

Current Laboratory Practice

Ontario Society for Clinical Chemists (OSCC)

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Estimating GFR

Suggested Implementation Guidelines

Glomerular filtration rate can be estimated (eGFR) and measured in a variety of ways. In order to facilitate the diagnosis and monitoring of chronic kidney disease (CKD), the OSCC in consultation with nephrologists and family physicians reviewed the currently available literature and data in this evolving field. The equation derived in the “Modification of Diet in Renal Disease study³” based on serum creatinine, age and sex (eGFR-MDRD) was accepted as the most efficient and practical generic estimate to implement for adults in Ontario laboratories. There is currently no provincial consensus on eGFR due to issues of standardization among laboratories, the clinical performance of GFR estimates in early CKD, a paucity of outcome studies and validation of its use in different ethnic, age and treatment populations. Therefore, eGFR implementation needs to proceed locally as a collaborative educational effort in order to ensure improved patient care. The following information may be useful when participating in local decisions.

- eGFR-MDRD can be automatically calculated and reported with serum creatinine (mL/min/1.73m²)**
 - eGFR-MDRD = 186 x (serum Creatinine (umol/L)/ 88.4)^{-1.154} x (Age)^{-0.203} x (0.742 if female).**
 - Always add comment: **“For patients of African descent, reported eGFR must be multiplied by 1.21”**
 - If creatinine method is traceable to IDMS, factor is **175** instead of **186**.
 - Upper reporting limit **“>120 mL/min/1.73m²”**. Lower reporting limit **“<15 mL/min/1.73m²”**.
 - Laboratories should implement delta checks for both serum creatinine and **eGFR-MDRD**, if possible.
- Early detection of CKD requires SERIAL MONITORING.**
 - Serum creatinine may be included with risk assessment for diseases such as diabetes, hypertension, and hyperlipidemias. Testing frequency will vary from a few repeats per year to a few per decade.
 - A 20% change in creatinine likely represents a *Real Change in Value* (RCV), and; a 30% change is clinically significant. An *average* annual decline in eGFR-MDRD of 10- 20% is clinically significant.
- Serum creatinine assay performance needs to be optimized.**
 - Precision <5%, bias < 5%, and total error <15% (Optimal: TE <7% based on biological variation).
 - Potential interferences should be identified.
- eGFR is recommended instead of 24 hour creatinine clearance testing. Simultaneous monitoring of serum creatinine and serum urea is not recommended and should be discouraged.**

eGFR Interpretations for Chronic Kidney Disease (CKD)

eGFR-MDRD >120 mL/min/1.73m² - Hyperfiltration may be present in early diabetic nephropathy.
eGFR-MDRD >90 mL/min/1.73m² - Normal eGFR.
eGFR-MDRD 60 - 89 mL/min/1.73m² - Mild decrease in eGFR is common in 30% of healthy adults. Suggest repeat testing in 6 to 12 months. Exclude kidney disease in those at high risk (diabetes or hypertension).
eGFR-MDRD 30 - 59 mL/min/1.73m² - Consistent with moderate chronic kidney disease if confirmed over 3 months. Consider nephrology referral if progressive deterioration of more than 20% for eGFR or creatinine.
eGFR-MDRD 15 - 29 mL/min/1.73m² - Consistent with severe chronic kidney disease. Consider nephrology referral.
eGFR-MDRD <15 mL/min/1.73m² - Consistent with kidney failure . Consider urgent nephrology referral.

****Always comment:** The reported eGFR must be multiplied by 1.21 for patients of African descent.

Additional information:

- eGFR is frequently used for **DRUG DOSING** using the Cockcroft-Gault equation. eGFR-MDRD has not been validated for this purpose.
- eGFR-MDRD assumes “**steady state**”. For rapidly changing kidney function, monitor serum creatinine.
- Creatinine and thus eGFR varies with muscle mass; the MDRD calculation³ includes a correction of “ x 1.21” for “African Americans”.
- MDRD is normalized for average height and weight. Consult a nephrologist if a patient has unusual physical considerations.
- Note that eGFR is less precise in its estimation of GFR when > 60 mL/min/1.73m².
- <18 years: eGFR-Schwartz (mL/min) = 38 (<12y) or 48 (boys>12y) x height (cm)/ serum creatinine (umol/L).** Use a more precise estimate of GFR, if risk of CKD is high.

Note: Serum creatinine assay-dependent false increases (false decrease in eGFR-MDRD) may occur with acetoacetate, ascorbic acid, fructose, pyruvate, cephalosporins, creatine, proline (avoid hyper-alimentation fluid contamination), chronic lidocaine administration; false decreases (false increase in eGFR-MDRD) may occur with bilirubin. In vivo inhibition of creatinine secretion can occur with cimetidine or trimethoprim. (sulphamethoxazole, ciprofloxacin, fenobibrate)

More Information: OSCC website (www.clinicalchemistry.on.ca) or email (oscc@eventsmanagement.ca)

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...more information on Estimating GFR

"More people die annually from kidney failure than from colon, breast or prostate cancer". As our population ages, chronic kidney disease (CKD) and the need for dialysis are going to increase dramatically. Early detection and effective treatment of CKD can halt or slow disease progression in many patients¹, while knowledge of CKD will avoid excessive medication in the elderly. The challenge is how best to identify early CKD.

