidney disease based upon a detailed medical and surgical history including comorbidities (e.g. diabetes, cardiovascular disease), as well as dietary, social, demographic, and cultural factors, a review of symptoms, and physical examination.

High-risk populations include those:

- with diabetes
- with a diagnosis of hypertension or cardiovascular disease
- with a family history of kidney disease
- belonging to specific high-risk ethnic groups (First Nations and Pacific Islanders).

**Notes:** Age greater than 60 years is associated with an increased risk of impaired kidney function. However, there is insufficient evidence at this point to recommend screening of individuals over 60 years on the basis of age.

**Recommendation 2: Screen high-risk populations**

Screen high-risk populations every 1-2 years depending upon clinical circumstances (e.g. yearly for patients with diabetes) using serum creatinine and random urine tests (see below for details).

The updated **Standardized Reporting of eGFR** is included from the same committee, which is the best laboratory method for kidney disease. More information is BC now automatically report eGFR when a serum creatinine is ordered (see **Standardized eGFR Conversion Table**).

- Percentage of eGFR values < 60 mL/min indicate substantial reduction in kidney function.
- Lower eGFR values, even with persistent eGFR values < 60 mL/min, indicate advanced kidney function, either as an isolated condition or as a component of a systemic disease.

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## Patient Materials

- Patient flow sheets and a guide for managing their own health
- Includes a patient log sheet to track key info, including medication use
- Website includes range of patient information on CKD and links to self-management resources

**Chronic Kidney Disease**  
A Guide for Patients

**What is chronic kidney disease (CKD)?**

Chronic kidney disease (CKD) is a condition where your kidneys' ability to filter wastes from your blood is impaired. CKD usually starts slowly and progresses over a number of years. If diagnosed and treated early, CKD may be slowed down or stopped. However, if things get worse, CKD can cause kidney failure, which can lead to dialysis or kidney transplantation. Your health care provider will monitor your kidney function and advise you on how to manage your condition.

**What are the symptoms of kidney disease?**

CKD is a silent disease. Many people do not have any symptoms in the early stages. Symptoms begin after most of your kidney function is lost. They may include:

- Fatigue or weakness
- Swelling in your legs, feet, or hands
- Trouble concentrating
- Changes in urination
- Itchy skin
- Loss of appetite

**What are the risks of developing CKD?**

The leading causes of kidney failure are **diabetes** and **high blood pressure**. These conditions affect the filtering ability of the kidneys and can lead to kidney failure. Early diagnosis and careful management of these conditions can help and even prevent the onset of kidney failure. Talk to your doctor if you have diabetes or hypertension. Other factors that increase a person's risk of developing CKD include:

- Family history of kidney disease (e.g. autosomal recessive)
- Certain ethnic groups (First Nations, Pacific Islanders)
- Certain medications (e.g. NSAIDs, antibiotics)
- Alcohol use (e.g. binge drinking)

**How can I prevent or control CKD?**

There are steps you can take to help prevent or control CKD. Your doctor will advise you on the best way to manage your condition. You can also take steps to help you when you feel your kidneys. Other important things you can do include:

- **Control diabetes:** Keep your blood glucose levels as close to normal as possible. Doing this will help you to prevent or delay kidney failure. You may need to take insulin or other medicines regularly. Your doctor should help you with your diabetes management plan.

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*The Program*

Use test samples that are commutable for the assessment of accuracy (human serum)

Select samples to challenge system at decision levels for stage 3 renal disease

Assign target value by ID-GC/MS

Capture reagent and calibrator lot numbers for creatinine at the time of data submission

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*The Program*

Determine a least squares regression equation for each laboratory

Confirm the transfer of accuracy and the correct application of the MDRD formula in each lab

Monitor system wide for analytical drift

Re-establish least squares regression if drift exceeds defined limits

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*The Program*

Lab continues to operate its creatinine method without change

IQC programs operate without change

Lab reports creatinine results as they are generated by the analyzer (without correction)

Creatinine result is corrected just prior to its use in the MDRD formula for estimating GFR (eGFR)

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*The Program*

eGFR is reported along with the creatinine result

The reporting comments for eGFR are standardized and harmonized on a province wide basis to Provincial guidelines

Lab continues to use its current reference intervals for the reporting of creatinine

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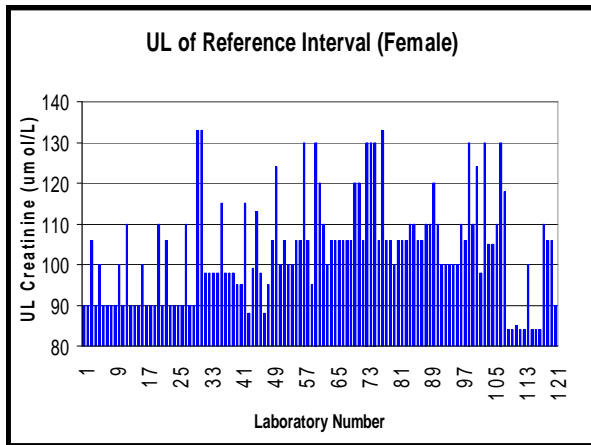
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**Upper Limit of Creatinine Reference Interval  
(Adult Males)**

\* Mean % Bias at 100 umol/L across all models

	% Bias*	Range	Mean	CV (%)
Beckman	6.6	106 - 120	111	3
Dade	5.7	98 - 126	118	6
DT 60	22.8	120 - 133	127	5
Ortho	4.8	110 - 133	127	6
Roche/Hitachi	3.7	98 - 130	112	9

