Chronic Kidney Disease in Queensland (CKD.QLD)

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Chronic kidney disease

- Major public health problem affecting 13.2% adult Australian\(^1\) 11% US population\(^2\)
- Most common chronic disease in Australia\(^3\)
- Monitored by National Chronic Disease Strategy Group
- 2007 AIHW established CKDMAC (Monitoring Advisory Committee)
- CKD defined and classified by NKF KDOQI (under review)
- Estimating equations for GFR evolving
- CV risk increased in CKD 10-20 times and 10 times more likely to die than reach ESKD
- Incidence RRT 110/10\(^6\)/yr prevalence 797/10\(^6\) \(^4\) (leading cause of hospital separations)
- Annual rate rise of 4-7.1%\(^4\)
- CKD costs > $697 million 2010
- Death certificate data, CKD contributes to 10% deaths directly or indirectly in Australia\(^5,6\)
- Annual mortality rate of dialysis patients is 20-25%\(^7\)

\(^3\) Australian Institute of Health and Welfare 2005
\(^4\) ANZDATA Report 2008
\(^5\) Li SQ et al. *Internal Medicine Journal* 2004; 34:259-65
\(^6\) Johnson DW *Internal Medicine Journal* 2004; 34:50-57
\(^7\) US Renal Data System  *Annual Report* 2007
# MDRD to CKD-EPI

## Table 3. Estimated Population Prevalence of CKD by Stage in the Australian Population Aged ≥ 25 Years

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>eGFR (mL/min/1.73m²)</th>
<th>MDRD Study Equation</th>
<th>CKD-EPI Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage(^a) with normal or increased eGFR</td>
<td>≥90</td>
<td>1.36 (1.02-1.81)</td>
<td>163,227</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage(^a) with mildly decreased eGFR</td>
<td>60 to &lt;90</td>
<td>4.27 (3.37-5.40)</td>
<td>512,966</td>
</tr>
<tr>
<td>3a</td>
<td>Moderately decreased eGFR</td>
<td>45 to &lt;60</td>
<td>6.65 (5.23-8.43)</td>
<td>798,716</td>
</tr>
<tr>
<td>3b</td>
<td>Moderately decreased eGFR</td>
<td>30 to &lt;45</td>
<td>0.82 (0.55-1.23)</td>
<td>98,537</td>
</tr>
<tr>
<td>4</td>
<td>Severely decreased eGFR</td>
<td>15 to &lt;30</td>
<td>0.28 (0.14-0.54)</td>
<td>33,383</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 (or dialysis)</td>
<td>NA</td>
<td>16,751</td>
</tr>
</tbody>
</table>

\(^a\) Decreased eGFR compared to age- and sex-matched adults.

New Patients 1960 – 2008
Australia and New Zealand

Year

New patients, Australia

New patients, NZ

© ANZDATA Registry
Primary Renal Disease Among People Starting Renal Replacement Therapy Australia and New Zealand

Note different y axis scales
CKD in Queensland

- Queensland total population: 4.4 million\textsuperscript{8,9}
- Queensland adult population (>25yrs) 2.43 million\textsuperscript{8,9}
- Estimated CKD prevalence (>25yrs) 340,000
- Multiethnic
- 110,000 Aboriginal & Torres Strait Islander people, with 25,000 remote
- One public health provider, Queensland Health
- Integrated service (SWCRN) across 15 Health Service Districts\textsuperscript{10}
- About 80 nephrologists/advanced trainees
- 20 dedicated CKD nurse/nurse practitioners (CKD.QLD site 1 survey)

\textsuperscript{8}2010 Health of Queenslanders Report (Chief Health Office Report)
\textsuperscript{9}Self reported Health Status 2010, Queensland & Health Service Districts Report
\textsuperscript{10}Queensland Health Corporate Information
CKD.QLD

- Collaborative multidisciplinary CKD program, established July 2009, which encompasses a CKD registry and practice network with the purpose of improving outcomes and building capacity in CKD research.
- Started as an NHMRC CRE grant application
- Evolved to CKD.QLD after grant submission in Sept 2009
- Meetings of Steering Committee since Sept 2009
Welcome to CKD.QLD

CKD.QLD is a statewide collaborative multidisciplinary research and practice program, established in July 2009, which encompasses a CKD registry, database and practice network, with the purpose of improving CKD patient outcomes and building capacity in CKD research.

The goals of CKD.QLD is to further improve health outcomes for CKD patients both in primary and specialist care, to conduct CKD epidemiological research and much needed high quality clinical trials, to identify means of early CKD detection using novel biomarkers, to assess and improve CKD models of care and hence achieve efficiencies in CKD service delivery, and to support health policy and planning for CKD and its many associated co-morbidities.

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Allied Health
06 April 2011

Co-Chairs

Professor Wendy Hoy
Prof Wendy Hoy has led numerous studies to better understand why certain...