Glomerular filtration rate (GFR) is considered the best index of kidney function in health and disease. It varies with body size, and hence also sex and age. As GFR cannot be measured directly, it has been estimated by urinary excretion of substances such as inulin, ¹²⁵I-iodothalamate, ⁵¹Cr-EDTA, ⁹⁹Tc-DTPA, cystatin C and creatinine, or plasma clearance of ¹²⁵I-iodothalamate, ⁵¹Cr-EDTA, iohexol or creatinine. Each of these options is challenged by limitations², resulting in much research and over 50 different indirect calculation estimates in the literature. The equation derived in the "Modification of Diet in Renal Disease study"³ based on serum creatinine, age and sex (eGFR-MDRD) for the adult population has been accepted by the OSCC as the most efficient and practical generic estimate for implementation in Ontario. While this is consistent with practice introduced or anticipated in many jurisdictions, implementation and interpretation needs to proceed as a *collaborative educational effort* in order to ensure maximal benefit with improved patient care. The K/DOQI Clinical Practice Guidelines⁴ for CKD from the American National Kidney Foundation (NKF) have been incorporated into the proposed eGFR-MDRD interpretations for each clinical decision limit. Several issues remain to be resolved, which include standardization of serum creatinine assays (methodology and performance), units for reporting and clinical utilization under different circumstances.

The MDRD study³ used the kinetic alkaline picrate assay on the Beckman Astra CX3 at the Cleveland Clinic in their original study resulting in an initial equation factor of "186". The MDRD group has reanalyzed the study samples with an isotope dilution mass spectrometry (ID-MS) traceable method in order to determine the correct initial equation factor of "175" for routine methods traceable to this preferred reference methodology. It is important that laboratories and clinicians ensure that the correct factor is chosen according to their current creatinine method when calculating eGFR or using on-line calculators⁵.

Several studies have illustrated that 10% of the eGFR-MDRD results are beyond 30% of their true value as determined by reference urinary/plasma clearance methods. These deviations are particularly concerning when creatinine concentrations are just starting to rise in early CKD. This combined with poor precision at low creatinine concentrations in some laboratories may translate into relatively wide confidence intervals for eGFR in this important range, resulting in the suggestion that eGFR-MDRD >60 mL/min/1.73m² should not be reported. As this melding of CKD Stages 1 (>90) and 2 (60-89) with healthy (>90) results may reduce the potential for early detection, the OSCC along with laboratories in British Columbia have decided to recommend the use of >120 mL/min/1.73m² as the upper reporting limit.

Ontario laboratories currently report serum creatinine in *umol/L*, urine creatinine in *mmol/L* and creatinine clearance in mL/s often normalized to 1.73m². However, eGFR-MDRD is reported as mL/min/1.73m². These units are used so that eGFR-MDRD roughly approximates the amount of kidney function remaining (e.g. 60 mL/min/1.73m² = approximately 60% kidney function). The CKD

decision limits are "rounded off" for easy recall: 15, 30, 60, 90 mL/min/1.73m².

As creatinine serum concentration is proportional to muscle mass, it is relatively stable for an individual's sex and age. While this variation within an individual (CVi) is small, the variation of creatinine among individuals (CVg) is relatively large, giving a low CVi/CVg ratio (e.g. < 0.6) or "marked individuality" (see Dr. Callum Fraser's book on *Biological Variation*⁶). This low CVi/CVg ratio for creatinine means that population reference ranges are of little utility as patient results could change significantly and still be within the reference limits. Thus, it is better to monitor serial results than to use population reference ranges for interpretation. A change of 20% should be reviewed for possible significance, while a change of 30% should be considered highly significant. The RCV for eGFR remains to be determined. Importantly, emphasis on stable versus progressive disease will help to avoid misdiagnosing patients with inherently low but stable eGFR-MDRD.

At this time there is currently no provincial clinical consensus on eGFR implementation. Several issues need to be addressed, including: between laboratory standardization, the functional performance of eGFR in early CKD, validation of eGFR-MDRD use in all populations, recommendations for patients with stable CKD, and studies on patients demonstrating improved clinical outcomes. Implementation of eGFR-MDRD in Ontario needs to proceed as a collaborative local educational effort in order to ensure improved patient care. The OSCC wants to emphasize the importance of **repeat testing** as an effective strategy to improve reliability, avoid over-interpretation of a single result, and focus on the differentiation of progressive versus stable CKD.

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3. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;130:461-470
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