

ROUTINE REPORTING OF eGFR

LABORATORY IMPLEMENTATION GUIDELINES

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This package provides advice and instructions for implementation of a recommendation by the Australasian Association of Clinical Biochemists (AACB), Royal Australasian College of Pathologists (RCPA), Australian and New Zealand Society of Nephrology (ANZSN) and Kidney Health Australia, that all laboratories in Australia and New Zealand report an estimate of Glomerular Filtration Rate (eGFR) using the MDRD equation with every request for serum creatinine in adults.

The recommendations have been published in the Medical Journal of Australia, 2005, 183:138-141 together with a supporting editorial (both available on-line at www.mja.com.au 1 Aug 2005 edition).

The following advice and enclosed documents outline the steps required by laboratories to implement this recommendation. This package includes:

- Background information
- Key issues for laboratories
- Limitations of the MDRD eGFR
- Other information
- Example letter to requesting doctors
- GP Desktop Resource Card from Kidney Health Australia (Attachment)

Background information

The GFR is a vital measure of kidney function. It is used for staging and monitoring progression of Chronic Kidney Disease (CKD), as well as in drug dosing decisions. It is also now recognized as an independent risk factor for cardiac mortality. Serum creatinine is by far the most widely performed test for assessment of GFR, however interpretation is complicated by the reciprocal relationship between serum creatinine and GFR, as well as the effects of age, sex, body size, and diet.

Recently a formula for estimating the GFR has been developed for which the only inputs are age, gender and serum creatinine. **This allows for routine calculation of the GFR from parameters already held in laboratory computer systems.** The formula is the “abbreviated MDRD” formula, named after the Modification of Diet in Renal Disease study where it was developed. There is also a term in the equation for race (African American or non African American) however this is only of minor relevance in the Australasian population.

The recommendation is for routine reporting of eGFR with every serum creatinine request in adults. The aim is to enhance recognition of moderate to severe kidney disease at a stage when it may still be clinically silent and allow valuable intervention to delay the disease progression. As part of providing this result a major educational exercise is required to optimize interpretation of these values.

Some important aspects of this formula to consider are:

- The equation was developed only with patients with kidney disease. Therefore the equation is less accurate in patients with normal renal function and *numerical results will be limited to eGFR ≤ 60 mL/min/1.73m².*
- As serum creatinine concentration is the dominant factor in determining the eGFR, *it is necessary to ensure that creatinine results are close to those originally used to define the formula.*
- The equation gives a result corrected for body surface area (BSA), where 1.73m² is taken as the BSA of an average person. Thus *results are reported in mL/min/1.73m².*

Key issues for laboratories

1. Serum Creatinine Assays

1.1. Assay performance criteria

The total error for the eGFR result has been set at +/- 30%. As the coefficients of the equation contribute +/- 15%, a **total error target** for serum creatinine assays of +/- 15% is recommended. This total error includes method bias, total analytical imprecision and assay non-specificity. Thus attention must be given to all these areas.

With regard to accuracy, serum creatinine assays for use with this equation must be aligned with either the Beckman-Coulter CX3, CX7 or LX20 “cup” assays (a CX3 analyser was used in the laboratory where the MDRD formula was developed), or with methods aligned with the international reference method (Isotope Dilution Mass Spectrometry, IDMS). The CX3 method runs with a small positive bias of about 6 μ mol/L compared to IDMS, however this difference is not considered significant. The Roche rate-blanked corrected Jaffe assay and Roche enzymatic assays are aligned with IDMS.

At this time, there is evidence that assays from the following manufacturers, if run exactly according to the manufacturer’s recommendations, are suitable for use:

- Abbott
- Beckman-Coulter
- Dade-Behring
- Roche Hitachi (enzymatic and rate-blanked, compensated Jaffe)
- Roche Integra (enzymatic and rate-blanked, compensated Jaffe)
- Ortho Clinical Diagnostics (Vitros)

Currently I have insufficient evidence to speak either for or against serum creatinine assays from other manufacturers.