Professor Rob Fassett
Professor Robert Fassett

Contact Us

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CKD.QLD objectives

- Define CKD distribution, characteristics, stages, associations, co-morbidities and management
- Evaluate longitudinal CKD population trends and outcomes
- Identify treatment gaps and promote best practice
- Conduct clinical trials in collaboration with AKTN
- Evaluate models of CKD health service delivery
- CKD biomarker study and biobank
- Investigate palliative care in CKD
- Develop CKD education and training streams
Collaborations and distribution of CKD sites in Queensland
Multidisciplinary collaborations

- CKD nurse practitioners and CNC’s
- Nephrologists
- General practice
- Palliative care providers
- Dietitians
- Social workers
- Pharmacists
- Psychologists
- Exercise physiologists
- Aboriginal health workers
- Scientists
- Molecular biologists
- Health economist
CKD clinic profiling

- Site visit 1 clinical Audit and Quality improvement process
- First broad profile, completed March 16, 2010
- Site visit 2 program via SurveyMonkey™ December 2010
Queensland Health sites visited

- Gold Coast Health Service District
- Logan Hospital
- Princess Alexandra Hospital and CKD clinic
- Nundah CKD Clinic
- Sunshine Coast Wide Bay Health Service District – northern cluster and southern cluster
- Keperra CKD clinic
- RBWH renal outpatients
- Redland Bay Hospital
- Rockhampton Hospital
- Townsville General Hospital
- Cairns Base Hospital
- Palm Island Hospital
- Toowoomba Hospital
- Bundaberg Hospital
- Mackay Base Hospital
- Private sites Parnham, Fleming, Herzig, Bofinger
<table>
<thead>
<tr>
<th>Service</th>
<th>CKD patients (n)</th>
<th>Nephrologists</th>
<th>Nurses</th>
<th>Stages of CKD seen</th>
<th>Database</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cairns</td>
<td>400</td>
<td>2</td>
<td>1 pre-dialysis, 1 CNC</td>
<td>Generally stages 3-5 without complications</td>
<td>Excel</td>
</tr>
<tr>
<td>GCHSD</td>
<td>183</td>
<td>4</td>
<td>1 NP, 1 CNC</td>
<td>Predominantly stages 4 &amp; 5 with some 3 (often diabetic)</td>
<td>Excel</td>
</tr>
<tr>
<td>RBWH-clinic</td>
<td>1500</td>
<td>7</td>
<td>All</td>
<td></td>
<td>Excel</td>
</tr>
<tr>
<td>RBWH-Nundah</td>
<td>230</td>
<td>1 P/T</td>
<td>1 NP, 3 CNC’s</td>
<td>Stage 3-5 that are stable, stage 2 if complex and need follow-up</td>
<td>Excel</td>
</tr>
<tr>
<td>RBWH-Kepperra</td>
<td>79</td>
<td>1 P/T</td>
<td>1 P/T CNC</td>
<td>Stage 3-5 that are stable, stage 2 if complex and need follow-up</td>
<td>Excel</td>
</tr>
<tr>
<td>PAH-CKD clinic</td>
<td>130</td>
<td>6</td>
<td>1 NP</td>
<td>Mostly stages 3 &amp; 4 but do service some stage 2s and some stage 5s.</td>
<td>Landmark 3 patients only + CPIC</td>
</tr>
<tr>
<td>PAH-nephrology outpatients</td>
<td>2043</td>
<td>6</td>
<td>All</td>
<td></td>
<td>Landmark 3 patients only + CPIC</td>
</tr>
<tr>
<td>Logan</td>
<td>500</td>
<td>0.5</td>
<td>1 NP</td>
<td>NP patients in stages 2-5</td>
<td>CPIC ERIC ASIM</td>
</tr>
<tr>
<td>Redlands</td>
<td>400-500</td>
<td>1 P/T</td>
<td>2 nurses shared</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>SCWBHDS Nth</td>
<td>&gt;300OPD</td>
<td>1</td>
<td>1 NP</td>
<td>All stages of CKD are treated</td>
<td>Excel</td>
</tr>
<tr>
<td>SCWBHDS Sth</td>
<td>&gt;1000 stage 3-5</td>
<td>2</td>
<td>1 CKD nurse</td>
<td>All stages of CKD are treated</td>
<td>Excel</td>
</tr>
<tr>
<td>Toowoomba</td>
<td>412</td>
<td>2</td>
<td>1 CNC CKD</td>
<td></td>
<td>Excel</td>
</tr>
<tr>
<td>Townsville</td>
<td>1-2000 OPD</td>
<td>2</td>
<td>1 NP, 1 CKD nurse Palm Is</td>
<td>CKD clinic mostly stage 2-3</td>
<td>? Excel</td>
</tr>
<tr>
<td>Rockhampton</td>
<td>365</td>
<td>2</td>
<td>1 CNC, 0.6 CN</td>
<td>KHA guidelines</td>
<td>Excel</td>
</tr>
<tr>
<td>Bundaberg</td>
<td>160</td>
<td>1.2</td>
<td>N/A</td>
<td>N/A</td>
<td>Excel for stages 4 and 5</td>
</tr>
<tr>
<td>Mackay</td>
<td>1 (based interstate)</td>
<td>1 (cardiac)</td>
<td>Stages 3-5 GP or specialist referral</td>
<td></td>
<td>HBCIS</td>
</tr>
<tr>
<td>Total</td>
<td>10,469</td>
<td>28</td>
<td>17.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
100 patients

50 patients

Indigenous Australians

Various ethnicities incl. Asian & Eastern European

Australian South Sea Islanders

Public patients
1. Demographics

1. Where is your CKD site?
   - City/Town: 
   - Email Address: 

2. Type of practice
   - Hospital Based
   - Community Based
   - Private practice

3. Patients are seen by
   - Nephrologist/Consultant
   - Advanced Trainee (Renal)
   - Basic Physician Trainee
   - Resident Medical Officer
   - CKD Nurse Practitioner
   - Clinic nurse consultant (CNC)
   - Dietician
   - Social Worker
   - Psychologist
   - Pharmacist
   - Exercise Physiologist
   - Other (please specify): 