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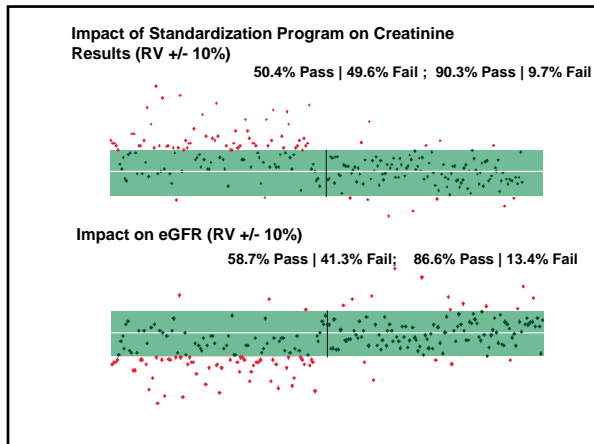
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**Percentage of Laboratories Meeting Performance Criteria (TE = 10%)**

Sample	A	B	C
Creatinine RV (umol/L)	74.5	109.5	131.6
eGFR (RV)	78	64	50
Cr (uncorrected)	42%	56%	67%
Cr (corrected)	79%	88%	93%
eGFR (Cr uncorrected)	14%	53%	70%
eGFR (Cr corrected)	69%	83%	85%

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*BC - Experience*

- Estimated 145,000 people in BC at increased risk of CKD
- Provincial creatinine testing system operating with a positive 16.5% bias
- If adult population is uniformly tested throughout this system – 535,000 people added to the at risk category (false positive)

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*BC - Experience*

- Standardization program reduced mean bias from 16.5% to 2.7%
- At a maximum the program theoretically reduced false positives by 84% keeping 449,400 people from being “incorrectly classified” as being “at risk” (2004 statistics)
- Follow-up testing on these patients would have cost the government \$36 million  
*(J Am Soc Nephrol 19:164-169 (2008))*

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*Creatinine Standardization (CRSM 108)*

99% participation rate (submitted subscriptions)  
3 labs – did not apply assigned CRF  
4 labs - made a mistake in applying CRF  
12 labs calculated eGFR incorrectly  
7 labs do not routinely report eGFR  
eGFR routinely reported by 93% of BC labs

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*Creatinine Standardization (CRSM 108)*

Some reasons for not reporting/or reporting an incorrect eGFR:  
“lot to lot variation in calibration too great”  
“using old formula at NKDEP website”  
“vendor won’t update LIS due to cost”  
“awaiting approval to update LIS”  
“using old formula – manual chart”

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*Experience (20080301)*

Participation – 100% (n=157)

49% of the labs now reporting that their calibration is traceable to IDMS (previous challenge – 26%)

Eleven IDMS traceable labs using the wrong formula for calculating eGFR

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*Experience (20080301)*

Five IDMS traceable labs reported an incorrect value for eGFR (reason unknown)

Some labs confused as to whether or not their system was IDMS traceable

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*Experience (20080301)*

	Sample A	Sample B	Sample C
RV (umol/L)	66.1	88.4	144.6
eGFR (ml/min)	117	60	42
Performance Goal	Percentage of Labs Meeting Performance Goal		
Cr (+/- 25%)	92.3%	95.5%	98.7%
Cr (+/- 15%)	76.5%	89.7%	95.6%
Cr (+/- 10%)	57.3%	76.5%	88.2%
eGFR (+/- 15%)	75.9%	87.3%	92.4%

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*Experience (20080301)*

Creatinine (alkaline picrate)				
Sample	RV (umoles/L)	Beckman	Siemens	Roche (IDMS)
A	66.1 (TE)	82.4 (24.7%)	71.3 (7.8%)	74.8 (13.2%)
B	88.4	102.4 (15.8%)	92.7 (11.9%)	97.5 (10.3%)
C	144.6	153.7 (6.3%)	146.2 (1.1%)	151.8 (5.0%)

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*Alkaline Picrate*

Plasma pseudo-creatinine chromogens over estimate true creatinine concentrations (glucose, ketones, protein); bigger problem in “non-adults”

Manufacturers often apply an off-set factor in their calibration to try to compensate (Roche Integra - compensated Jaffe offset – 18 umoles/l)

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*Alkaline Picrate*

Off set not needed if measuring urinary creatinine

Other interferences noted – bilirubin, pyruvate, hemoglobin, drugs

Enzymatic Assays for Creatinine: Time for Action  
(Clin Chem Lab Med 2008;46(4):567-572)

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*Experience (20080301)*

Creatinine (amidohydrolase)				
Sample	RV (umoles/L)	Ortho	Ortho (IDMS)	Roche (IDMS)
A	66.1 (TE)	84.6 (27.9%)	72.9 (10.3%)	65.6 (0.8%)
B	88.4	108.6 (22.8%)	95.2 (7.7%)	88.4 (0.0%)
C	144.6	166.0 (12.9%)	148.8 (2.9%)	146.6 (1.4%)

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*Experience (20080301)*

Calibration process can vary between platforms within a manufacturer

Calibration can vary significantly from lot to lot

Regulatory PT in the US places emphasis on the peer group and rewards precision – works against standardization

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*Experience (20080301)*

Single point calibrations are not done at a clinically relevant concentration; some products sold with different calibrations

Methods do not perform well at the lower concentrations of creatinine (problem for pediatrics)

IFCC recommending move to enzymatic assays for creatinine

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*Experience (20080301)*

Not all manufacturers have moved to standardize their creatinine methods. No post-approval monitoring of accuracy

US labs hesitating to move to IDMS calibration – drug dosing algorithms have been developed using creatinine methods that have not been standardized

Don't want to fail my "PT"

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*Experience (20080301)*

Don't want to change my reference intervals

Changing might upset the physicians

"Don't really understand the point of doing this"

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Thank you

dseccombe @ ceqal.com

(604) 222-3907

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