The eGFR Study: A longitudinal cohort study of kidney health and CKD progression in Aboriginal and Torres Strait Islander Australians

2007- current

Aboriginal Health Council South Australia
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Health is...

“a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”

*World Health Organisation*
Aboriginal Health

• “not just the physical well-being of an individual but refers to the social, emotional and cultural well-being of the whole community in which each individual is able to achieve their full potential as a human being thereby bringing about the total well-being of their Community. It is a whole of life view and includes the cyclical concept of life-death-life”

(National Aboriginal Health Strategy 1989)
Healthy Non-communicable chronic diseases

Diabetes
Cardiovascular Disease
CKD

RRT

Born → Healthy → Non-communicable chronic diseases → Death

Lived Well
Indigenous Australians

- Diabetes: 10 x higher, aged 20-50 years
- Diabetes, heart and CKD: account for 50% of the 17 year gap in life expectancy
- Incidence of ESKD is up to 15-30 x higher
- Health care costs: Dialysis for 500 in NT costs $30M/year
- Personal and family Costs
Disparity in treatment access
Key Questions

• How do I detect CKD?
• Can I identify features which are associated with rapid decline in kidney function?
• What interventions are successful in slowing decline in kidney function?
  – Are these sustainable?
  – Can they be targeted?
  – What are individual & systems approaches
  – What are the policies needed
Accurate assessment of renal function in Indigenous Australians

Short Study name: eGFR Study

Funded by: NHMRC, Kidney Health Australia, Menzies School of Health Research and Rebecca L. Cooper Medical Research Foundation

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eGFR Study: Accurate assessment of renal function and progression of chronic kidney disease in Indigenous Australians

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There is an important relationship between body shape and health and illness

**Adiposity:**
Obesity and Overweight increase the risk of developing
Diabetes, Hypertension, Dyslipidaemia
Accelerates renal disease (proteinuria)
Other: fatty liver, restrictive lung dx, arthritis,

**Lean Tissue:**
Measurement of renal function depends on serum
Creatinine, a by-product of muscle mass.
• Invasive Kidney Function Tests
• Non-Invasive Kidney Function Tests (eGFR)

• GFR: Glomerular Filtration Rate
  – Glomerulus (nephron): single unit of kidney filtering
  – 1.4 million nephrons
    • Capacity to hyper-function when stressed
    • Cannot regenerate.

• As a Torres Strait Islander woman (high risk of T2DM, CKD), I want a practical and accurate, non-invasive kidney function test (eGFR)
Background

2005 Consensus Statement\(^1\) recommended use of eGFR = formula-based estimate of GFR, based on creatinine, gender & age\(^2\)

The revised MDRD formula (the “175” formula)\(^6\)
\[
eGFR = 175 \times (S_{CR} \times 0.0113)^{-1.154} \times (age)^{-0.203} \times (0.742 \text{ if female})
\]
where MDRD = Modification of Diet in Renal Disease,\(^2\) eGFR = estimated glomerular filtration rate (mL/min/1.73 m\(^2\)), \(S_{CR}\) = serum creatinine concentration (\(\mu\)mol/L), and age is expressed in years.

Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: a position statement

The Australasian Creatinine Consensus Working Group

1 Comparison between original and revised recommendations: summary

<table>
<thead>
<tr>
<th>Original key recommendations</th>
<th>Revised recommendations</th>
</tr>
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<tbody>
<tr>
<td><strong>An eGFR shall be calculated and reported with every request for serum creatinine concentration</strong></td>
<td><strong>No change</strong></td>
</tr>
<tr>
<td>eGFR values over 60 mL/min/1.73 m² should be reported as “&gt; 60 mL/min/1.73 m²”, rather than as a precise figure</td>
<td>eGFR values over 90 mL/min/1.73 m² should be reported as “&gt; 90 mL/min/1.73 m²”, rather than as a precise figure</td>
</tr>
</tbody>
</table>

Automatic reporting of eGFR may include age-related reference intervals for people aged ≥65 years

Drug dosing — no recommendation was made, but it was noted that “an uncorrected eGFR may be preferred for clinical use in some situations, such as drug dosing”