2. Patient numbers, type, referral and follow-up
<table>
<thead>
<tr>
<th>Location</th>
<th>CKD patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Toowoomba</td>
<td>506</td>
</tr>
<tr>
<td>2. Cairns</td>
<td>600</td>
</tr>
<tr>
<td>3. Mackay</td>
<td>191</td>
</tr>
<tr>
<td>4. Bundaberg</td>
<td>492</td>
</tr>
<tr>
<td>5. Rockhampton</td>
<td>390</td>
</tr>
<tr>
<td>6. Townsville</td>
<td>609</td>
</tr>
<tr>
<td>7. RBWH</td>
<td>1525</td>
</tr>
<tr>
<td>8. PAH</td>
<td>4171</td>
</tr>
<tr>
<td>9. Nundah</td>
<td>387</td>
</tr>
<tr>
<td>10. Northwest</td>
<td>95</td>
</tr>
<tr>
<td>11. Nambour</td>
<td>700</td>
</tr>
<tr>
<td>12. Gold Coast</td>
<td>617</td>
</tr>
<tr>
<td>13. Logan</td>
<td>500</td>
</tr>
<tr>
<td>14. Hervey Bay</td>
<td>556</td>
</tr>
<tr>
<td>Total</td>
<td>11,339</td>
</tr>
</tbody>
</table>
1. Antihypertensive treatment routinely includes

- Angiotensin converting enzyme inhibitors (ACEI)
- Angiotensin II Receptor Blockers (ARBs)
- Both ACEI & ARBs preferably
- Both ACEI & ARBs case by case
Blood glucose monitoring includes:

- Fasting blood glucose levels
- Random blood glucose levels
- HbA1C levels
- We don't monitor. Leave it to patient's GP
CKD.QLD registry

- Existing Excel databases
- Design new database
- QH Renal information system
- Audit 4 (S4S)
- Audit 4 supplemented by UQ Centre for Chronic Disease
- Support for data entry
- Others (GP practice software)
Outcomes

- Consensus on database for CKD.QLD and content.
- Timelines for the registry
- Proposed databases for CKD.QLD (Audit 4, Centre for Chronic Disease, others)
- Central data storage (Queensland Health)
- Minimal dataset
- Ethical issues
- Staffing and personnel requirements and support
- Budget/funding
- Governance structure, roles responsibilities and terms of reference
Audit4

Positives
• Already accepted by many nephrologists throughout Australia (4000 patients)
• Approved in Cairns- set precedent in QH
• Now approved at RBWH, Gold Coast and Rockhampton
• In private nephrology sector (eKIDNAA)
• Flexible work sheets
• Already has capability of electronic transfer of de-identified data

Negatives
• Uncertain viability of a private company
• Costs
• Might not suit all sites
• Data entry
• Not linked to primary care
• No billing incorporated
<table>
<thead>
<tr>
<th>Electrolytes and Creatinine</th>
<th>Bone and Mineral</th>
<th>Full Blood Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na+ 140 mmol/L</td>
<td>Ca 2.36 ± 0.99 mmol/L</td>
<td>Hb g/L</td>
</tr>
<tr>
<td>K+ 3.90 ± 0.32 mmol/L</td>
<td>Ca corr. 3.96 ± 0.53 mmol/L</td>
<td>RCC x10^12/L</td>
</tr>
<tr>
<td>Cl- 104 mmol/L</td>
<td>Ionised Ca++ 3.96 ± 0.53 mmol/L</td>
<td>Htct ratio</td>
</tr>
<tr>
<td>HCO3- 31 mmol/L</td>
<td>Ca++ pH adj. 3.96 ± 0.53 mmol/L</td>
<td>MCH pg</td>
</tr>
<tr>
<td>Urea 319073486 mmol/L</td>
<td>PTH pmol/L</td>
<td>MCHC g/L</td>
</tr>
<tr>
<td>Creat 982118607 mmol/L</td>
<td>Urine Protein</td>
<td>MCV fl</td>
</tr>
</tbody>
</table>

| Liver Function | | | |
|----------------|----------------|----------------|
| Bili umol/L | Spot ur alb:cre 3.00 ± 0.47 mg/mmol | RDW % |
| ALP U/L | UAE mcg/min | |
| ALT U/L | UPE g/d | |
| AST U/L | Glycaemia | |
| GGT U/L | Fruc umol/L | |
| LDH U/L | Gluc mmol/L | |
| Alb g/L | HbA1c 9.80 ± 0.25 % | |
| Glob g/L | TRAB IU/L | |
| Prot g/L | TRAB IU/L | |

<table>
<thead>
<tr>
<th>Lipids</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Chol 380926514 mmol/L</td>
<td>FT3 pmol/L</td>
<td></td>
</tr>
<tr>
<td>Trigs 395231628 mmol/L</td>
<td>FT4 pmol/L</td>
<td></td>
</tr>
<tr>
<td>HDL chol 302384186 mmol/L</td>
<td>TSH mIU/L</td>
<td></td>
</tr>
<tr>
<td>LDL chol 3 mmol/L</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>endocrinology</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Trigs</td>
<td>Ca</td>
<td></td>
</tr>
</tbody>
</table>

![Graph](image.png)
Ethical issues
Queensland Health and The University of Queensland

• CKD.QLD profiling
• CKD.QLD registry
• Individual research projects
• Registry- Ethics and Governance
## State Site Specific Governance update