Note that any alteration to the manufacturer’s recommendations (eg alternate calibrator; post-analytical correction factors; change in assay parameters) may affect assay performance and suitability for use. If there is any doubt laboratories can validate their assay against one of the following methods:

- Vitros enzymatic creatinine
- Roche Enzymatic creatinine
- Roche Rate-blanked compensated creatinine
- Beckman-Coulter “cup” assay

These assays are chosen either because of alignment with the standards mentioned above or because of combined low bias and low imprecision. Such comparisons should include a minimum of 20 samples covering the full range of serum creatinine results. The average bias

should be less than 7% at all creatinine concentrations greater than 100 µmol/L. To check the accuracy and linearity of your creatinine method, a creatinine accuracy-based linearity survey (designated LN24) will be available from the College of American Pathologists (A\$250 plus A\$105 freight, shipping December 19, orders to tmoreno@cap.org). This will consist of seven 1.0 mL fresh frozen serum patient pools with values assigned by IDMS.

Note that between-method bias cannot be assessed using QAP or QC material due to variable reaction of Jaffe assays with non-creatinine chromogens. QAP results can however be used to demonstrate equivalent performance between identical methods from the same supplier.

1.2. Creatinine Reporting

Serum creatinine results should be reported in µmol/L. This recommendation supersedes a previous College recommendation from 1978 and brings local laboratories into line with other SI users world-wide. Note that there is no change to the previous recommendation that urine creatinine be reported in mmol/L.

1.3. Measurement requirements

Creatinine assays should be run measuring results to the nearest 1 µmol/L for quality control purposes and MDRD GFR calculation. There is no recommendation concerning the increments used for reporting serum creatinine concentrations on laboratory reports.

1.4. Quality Control

It is recommended that laboratories run a QC sample with a creatinine concentration near 100 µmol/L in order to be able to assess performance near this important cut-off (this corresponds to an eGFR near 60 mL/min/1.73m²). This is in addition to any other levels of QC considered important for assay control. Note at least two concentrations of QC material are required for assay control.

2. Routine eGFR reporting

2.1. Abbreviated MDRD equation:

$$\text{eGFR} = 186 \times \{[\text{S}_{\text{Cr}} (\mu\text{mol/L}) \times 0.0113]^{-1.154}\} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$$

The serum creatinine measured to the nearest 1 µmol/L should be used for this calculation. This recommendation is based on the principle that any calculations should be performed on the most precise available data. The correction factor for sex allows the use of the same decision points for males and females.

2.2. eGFR Reporting

The eGFR should be reported for all requests for serum creatinine with the following exceptions:

- Patients under the age of 18 years of age (no eGFR to be reported)
- Patients on dialysis treatment (no eGFR to be reported, provided these patients can be identified in the LIS)

2.3. Reporting Format

Results for eGFR should be reported as follows:

- Units of mL/min/1.73m²
- A reporting interval of 1 mL/min/1.73m²
- Results calculated to be greater than 60 mL/min/1.73 m² to be reported as ">60 mL/min/1.73m²"
- Results less than or equal to 60 mL/min/1.73 m² to be reported numerically

The purpose of expressing results relative to 1.73m² BSA is to correct for different body sizes. A large healthy person (with size determined by BSA) is expected to have a higher GFR than a small healthy person. The use of 1.73m² is based on the assumption that this is the body surface area of an "average" person. In practice Australian males on average have a larger BSA than 1.73m² but this value is used internationally for this purpose.

2.4. Reference Intervals / Decision Points

All results less than or equal to 60 mL/min/1.73m² should be marked with an asterisk. No numerical reference interval should be provided. A footnote may be attached to results. Various formats for footnotes are possible depending on the capability of the laboratory reporting system. Some examples are shown below.

The well-known age-related decline in renal function has not been used as part of the recommended responses to low eGFR results as it is thought this change may reflect the effects of diseases related to ageing rather than the effects of ageing itself. Thus a 70 year old with a reduced eGFR requires the same further investigation as a 30 year old with the same result. At extremes of old age where life expectancy is unlikely to be limited by progressive renal disease further investigation of reduced eGFR is unlikely to be of benefit.