In the absence of agreed age-related reference intervals, eGFR values in the range 45–59 mL/min/1.73 m² in people aged ≥70 years should be interpreted with caution. If no other signs of kidney damage (e.g., proteinuria, haematuria) are present, a stable eGFR in this range may be consistent with typical GFR for this age and an absence of CKD-related complications

In most out-of-hospital settings, particularly general practice, where an eGFR (based on the MDRD formula) is on hand and no other measure of GFR is known or readily accessible, it is clinically appropriate to use eGFR to assist drug-dosing decision making

Use of eGFR in various ethnic populations — no recommendation was made, but it was noted that “specific clinical settings in which eGFR is not appropriate for use and GFR should be measured directly include ... populations in which the MDRD equation is not validated (eg, Asian people) or in which validation studies have not been performed (eg, Aboriginal and Torres Strait Islander populations)”

Pending publication of validation studies, it is recommended that Australasian laboratories continue to automatically report eGFR in Aboriginal and Torres Strait Islander peoples and other ethnic groups

CKD = chronic kidney disease. eGFR = estimated glomerular filtration rate. MDRD = Modification of Diet in Renal Disease.²

• Kidneys Essential Functions:
  • Water balance
  • Salt regulation
  • Bone Health
  • Blood Pressure
  • Regulation EPO production (prevent anaemia)
  • Excretion of water-soluble end-products of metabolism

• Renal Injury can be asymptomatic even in severe injury.

• Diverse causes of renal injury

• GFR (ml/min/1.73m2)

• Generate Stages of Renal Impairment

  • Stage 1: >=90 (**)
  • Stage 2: 60-89
  • Stage 3: 30-59
  • Stage 4: 15-29
  • Stage 5: <15

• ** structural abnormality or urinary abnormality
• n=1628 participants with CKD
  – Mean age 50 years
  – Mean GFR 39.8ml/min/1.73m²
• 6% (n=99) diabetes
• 12% (n=197) African American
• Measured GFR by renal clearance of $^{125}$I-iothalamate

• Differences in body builds & compositions in Indigenous Australians\(^3\)
  ➔ eGFR derived for Europeans may not be appropriate

• creatinine is a by-product of muscle cells
  – affected by CKD, age, gender & lean muscle mass.
  – ethnicity – formula has correction factor for African Americans but this related to differences in muscle mass

Piers et al.\textsuperscript{3}

- n=250 Indigenous Australians (remote central & Northern communities) vs European Australians (n=130)
- Body composition assessed by weight, waist/hips, skinfold thickness & BIA
- Reported more fat mass for a given weight or BMI amongst Indigenous Australians
  - & different fat distribution: ↑ central adiposity

Limitations of eGFR

- Ethnicity
- Body build
- Disease states
- “healthy” GFR
- Many of above relate to creatinine measures which have recently been standardised internationally (IDSM)
• ANZDATA: n=207 Indigenous Australians commenced dialysis in 2005
  – 35% from NT
  – 23% from Qld
  – 22% from WA
  – 66% T2DM as lead primary cause
    (vs 24% non-Indig)
  – 77% T2DM as co-morbidity
    (vs 33% non-Indig)
• There is an epidemic of chronic disease (diabetes, CKD & cardiovascular disease) in Indigenous Australians

• A validated measure of GFR is vital in this high risk population in order to guide best-practice clinical care to ameliorate the rapid progression of CKD & its impact on the health and well-being of Indigenous individuals & communities
The eGFR Study

• responding to concerns by Indigenous Australian clients and their communities and clinicians.
  – NT dialysis clients experience social and emotional wellbeing issues related to the illness, navigating health care systems and dislocation from community when accessing dialysis.
Aim

To determine a validated & practical measure of GFR suitable for use in all Indigenous Australians, taking into account heterogeneity of body builds across different populations.
• NHMRC-funded study of 600 Indigenous Australians across NT, FNQ & WA

Phase 1 (2009-11): Assess accuracy of test of kidney function

Phase 2 (2012-15): Assess which factors contribute to rapid progression of kidney damage

Phase 3: Work with communities to design intervention to prevent progression
Methods: Participants

n=600

Top End  CA  FNQld  WA

Strata of kidney function:
1. “healthy”
2. Diabetes & eGFR>90mls/min/1.73m²
3. eGFR 60-90
4. eGFR 30-60
5. eGFR<15-29