**27.10.11**

<table>
<thead>
<tr>
<th>Sites (12)</th>
<th>Investigator</th>
<th>Governance Status</th>
<th>Nursing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RBWH</strong></td>
<td>Dr Helen Healy</td>
<td>Approved 11.02.11</td>
<td>Sonya Coleman NP &amp; Anne</td>
</tr>
<tr>
<td><strong>Toowoomba</strong></td>
<td>Dr Govindarajulu</td>
<td>Approved 25.03.11</td>
<td>Rebecca Barton ACNC CKD</td>
</tr>
<tr>
<td><strong>Mackay</strong></td>
<td>Ms Chris Banney</td>
<td>Approved 12.04.11</td>
<td>CKD CNC Chris Banney</td>
</tr>
<tr>
<td><strong>Rockhampton</strong></td>
<td>Dr Thin Han</td>
<td>Approved 31.03.11</td>
<td>Katrina Duff NP</td>
</tr>
<tr>
<td><strong>Bundaberg</strong></td>
<td>Dr Peter Miach</td>
<td>Approved 07.04.11</td>
<td>Barb Harvie NP</td>
</tr>
<tr>
<td><strong>Cairns</strong></td>
<td>Dr Murty Mantha</td>
<td>Approved 20.04.11</td>
<td>Stella Green, Trial Coordinator</td>
</tr>
<tr>
<td><strong>Hervey Bay &amp; Maryborough</strong></td>
<td>Dr Krishan Madhan</td>
<td>Approved 01.06.11</td>
<td>Leanne Brown NP</td>
</tr>
<tr>
<td><strong>Gold Coast</strong></td>
<td>Dr Thomas Titus</td>
<td>Approved 26.07.11</td>
<td>Michele Harvey NP &amp; Lorraine Bublitz CNC CKD</td>
</tr>
<tr>
<td><strong>PAH</strong></td>
<td>Dr David Johnson</td>
<td>Approved 06.10.11</td>
<td>Bettina Douglas NP</td>
</tr>
<tr>
<td><strong>Logan</strong></td>
<td>Dr Ken-Soon Tan</td>
<td>Approved 17.10.11</td>
<td>Cassy Stone NP</td>
</tr>
<tr>
<td><strong>Townsville</strong></td>
<td>Dr George Kan</td>
<td>Approved 19.10.11</td>
<td>Anne Blong NP</td>
</tr>
<tr>
<td><strong>Sunshine Coast</strong></td>
<td>Dr Nick Gray</td>
<td>With Governance Office</td>
<td>Andrea Pollock, Trials Coordinator</td>
</tr>
</tbody>
</table>
Governance of CKD.QLD

- Management Committee (Co-Directors)
- Finance Committee
- Scientific Committee
- General Membership
Terms of reference

- Membership (terms)
- Frequency of meetings
- Ownership of data
- Authorship of abstracts and publications
- Investigators on grant applications
The proposed CRE in CKD will, though the registry and practice network:

1. Conduct epidemiological research using longitudinal observational studies in primary and specialist care that will characterise the distribution of people with CKD in Queensland, their demographics, stages, associations, co-morbidities, management and outcomes.

2. Conduct high standard clinical trials in CKD in collaboration with the Australasian Kidney Trials Network (AKTN)

3. Evaluate CKD models of health service delivery, identify evidence based treatment gaps and support and promote best and cost effective practice

4. Conduct much needed Australian palliative care nephrology research

5. Initiate CKD biomarker research in collaboration with established International links

6. Build multidisciplinary research capacity through mentoring and leadership training.

7. Develop multidisciplinary training and educational streams
Epidemiology

- Primary care
- Specialist nephrology-public
- Specialist nephrology-private
- Pathology laboratories
- Indigenous healthcare settings
Clinical trials

- AKTN CKD-FIX (To be resubmitted 2012)
- Fish oil in CKD
- Dietary sodium reduction
- Industry trials (BEACON with Bardoxolone)
CKD models of care

- Traditional model nephrologist centered public clinic
- Private nephrology CKD practice
- New model of CKD nurse practitioner lead and nephrologist supported community multidisciplinary clinics
A Nurse-coordinated Model of Care versus Usual Care for Stage 3/4 Chronic Kidney Disease in the Community: A Randomized Controlled Trial

Brendan J. Barrett,* Amit X. Garg,† Ron Goeree,‡ Adeera Levin,§ Anita Molzahn,‖ Claudio Rigatto,§ Joel Singer,§ George Soltys,** Steven Soroka,‡‡ Dieter Ayers,‡‡ and Patrick S. Parfrey*

Summary

Background and objectives It is unclear how to optimally care for chronic kidney disease (CKD). This study compares a new coordinated model to usual care for CKD.

Design, setting, participants, & measurements A randomized trial in nephrology clinics and the community included 474 patients with median estimated GFR (eGFR) 42 ml/min per 1.73 m² identified by laboratory-based case finding compared care coordinated by a general practitioner (controls) with care by a nurse-coordinated team including a nephrologist (intervention) for a median (interquartile range [IQR]) of 742 days. 32% were diabetic, 60% had cardiovascular disease, and proteinuria was minimal. Guided by protocols, the intervention team targeted risk factors for adverse kidney and cardiovascular outcomes. Serial eGFR and clinical events were tracked.

Results The average decline in eGFR over 20 months was −1.9 ml/min per 1.73 m². eGFR declined by ≥4 ml/min per 1.73 m² within 20 months in 28 (17%) intervention patients versus 23 (13.9%) control patients. Control of BP, LDL, and diabetes were comparable across groups. In the intervention group there was a trend to greater use of renin-angiotensin blockers and more use of statins in those with initial LDL >2.5 mmol/L. Treatment was rarely required for anemia, acidosis, or disordered mineral metabolism. Clinical events occurred in 5.2% per year.

Conclusions Patients with stage 3/4 CKD identified through community laboratories largely had nonprogressive kidney disease but had cardiovascular risk. Over a median of 24 months, the nurse-coordinated team did not affect rate of GFR decline or control of most risk factors compared with usual care.