Examples of possible footnotes / comments

If footnote is adjustable dependent on result:

- | | |
|---|--|
| If result ≥ 60 : | "eGFR ≥ 60 mL/min/1.73m ² does not exclude kidney disease." |
| If result 30-59 mL/min/1.73m ² : | "eGFR 30 - 59 mL/min/1.73m ² suggests moderate chronic kidney disease and indicates the need for further investigation including assessment of proteinuria and cardiovascular risk factors" |
| If result <30 mL/min/1.73m ² : | "eGFR <30 mL/min/1.73m ² usually indicates a need for referral for assessment and management of chronic kidney failure." |

If footnote / comment is adjustable dependent on other parameters:

A footnote or comment also may take into account previous results (rate of change of eGFR), presence of proteinuria or albuminuria, presence of diabetes and known clinical referrals (eg patient has seen a nephrologist).

The following are examples of patient-specific comments:

- "eGFR has fallen by over 15% in the last three months. Referral to a nephrologist is indicated"

- “No significant change in eGFR since last measurement”
- “The combination of albuminuria and an eGFR < 60 mL/min/1.73 m² indicates the need for referral to a nephrologist”

Factors that may be taken into account in placing comments are shown in the GP Desktop Resource Card from Kidney Health Australia (Attachment).

It is important to note that a result >60 does not imply a normal GFR. When the eGFR is reported as “>60” then assessment should be made on usual criteria, eg comparison of serum creatinine with previous results from the same patient if available, or against population-based reference intervals if previous results not available.

Limitations of the MDRD eGFR

The MDRD formula generally provides an excellent estimate of GFR. In the vast majority of cases it is more accurate as well as being more convenient than Cockcroft and Gault estimates or measurement of creatinine clearance with a timed 24 hour urine sample. The MDRD formula generally should be used in place of these investigations. There are however some important limitations of the MDRD estimates of GFR that laboratories and doctors need to be aware of.

- The formula is not appropriate for use in persons under 18 years of age. Use of other formulae or direct measurement is recommended.
- The formula will give erroneous results in patients on dialysis.

The MDRD formula should not be used in the conditions described in the above 2 dot points.

- The formula may misrepresent GFR in cases of very rapidly changing renal function due to delays in accumulation or removal of creatinine from the serum in such cases. Note this limitation applies to any assessment of renal function based on serum creatinine.
- Exceptional dietary intake such as vegetarian, high protein or creatine intake may influence test results.
- Severe liver disease may markedly influence results with over-estimation of renal function in the moderate or severe renal impairment range.
- Extremes of body composition such as emaciation, limb amputation or paraplegia. Note that the formula has been validated in obesity.
- The formula is not validated in certain ethnic groups such as Asians, Aborigines, Torres Strait Islanders.
- The formula is not validated in pregnancy

Where accurate estimation of GFR is required in the groups described in the above 6 dot points an alternate method of estimating kidney function should be performed.

- The MDRD formula has not been validated for drug dosing. The recommendations in the Australian Medicines Handbook and MIMS are to estimate GFR with the Cockcroft and Gault formula. This remains the recommended procedure.
- The formula is dependent on the creatinine measurement so any drug interference in the serum creatinine measurement will affect the results.
- The reliance on serum creatinine measurements also affects precision and accuracy. When monitoring a patient over time it is preferable to use results from the same laboratory. A change in eGFR of greater than 15% in results from the same laboratory

indicates that the change is unlikely to be due to random variation. Repeat testing on a new sample should be performed to confirm significant changes in eGFR.

- Serum creatinine remains an important test. Changes of serum creatinine in a patient are the most sensitive test of changes in renal function, especially with results in or near the reference interval. A serum creatinine above the population reference interval, even if the eGFR is normal, may require further investigation.

Other information

Timing of implementation of the routine eGFR.