Setting: community-based in >20 sites
Methods

• Compare eGFR v mGFR (reference test)

• ACCURACY

• PRECISION

• BIAS
Method
Results

<table>
<thead>
<tr>
<th></th>
<th>Accuracy</th>
<th>Bias</th>
</tr>
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<tbody>
<tr>
<td>eGFR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDRD</td>
<td>Yes</td>
<td>Present: underestimated eGFR</td>
</tr>
<tr>
<td>CKD-EPI</td>
<td>Yes</td>
<td>Reasonably Unbiased</td>
</tr>
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</table>

*without AA correction factor

Accuracy: within the 30% lines of zero difference

Summary eGFR Study Findings

• eGFR using CKD-EPI provides reasonably unbiased & accurate estimate of GFR in Indigenous Australians

• CKD-EPI outperforms other formulae (MDRD & Cockcroft-Gault) however bias remains higher in those with diabetes than without diabetes, especially where eGFR>90

• Addition of weight or FFM to age, gender, creatinine in eGFR did not significantly improve prediction of GFR

• Further work: Cystatin-c did not improve precision, but was associated with inflammation*
Indigenous Australians have up to 30 times higher incidence of ESKD than other Australians.

- Macroalbuminuria was an identified risk factor for renal and all-cause death in several Indigenous communities

Prospective cohort studies recruiting participants across multiple communities and geographical regions have not previously been reported.
The eGFR Study: Phase 2

• Progression of kidney damage: follow-up of cohort 2-4 years after baseline

• Aim:
  To assess the progression of kidney disease in an Indigenous Australian cohort from the regions of Australia with the greatest burden of ESKD
Methods: Follow-Up

- Urine ACR & eGFR were re-assessed in adults participating in baseline eGFR Study
  - Albuminuria (mg/mmol) defined using KDIGO criteria: normo, micro-, macro-: <3, 3-30, >30 mg/mmol
  - Serum creatinine (centrally measured, IDMS standardised)
  - eGFR (ml/min/1.73m²) calculated using the CKD-EPI equation

- Outcomes:
  - mean annual eGFR change
  - Combined renal end-point: first of ≥30% decline eGFR with follow-up eGFR<60 ml/min/1.73m², progression to RRT or renal death
Participants in eGFR Follow-Up

n=654

654 Indigenous Australian participants assessed at Baseline
- N=7, consent withdrawn for FU
- N=13, age < 18 yrs at BL
- N=15, nil BL blood sample

n=619

N=619 eligible for FU
- N=8, lost to FU
- N=15, time to FU < 6 mo and/or BL inter-current illness

n=596

N=596 participants assessed at BL were followed-up
- N=46, nil sCreat at FU

n=550

N=550 participants with both ACR and sCreat measures at BL and FU
### Participant Characteristics

**Baseline Factor** | eGFR<60 n=85 | eGFR 60-90 n=125 | eGFR≥90 n=340
--- | --- | --- | ---
Age (years) | 60 | 54 | 40
Male (%) | 42% | 38% | 34%
Weight (kg) | 76 | 84 | 83
BMI (kg/m²) | 27.8 | 30.2 | 30.0
WHR | 1.00 | 0.95 | 0.93
Diabetes (%) | 67% | 47% | 37%
HbA1c (mmol/mol) | 47.5 | 44.3 | 42.1
Creatinine (µmol/L) | 150 | 80 | 60
CKD-EPI eGFR | 38 | 82 | 108
mGFR (ml/min/1.73m²) | 46 | 87 | 114
Microalbuminuria (3-30mg/mmol) | 27% | 22% | 21%
Macroalbuminuria (>30mg/mmol) | 65% | 21% | 10%

*n=550, Data are median or %*
Results

n=550 adults
Median (IQR) years of follow-up: 3.0 (2.5-3.3)

Mean eGFR in all participants
- Baseline 83.9 (80.7, 87.3)
- Follow Up 70.1 (65.9, 74.5)