• 2 years too short? Slow CKD progression
• Patient selection, lab data from general population, wide range of patient risk
• Excluded elderly >75yrs, advanced CVD (ill defined) and eGFR < 25
• Findings cannot be extrapolated to these groups
Cost-Effectiveness Analysis of a Randomized Trial Comparing Care Models for Chronic Kidney Disease

Robert B. Hopkins,‡† Amit X. Garg,‡ Adeera Levin,§ Anita Molzahn,‖ Claudio Rigatto,¶ Joel Singer,§ George Soltys,** Steven Soroka,†‖ Patrick S. Parfrey,‡‡ Brendan J. Barrett,‡‡ and Ron Goeree‡†

Summary

Background and objectives Potential cost and effectiveness of a nephrologist/nurse–based multifaceted intervention for stage 3 to 4 chronic kidney disease are not known. This study examines the cost-effectiveness of a chronic disease management model for chronic kidney disease.

Design, setting, participants, & measurements Cost and cost-effectiveness were prospectively gathered alongside a multicenter trial. The Canadian Prevention of Renal and Cardiovascular Endpoints Trial (CanPREVENT) randomized 236 patients to receive usual care (controls) and another 238 patients to multifaceted nurse/nephrologist–supported care that targeted factors associated with development of kidney and cardiovascular disease (intervention). Cost and outcomes over 2 years were examined to determine the incremental cost-effectiveness of the intervention. Base-case analysis included disease-related costs, and sensitivity analysis included all costs.

Results Consideration of all costs produced statistically significant differences. A lower number of days in hospital explained most of the cost difference. For both base-case and sensitivity analyses with all costs included, the intervention group required fewer resources and had higher quality of life. The direction of the results was unchanged to inclusion of various types of costs, consideration of payer or societal perspective, changes to the discount rate, and levels of GFR.

Conclusions The nephrologist/nurse–based multifaceted intervention represents good value for money because it reduces costs without reducing quality of life for patients with chronic kidney disease.

A study of nurse practitioner service in CKD clinics in Queensland (cKiDNaP)

• Investigators

• Professor Glenn Gardner, QUT & RBWH

• Professor Ann Bonner, QUT

• Barb Harvie, ACT Health

Sponsor: CKD QLD

Funding: Amgen Australia
The cKiDNaP study
Research Objectives

1. Explore the features of the model of care of the CKD NP

2. Develop operational definitions for the NP role in clinical care of patients with CKD

1. Develop operational definitions for the role of the renal nurse in clinical care of patients with CKD

2. Evaluate the multidisciplinary team’s acceptability of the NP role in CKD
The cKiDNaP study
Data collection

• NP/patient Consultation analysis

• Retrospective chart audit of NP patient care

• Survey interview of nursing staff in CKD clinics

• Survey of clinicians in multidisciplinary teams
The cKiDNaP study
Study outcomes

1. Operational definitions for:
   - CKD nurse practitioner service model
   - Renal nurse assist nephrologist service model

2. Research information and proof of concept for a larger study into CKD service models

3. NHMRC project grant application

4. Work in progress ....
   - Completion of data analysis consultation review
   - Data analysis for MDT survey
   - Preparation of journal manuscripts
   - Preparation of abstracts for conference presentations (ANZSN).
Health services research program

Pilot CKD nurse practitioner role study
Models of care study (health service delivery)
  • Consultant model (nephrologist only)
  • Nurse specialist model (nurse combined nephrologist led)
  • Collaboration model (nurse practitioner led)
Primary outcome rate of change of eGFR
Secondary outcomes QOL, depression, health economics, BP targets
Palliative care study

Assess the efficacy of early palliative care in CKD
RCT of early palliative care intervention v standard care
Outcomes QOL, depression, pain and other symptom control and survival
CKD.QLD Nutrition Study

Research Team:
• Katrina Campbell (PAH)
• David Johnson (PAH)
• Philip Juffs (RBWH)
• Meri Manafì (Gold Coast)
Influence of nutrition status on clinical outcome in CKD patients

To characterise potentially-modifiable dietary factors in CKD, map change over time and identify how these factors relate to patient outcomes.

The aims of this study are to:

• Phase I: assess the relationship between dietary intake (including fat and sodium intake), nutrition status, body composition (degree and distribution of adiposity) and cardiovascular risk factors in CKD patients.

• Phase II: assess the relationship between dietary intake (including sodium), body composition (degree and distribution of adiposity), cardiovascular risk factors and clinical outcome in CKD patients.

• Phase III: assess the impact of change in body composition and nutritional status over time on clinical outcome in CKD patients.

Design: Prospective, observational; Longitudinal (Phase III)
Sample: Aiming for 500 (across 5 sites; PAH, Royal Brisbane, Townsville, Toowoomba, Gold Coast)
Funding: Seeding only ($16,000 CKD.QLD; AMGEN) (Campbell, Murray, Juffs, Johnson)
Progress: Multi-site ethics complete; Governance sign-off complete. Data collection commenced
Biomarkers in CKD

• “Current measures to detect kidney function and damage in CKD are inadequate. There is a need to identify new biomarkers and rigorously validate already identified biomarkers...which reflect kidney function, injury, repair and progression and regression of damage, identify early disease and predict prognosis and response to therapy. The ideal biomarker is measured in a minimally invasive way and gives reliable and reproducible results over time”. NIH/NIDDK RFA-DK-08-015, 2008, www.kidney.nih.gov

Biomarkers in CKD

- "Current measures to detect kidney function and damage in CKD are inadequate. There is a need to identify new biomarkers and rigorously validate already identified biomarkers...which reflect kidney function, injury, repair and progression and regression of damage..."

