"Experience and Expectations: eGFR Reporting in Canada"

British Columbia Society of Laboratory Science

October 16, 2008

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

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

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

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

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			

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 133µmol/L

Reality

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

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)

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

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)

Canadian Society of Nephrology

Position Paper

CSN endorses the routine reporting of eGFR (Cockroft 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

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

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

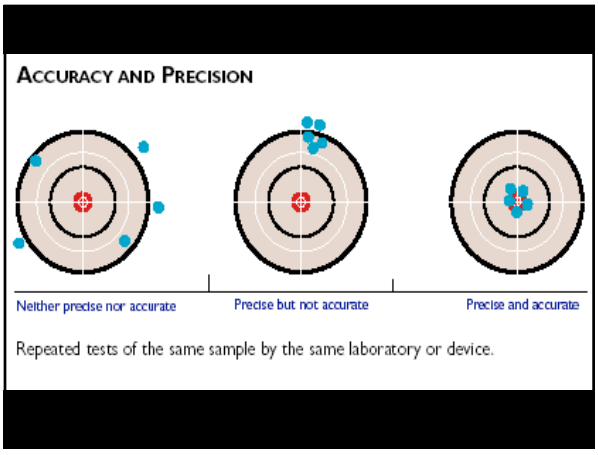
Nephrologists routinely use an estimating equation for GFR

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



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 %

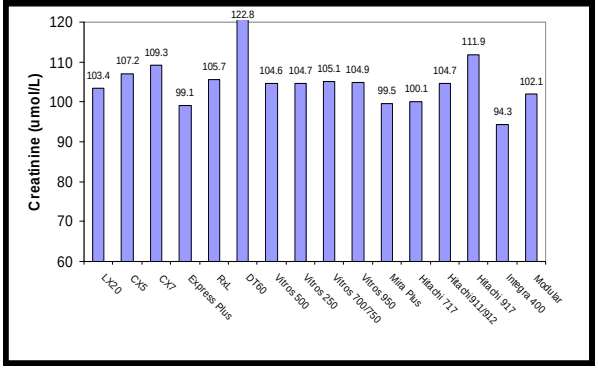
"How variable are creatinine measurements between clinical laboratories in Canada?"

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

Instrument to instrument variation in reported creatinine given a true creatinine value of 100 umol/L



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 umol/L (eGFR = 62 ml/min)?

Impact on Classification of Patients

False positive misclassification rate of 69%

75% of the labs in the study would have miss-classified this patient

The BC Standardization Program (20040201)

Objectives

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

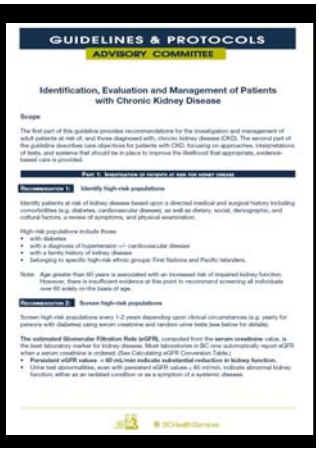
Minimize the contribution of lab error in the reporting of eGFR

Standardize the reporting of eGFR on a province-wide basis

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

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

BCHealthServices

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

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

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)

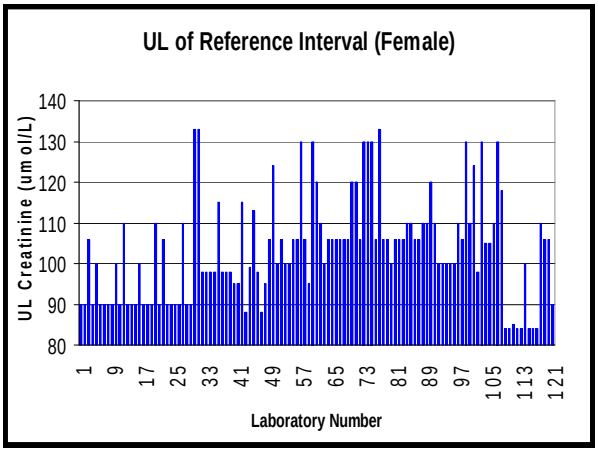
Creatinine result is corrected just prior to its use in the MDRD formula for estimating GFR (eGFR)

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

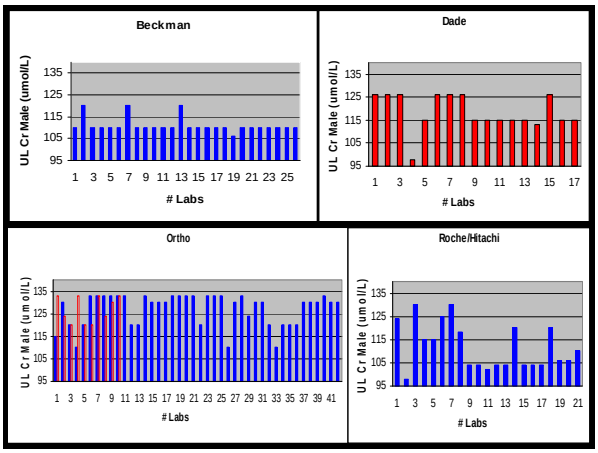
Lab continues to use its current reference intervals for the reporting of creatinine

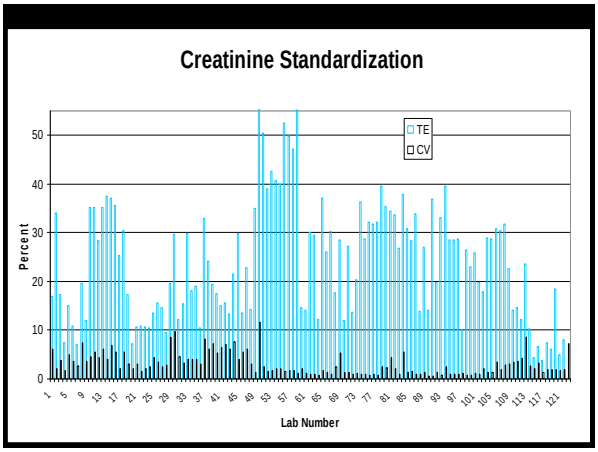


Upper Limit of Creatinine Reference Interval (Adult Males)

* 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



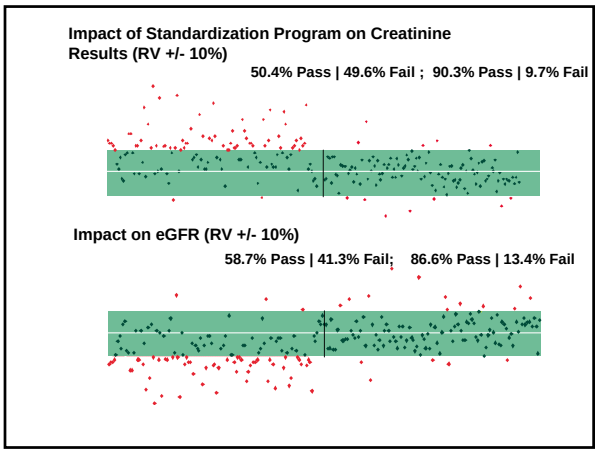


Creatinine – British Columbia

Mean TE = 23.9%

Mean Bias = 16.5% (+)

Mean CV = 3.02 ; SD = 2.24



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%

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)

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)

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

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"

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

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

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%

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%)

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)

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)

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%)

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

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

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"

Experience (20080301)

Don't want to change my reference intervals

Changing might upset the physicians

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

Thank you

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