<table>
<thead>
<tr>
<th></th>
<th>Mean Annual eGFR Change, ml/min/1.73m²</th>
</tr>
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<tbody>
<tr>
<td>Overall</td>
<td>-3.1 (-3.6, -2.5)</td>
</tr>
<tr>
<td>By baseline eGFR Group</td>
<td></td>
</tr>
<tr>
<td>≥90</td>
<td>-3.0 (-3.6, -2.5)</td>
</tr>
<tr>
<td>60-90</td>
<td>-1.9 (-3.3, -0.5)</td>
</tr>
<tr>
<td>&lt;60</td>
<td>-5.0 (-6.5, -3.6)</td>
</tr>
</tbody>
</table>

*Data are geometric mean (95% CI)
Annual eGFR decline:
greatest among adults with baseline macroalbuminuria, regardless of eGFR category

Legend: Significant change annual decline in eGFR in comparison eGFR>90 & ACR <3mg/mmol: # p value=0.047; *p value=<0.001
• Cox regression of combined Renal Endpoint
(48 events)

• Commenced RRT
• Renal death
• >30% decline eGFR & follow-up eGFR < 60 ml/min/1.73 m²
Disparity in treatment access

- Nearly all patients started treatment with haemodialysis. A single patient accessed kidney transplantation at start of care.
- Few patients had access to haemodialysis at home or through self-care.
- 61% started temporary dialysis with catheter.

We wish to acknowledge that this summary is based on information provided by Australian patients and kidney units each year to ANZDATA.
Living Well with kidney failure treatments, close to home and country

Indigenous Patient Voices Symposium:
**MKC**
Commissioned by Health Service
In-depth interviews
April-Nov 2017
Top-End NT Region
N=26
CKD, HD, PD, Tx
Top End Health Service
*AHL

**IPV**
Developed in ANZSN ASM, to raise need
Focus Group
September 2017
Darwin
N=35: HD, TX, PD
N=55 Staff
Min Indigenous Health CTG Campaign

**C-AIR**
Guidelines Development
KHA-CARI, ANZDATA
Focus Group
April- September 2018
Darwin, Thursday Island, Alice Springs
N=150
HD, TX, PD
Min Indigenous Health Shadow Min Indig Health
ANZDATA, KHA-CARI NSAPKD
MKC
Local programs
Workforce
Sustain reference group

IPV
Nov 2017, Report
Nov 2017, MBS Clinical Review Committee
Fed Budget (May 2018)
*Nov 2018
Feb 2018, Report
Published Nephrology
Feb 2018, Renal Health RoadMap Roundtable
*Mar 2019
*Sept 2019

C-AIR
Policy Document
-Fed Government Dec 2018
-NSAPKD May 2019
Workforce Roundtable
- Min Indig Health
- Jan 2019
Guidelines recommendations
-Data – ANZDATA Aug 2019
-Clinical Care- KHA-CARI
June 2019
March 2018
- TSANZ Meeting
  with Min Wyatt

June 2018
- Commissioned EAP
  for Transplant Access
  and Outcomes

July 2019
- TSANZ National
  Indigenous Kidney
  Transplantation
  Taskforce
Journey to Transplantation

Dialysis: Day 0

Dermatology issue

Start Workup: day 34

Activate (1)

Transplant suitability review

Activate (2)

Testing

Inactive

Transplant: day 950

Pre-transplant timeline

Activation Status

0 30 60 90 120 150 180 210 240 270 300 330 360 390 420 450 480 510 540 570 600 630 660 690 720 750 780 810 840 870 900 930 960 990 1020 1050 1080

840

870

900

930

990

1020

1050

1080

960

930

900

870

840

810

780

750

720

690

660

630

600

570

540

510

480

450

420

390

360

330

300

270

240

210

180

150

120

90

60

30

0

Dialysis: Day 0

Start Workup: day 34

Activate (1)

Activate (2)

Transplant: day 950

Transplant suitability review

Testing

Activation Status

Pre-transplant timeline

Dermatology issue
Efficacy: Communication

We want to be involved in health care planning decisions that affect us and our community.

We want clear and useful information about kidney disease.

We want to share the right information with our communities (young people), so they are not impacted by kidney disease (like I have been).
Information about the eGFR kidney function blood test
The eGFR kidney function blood test

- Each healthy kidney has more than 1 million blood filters. The **glomerulus** is part of the kidney filter.