Biomarkers in chronic kidney disease: a review

Robert G. Fassett¹,²,³, Sree K. Venuthurupalli³,⁴, Glenda C. Gobe³, Jeff S. Coombes², Matthew A. Cooper⁵ and Wendy E. Hoy³

¹Renal Research, Royal Brisbane and Women’s Hospital, Brisbane, Queensland, Australia; ²School of Human Movement Studies, The University of Queensland, Brisbane, Queensland, Australia; ³Centre for Kidney Disease Research, School of Medicine, The University of Queensland, Brisbane, Queensland, Australia; ⁴Renal Medicine, Toowoomba Hospital, Toowoomba, Queensland, Australia and ⁵Institute for Molecular Bioscience, The University of Queensland, Brisbane, Queensland, Australia
Biomarker

Characteristic that is measured and evaluated as an indicator of
• normal biological processes
• pathological processes
• pharmacological responses to a therapeutic intervention

Surrogate marker
• biomarker substitute for clinical endpoints (ESKD, dialysis)
CKD biomarker requirements

• Early detection of those who are going to progress
• Easily measurable in blood, urine and/or tissue
• Reliable validated surrogate for hard clinically relevant outcome measures
Biomarker or risk factor

Biomarkers are

• biochemical signatures that correlate with increased risk of disease determined by clinical and epidemiological studies

Risk factors are

• more reliable measurement of the pathological status and often related to the molecular basis of the disease process
Restoration of abnormal “biomarker”

- Flecainide and encainide (CAST)
- Hb with ESA
- Lipids in ESKD (AUROA and 4D)
- HDL with CETP (torcetrapib)
- NICE-Sugar
- PROWESS-SHOCK study (Xigris-activated protein C)
Validated risk factor/biomarker

• The Framingham Heart Study - cholesterol as major risk factor for CVD, first biomarker for atherosclerosis.
• Increased Total and LDL-C in people at risk of CV events
• Pharmacological reduction has a beneficial effect.
• Many subjects with normal lipids still develop atherosclerosis
Biomarkers of CKD progression