Individual laboratories may choose when to implement the eGFR however it may be useful to be aware of a number of supportive events as follows:

A GP Desktop Resource Card titled '*Chronic Kidney Disease and eGFR*', developed by Kidney Health Australia (KHA) will be distributed with the October issue of Australian Family Physician (publication date 5th October) to approximately 24,000 GPs and 9,000 physicians. (A copy of this GP Card which contains the eGFR Action Plan is provided as an attachment with these Guidelines).

Other articles/strategies include:

- "Measurement of kidney function", Mathews, T. & Johnson, D.(2005) Medical Observer [Update], 29 July.
- November theme in November issue of Australian Family Physician is "Renal Problems" and will contain the following 2 articles:
Johnson, DW & Usherwood, T; Automated reporting of GFR: Coming soon to a laboratory near you!
Johnson, DW & Usherwood, T; Management of Chronic Kidney Disease: Be alert but not alarmed
- Article in RACGP newsletter GP Review – to be distributed with the September edition of Australian Family Physician
- Letters to Divisions of General Practice promoting the recommendations.

Laboratories wishing to obtain more information about KHA activities in this area, including copies of material sent to GPs, may contact:

Ms Chris Archibald
National Project Officer
Kidney Health Australia
Ph: (08) 8334-7501,
Email: chris.archibald@kidney.org.au

Future Developments

The proposal for routine reporting of eGFR with all requests for serum creatinine has also been made by the National Kidney Disease Education Program (NKDEP) in the USA and by the Renal Association in the UK. The NKDEP and the IFCC also have established working groups on creatinine measurement and GFR estimation and have been liaising with manufacturers for some time to improve the standardization and precision of serum creatinine assays. These bodies are likely to make further recommendations such as adjustments to the current version of the MDRD eGFR formula in the light of changing

creatinine assays and to allow reporting of higher values for eGFR and in different populations. As these developments arise it will be necessary to consider their implications for Australia and New Zealand with the likelihood that changes and adjustments will be required. Our ability to provide consistency in measurement and reporting, both now and into the future, will be of great benefit to clinicians and patients in the management of kidney disease.

Further information is available on the following websites:

Kidney Health Australia: www.kidney.org.au

Kidney Diseases: Improving Global Outcomes (International): www.kdigo.org

National Kidney Disease Education Program (USA): www.nkdep.nih.gov

National Kidney Foundation (USA): www.kidney.org

The Renal Association (UK): www.renal.org

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I would like to acknowledge the active input of many members of the Chemical Pathology and Renal communities in the preparation of this Laboratory Guide
– Graham Jones

Example Letter to Requesting Doctors

DEAR DOCTOR,

Re: Automatic reporting of eGFR with every request for serum creatinine

Recently a formula for the estimation of Glomerular Filtration Rate (eGFR) has been developed for which the only inputs are age, gender and serum creatinine. This allows for routine calculation of the GFR from parameters already held in laboratory computer systems. The formula is the “abbreviated MDRD” formula, named after the Modification of Diet in Renal Disease study where it was developed.

As from the dd/mm/2005 XYZ pathology will be reporting an eGFR with every request for a serum creatinine in patients 18 years of age and over. The aim of this process is to increase awareness of moderate to severe kidney disease to allow appropriate early investigation and referral if required.

This development is recommended by Kidney Health Australia, the Australian and New Zealand Society of Nephrology, the Royal College of Pathologists of Australasia and the Australasian Association of Clinical Biochemists and is endorsed by the Australian Diabetes Society. More details are available in a Position Statement in the Medical Journal of Australia (2005;183(3):138-141). In order to maximise the benefit of the eGFR some supporting information from Kidney Health Australia is enclosed (attachment).

The routine reporting of eGFR will highlight moderate to severe kidney disease at a time when it still may be asymptomatic. This will allow early investigation and management with the aim of minimising progression to more severe kidney impairment. The eGFR will also highlight those patients where reduced kidney function should be considered with regard to drug dosing decisions and where reduced GFR leads to an increased risk from cardiovascular disease. There are a number of important conditions where the use of the MDRD equation is not appropriate for estimation of GFR and these are listed on the attached sheet.

Further information is available on the Kidney Health Australia website (www.kidney.org.au) or feel free to contact the laboratory.

Yours sincerely,