- The blood test of kidney function is called “eGFR”, or **estimated glomerular filtration rate**.
Fuel Tank
• 15ml/min/1.73m² - kidney failure

• 90 ml/min/1.73m² – healthy kidneys

Treatments for kidney failure can include haemodialysis or peritoneal dialysis or kidney transplantation.
• In the old days (before 2005), the serum creatinine blood test was used to report kidney function.
• Creatinine is a protein from muscle cells
• This test was good at reporting advanced kidney damage
• This test was not so good at reporting early kidney damage.
• The eGFR kidney function blood test came to Australia from America in 2005.

• The eGFR blood test used the serum creatinine level in a new way. It could show early kidney damage as well as late kidney damage. The eGFR test was used differently in African American people, because they had more muscle.

• We did not know if muscle size or body size would affect the accuracy of the eGFR test for Aboriginal and Torres Strait Islander adults. We needed a research study to prove this.
During 2007-2011, the eGFR Study worked together with 20 communities across

Top-End NT,

Central Australia,

Western Australia and

North Queensland.
The eGFR Study- Baseline study

- We showed....
- The $\text{eGFR}_{\text{CKDEPI}}$ blood test is the best easy test of kidney function
- It is an accurate test of kidney function in Aboriginal and Torres Strait Islander adults.
- Does not need to be used differently in Aboriginal and Torres Strait Islander people than in non-Indigenous people
- Does not need information about body size or muscle
The eGFR Follow-up Study showed...

- Every year there was 3 ml/min/1.73m² of lost kidney function.
- This was 3 times more than expected for healthy aging
- Some people had fast-loss of kidney function, 5 ml/min/1.73m²
  - Diabetes
  - a higher urine ACR test
  - a blood test showing some inflammation
- Urine ACR test (from 30mg/mmol ACR level) was powerfully predictive of fast-loss of kidney function over 3 years.
- Some people had started dialysis or passed away during the 3 years
The eGFR Study showed there was 3 to 5 times faster loss of kidney function each year, than expected for just getting older.

In just 3 years, there was 3-5 times lower eGFR test.
Advice about kidney health

• Have a kidney health check every year
  • This includes a blood pressure, eGFR test, urine ACR
  • Start at 18 years old
• Know your kidney function test level
• Talk with your health team
  • Right information
• Your own health action plan
We have good knowledge about kidney health over three years.

We don’t yet have enough knowledge about kidney health after three years.

Checking kidney health of everyone in the eGFR Study at 10 years may provide this knowledge.
Planning for the eGFR 3 Study

• Since 2007 (10 years of research), we have learned new kidney health knowledge in Aboriginal and Torres Strait Islander peoples.

• We want to learn more about why some people have fast-loss of kidney function, and why people may need hospital care and why people have passed away.

• We believe a eGFR3 Study involving a 10 year follow-up will help us understand this.
eGFR3 Study

- We want to meet people again
- check the eGFR kidney function blood test and urine test
- learn about hospital care for people over the 10 years
- find out if the fast-loss of kidney function is different for men and women
- learn about the reasons people start dialysis or pass away

- This information will be used to help patients, families, communities and health services know the reasons for fast-loss of kidney function, and work improve kidney health.
Advice about kidney health

- Have a kidney health check every year
  - This includes a blood pressure, eGFR test, urine ACR
  - Start at 18 years old
- Know your kidney function test level
- Talk with your health team
  - Right information
- Your own health action plan
Ms Maria Nickels, AHP
Grandmother Liaison, Wheatbelt Aboriginal Health Service,
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This flipchart was developed and piloted in 2018 by Dr Hughes and
Ms Nickels as part of eGFR Study knowledge exchange events,
which were funded by the Menzies Small Grants Award 2018.

https://bit.ly/2vU6Lu1

The eGFR Study
is a longitudinal study of kidney health in Aboriginal and Torres Strait Islander people. Information about this Menzies-led research is found at
https://bit.ly/2vU6Lu1
Thanks ....
1. NHMRC ECF
2. My Team: TEHS & Top-End Renal Services
3. Patient-experts
4. eGFR Study (Baseline and Follow-Up – funded by NHMRC

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