Currently used
- Proteinuria
- eGFR

New and not yet validated
- Neutrophil gelatinase-associated lipocalin (NGAL)
- Kidney injury molecule-1 (KIM-1)
- Liver-fatty acid binding protein (L-FABP)
- Others
<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Biological source of origin</th>
<th>Method of estimation</th>
<th>Biological sample to be tested</th>
<th>Mechanism of alteration in CKD</th>
<th>Clinical relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystatin C</td>
<td>Cysteine protease inhibitor produced by all nucleated cells and released into blood</td>
<td>Immunonephelometry or ELISA</td>
<td>Blood</td>
<td>Filtered and metabolised after tubular absorption</td>
<td>Predicts CKD progression</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>Circulating protein</td>
<td>Immunoturbidimetric method, RIA,</td>
<td>Urine</td>
<td>Damage to glomerular filtration and decreased tubular reabsorption</td>
<td>Indicator of CKD progression</td>
</tr>
<tr>
<td>Adrenomedullin</td>
<td>Ubiquitously expressed peptide in adrenal medulla, ventricle, kidney, lung and endothelial cells</td>
<td>ELISA</td>
<td>Blood</td>
<td>Uncertain</td>
<td>Increased level associated with CKD progression</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>Peptide produced by atrial and ventricular myocytes</td>
<td>ELISA</td>
<td>Blood</td>
<td>Decreased renal filtration and clearance by neutral endopeptidases within the kidney</td>
<td>Associated with CKD progression</td>
</tr>
<tr>
<td>MRproANP and MRproADM</td>
<td>Peptide produced by atrial and ventricular myocytes</td>
<td>ELISA</td>
<td>Blood</td>
<td>Decreased renal filtration and clearance by neutral endopeptidases within the kidney</td>
<td>Predicted CKD progression</td>
</tr>
<tr>
<td>GGT</td>
<td>Cell surface enzyme (polypeptide) epithelial, proximal tubular cells, atherosclerotic plaque</td>
<td>Enzymatically in an automatic analyzer</td>
<td>Blood</td>
<td>A measure of oxidative stress</td>
<td>(NHANES) 2001-2006 strong independent association between GGT and CKD</td>
</tr>
<tr>
<td>CRP and hs-CRP</td>
<td>Liver cells</td>
<td>Immunoturbidimetric method ELISA</td>
<td>Blood</td>
<td>A measure of inflammation</td>
<td>CRP was associated with the presence of CKD\textsuperscript{50} but not progression</td>
</tr>
<tr>
<td>---------------</td>
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<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>sTNF\textsubscript{rii}</td>
<td>Receptor of TNF-\textalpha expressed on leukocytes and renal cells</td>
<td>ELISA</td>
<td>Blood</td>
<td>Surrogate marker of TNF-\textalpha and hence inflammation of the kidney</td>
<td>Correlates with progression of AKI, lupus nephritis and diabetic nephropathy</td>
</tr>
<tr>
<td>Neutrophil gelatinase-associated lipocalin (NGAL)</td>
<td>Lipocalin iron transporting protein in tubular epithelial cells</td>
<td>ELISA</td>
<td>Blood</td>
<td>Release from damaged tubular epithelial cells and reduced reabsorption</td>
<td>NGAL was elevated with the highest levels seen in the most advanced CKD stage\textsuperscript{52}.</td>
</tr>
<tr>
<td>uNGAL</td>
<td>Lipocalin iron transporting protein in tubular epithelial cells</td>
<td>ELISA</td>
<td>Urine</td>
<td>Release from damaged tubular epithelial cells and reduced reabsorption</td>
<td>Serum and urinary NGAL at baseline were predictors of eGFR decline\textsuperscript{63}</td>
</tr>
<tr>
<td>ADMA</td>
<td>Naturally occurring amino acid</td>
<td>Competitive enzyme-linked immunosorbent assay</td>
<td>Blood</td>
<td>Associated with endothelial dysfunction</td>
<td>Associated with CKD severity</td>
</tr>
<tr>
<td>FGF-23</td>
<td>Polypeptide synthesised and secreted by bone cells, mainly osteoblasts</td>
<td>C-terminal ELISA Kit</td>
<td>Blood</td>
<td>Reduced renal excretion</td>
<td>Risk factor for worse outcomes in CKD (mortality ArMORR and CKD progressionMMKD)</td>
</tr>
<tr>
<td>Liver-type fatty acid binding protein (L-FABP)</td>
<td>Protein expressed in proximal tubular cells</td>
<td>ELISA</td>
<td>Blood</td>
<td>Released with tubular damage</td>
<td>Correlates with degree of tubulointerstitial damage</td>
</tr>
<tr>
<td>u-L-FABP</td>
<td>Protein expressed in proximal tubular cells</td>
<td>ELISA</td>
<td>Urine</td>
<td>Released with tubular damage</td>
<td>Sensitive marker of tubulointerstitial damage Correlation with CKD progression</td>
</tr>
<tr>
<td>KIM-1</td>
<td>Tubular transmembrane protein</td>
<td>ELISA, microbead-assay, immunochromatographic dipstick</td>
<td>Urine</td>
<td>Expressed by injured proximal tubular cells</td>
<td>Increased with tubulointerstitial damage</td>
</tr>
<tr>
<td>Protein</td>
<td>Description</td>
<td>Detection Method</td>
<td>Sample</td>
<td>Function</td>
<td>Clinical Relevance</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>---------------------------</td>
<td>--------</td>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>ApoA-IV</td>
<td>Glycoprotein synthesised in intestinal enterocytes and incorporated into chylomicrons</td>
<td>ELISA</td>
<td>Blood</td>
<td>Increased in CKD</td>
<td>MMKD study proteinuric non-diabetic CKD patients with elevated ApoA-IV had significantly faster CKD progression</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Hormone secreted exclusively by adipocytes</td>
<td>Time-resolved immunofluorometric assay</td>
<td>Blood</td>
<td>Secretion increased by renal failure</td>
<td>Predictive of progression in diabetics with macroproteinuria</td>
</tr>
<tr>
<td>NAG</td>
<td>Renal tubular lysosomal enzyme</td>
<td>Colorimetric assay, using sodium-3-cresolsulfonphthaleinyl-N-acetyl-b-D glucosaminide as substrate</td>
<td>Urine</td>
<td>Released with proximal tubular damage</td>
<td>Increased in renal tubulo-interstitial damage</td>
</tr>
<tr>
<td>AGEs and Pentosidine</td>
<td>Proteins modified by oxidative stress</td>
<td>HPLC or ELISA</td>
<td>Blood and urine</td>
<td>Accumulate in diabetes and renal failure</td>
<td>Predicts diabetic nephropathy</td>
</tr>
<tr>
<td>Nephrin, Podocin and Podocalyxin</td>
<td>Podocytes</td>
<td>Quantitative PCR, ELISA for mRNA or protein levels of podocyte specific molecules</td>
<td>Urine</td>
<td>Released with detached damaged podocytes</td>
<td>Increased in diabetic nephropathy, active lupus nephritis, IgA nephropathy and post-streptococcal GN</td>
</tr>
<tr>
<td>IL-18</td>
<td>Proinflammatory cytokine produced by leukocytes, blood vessels and renal tubules</td>
<td>ELISA</td>
<td>Urine</td>
<td>Released with tubular injury</td>
<td>Increased in AKI, nephritis, post transplant delayed graft function</td>
</tr>
<tr>
<td>β-Trace protein</td>
<td>Lipocalin glycoprotein</td>
<td>Immunoassay</td>
<td>Blood</td>
<td>Filtered by glomeruli</td>
<td>Sensitive marker of glomerular function</td>
</tr>
</tbody>
</table>
Figure 1 | Biomarkers of chronic kidney disease (CKD) progression and renal cardiovascular disease (CVD).
The Canadian Study of Prediction of Risk and Evolution to Dialysis, Death and Interim Cardiovascular Events Over Time study is evaluating whether

ADMA, IL6, CRP, ProBNP, Troponin, Vitamin D (25 and 1,25) and Cystatin C

• add predictive value compared with standard clinical parameters in 2500 CKD patients with eGFR of 15-45 ml/min over 36 months.
Patient platform, registry and specimens

• Study participants consenting CKD patients in three CKD.QLD sites

• Target enrolment is 700 patients each site, (2,100 total) over the first 18 months with follow-up for 2.5-4 years.
Eligibility criteria

• Patients age >18 years CKD stages 1-5 will be eligible.
• Inclusion criteria: newly referred and those with <12 months follow-up
• Exclusion criteria: non-consenting, ESKD
Data collection

• Electronic Case Report Forms
• Demographic data
• Physical exam weight, height, waist circumference and BP
• Lab tests HbA1c, lipids, serum creatinine, cystatin C eGFR and urine Documented at least yearly.
• Events: changed medications, AE’s, morbidities DM, BP, heart failure, CHD, PVD, ER visits, hospitalisations, ESKD, dialysis and death
Outcomes

• eGFR, proteinuria/albuminuria BP cystatin C
• Rate of eGFR decline, ESKD
• CV endpoints
• Death
Biomarker research

- Serum, plasma and urine flash frozen and sent to the IMB for mass spectrometry analysis and storage at -80C degrees for biomarker discovery and validation. Aliquots will also be stored at -80C degrees in the CKD.QLD BioBank.
# Inflammatory markers in CKD

## Table 2. Effect of atorvastatin on rate of change of eGFR (MRDR) in patient groups with different inflammatory markers

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Placebo</th>
<th>Atorvastatin</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean (SD)</td>
<td>N</td>
</tr>
<tr>
<td>1</td>
<td>14</td>
<td>-2.70 (4.82)</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>-1.65 (4.72)</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td>0.10 (4.73)</td>
<td>24</td>
</tr>
</tbody>
</table>

1. Patient groups defined by initial levels of inflammatory markers: 1) Elevated levels of IL6 (>30), IL8 (>10), IL10 (>35) and/or Pentraxin3 (>1.6); 2) Levels of all inflammatory markers not elevated; and 3) TNFa (>11) whether the other inflammatory makers are elevated or not.

2. Values estimated by repeated measures mixed methods linear regression.

3. The change (mean difference) in response to atorvastatin differed significantly in Group 2 (P=0.032) and Group 3 (P=0.003) compared to Group 1.
Neutrophil Gelatinase-Associated Lipocalin (NGAL) and Progression of Chronic Kidney Disease

Davide Bolignano,* Antonio Lacquaniti,* Giuseppe Coppolino,* Valentina Donato,* Susanna Campo,* Maria Rosaria Fazio,* Giacomo Niccio,† and Michele Buemi*

Departments of *Internal Medicine and †Pathology and Experimental Microbiology, University of Messina, Messina, Italy

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Figure 4. Kaplan-Meier survival curves of renal end-point in patients with serum neutrophil gelatinase-associated lipocalin (sNGAL) levels above and below the optimal receiver operating characteristics cut-off level of 435 ng/ml. Patients with sNGAL >435 ng/ml showed a significantly faster progression to endpoint (P = 0.002, log-rank test), with a hazard ratio of 3.37 (95% CI, 1.86 to 7.62). The number of nonprogressor subjects still in the study at specific time points is reported.

Figure 5. Kaplan-Meier survival curves of renal end-point in patients with urinary neutrophil gelatinase-associated lipocalin (uNGAL) levels above and below the optimal ROC cut-off level of 231 ng/ml. Patients with uNGAL >231 ng/ml showed a significantly faster progression to endpoint (P < 0.0001, log-rank test), with a hazard ratio of 7.45 (95% CI, 3.58 to 15.53). The number of nonprogressor subjects still in the study at specific time points is reported.
In patients with CKD, NGAL closely reflects the entity of renal impairment and represents a strong and independent risk marker for progression of CKD.
Point of care assays

At baseline and each annual visit point of care (POC) analysis using the Triage SOB Panel including

• plasma troponin, myoglobin, CK-MB, BNP, D-dimer, hs-CRP, NGAL, IL18 and L-FABP.
Evaluation of additional candidate biomarkers

Oxidative stress: plasma F$_2$-isoprostanes, MDA, protein carbonyls and ox- LDL.

Inflammation: hs-CRP, pentraxin-3, IL6, TNT$\alpha$ and IL10

Vascular damage and repair: endothelial microparticles and progenitor cells, ADMA (34) MMP 2 and MMP6, cystatin C

Urine biomarkers tested will include NGAL, and $\beta$2 microglobulin.
Novel biomarker discovery

- Mass Spectrometry analysis of urine and blood samples according to the Human Kidney and Urine Proteome Project guidelines.
- If known proteins (previously not correlated with CKD, ESKD or CVD) are identified, these putative candidate markers will be verified by ELISA, western blotting, HPLC-MRM. Differential protein expression profiling, relative protein quantification will be carried out through isotope coded affinity tags, iTRAQ.
Biomarker overview

• CKD is common
• Early detection is essential
• Identifying those likely to progress is a priority
• Current biomarkers inadequate
• New biomarkers are required
• These will need validating in longitudinal clinical studies
• Testing interventions using biomarkers need calibrating with hard outcome studies
• CKD biomarker studies are in the design stage and some are in progress
International collaborations

- Adeera Levin British Colombia Canada
- Scott Terbut and Rhonda Wideman PROOF Institute British Columbia Canada
End-users who will benefit:

- CKD patients, through better outcomes from trials assessing old and new therapies to slow CKD progression, better and earlier identification of those likely to progress and better health service delivery.
- Multidisciplinary CKD health care professionals, from improved models of care.
- Health systems (QH initially), from more cost efficient models of care.
- The taxpayer, from cost containment achieved through more efficient services and delay in CKD progression and containment of expensive therapies such as dialysis.
- The general population, through better CKD health awareness.
- Commercial interests, through the clinical trials and biomarker studies.
- Teaching and training institutions, through new tools and training curricula.
The future

• Expansion into primary care and other speciality practices
• CKD.AUS
• Linkage to national data sets
• Practice improvement initiatives
• Nationwide research initiative, including possible Cooperative Research Centre application
Summary

- Established a CKD registry and practice network in Queensland
- Ethics approved
- Governance approved
- Recruitment started
- Seeding funding obtained
- Research program on CKD nurse practitioner role and dietary intake and CKD have started, CKD site profiling ongoing
Supporters

- AMGEN
- NHMRC Australia Fellowship – Professor Wendy Hoy
- Centre for Chronic Disease The University of Queensland
- Queensland Health (in kind)
Some members of the CKDLD Team