KHA-CARI GUIDELINE RECOMMENDATIONS FOR THE DIAGNOSIS AND MANAGEMENT OF AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

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SCOPE OF THE GUIDELINE

This guideline addresses issues relevant to the diagnosis, management and extra-renal complications of autosomal dominant polycystic kidney disease (ADPKD). Also included in this summary is a screening algorithm for ADPKD in at-risk individuals (Figure 1) and an algorithm for screening intracranial aneurysms (Figure 2).

PART I: DIAGNOSIS, GENETIC COUNSELLING AND SCREENING

ADPKD is the most common inherited cause of kidney failure in adults, with a prevalence rate ranging between 1:500 and 1:4000 (1-6) Its well-known characteristic phenotype is the development of numerous bilateral renal cysts which grow at an exponential rate through adult life, and compress normal renal tissue, resulting in at least a 50% risk of end-stage kidney disease (ESKD). In developed countries, ADPKD constitutes ~5-10% of dialysis populations (7-11). Heterozygous germ-line mutations, predominantly in the *PKD1* gene (~85% of cases) (12) or to a lesser extent in the *PKD2* gene (15% of cases) (13), cause ADPKD and are identified in up to 90% of patients. In 10% of patients who meet clinical diagnostic criteria for ADPKD, mutations in *PKD1* or *PKD2* are not detected with current testing methodologies.

ADPKD is relatively asymptomatic during the first three decades of life and even renal function can misleadingly remain preserved despite significant cystic renal abnormalities, in part due to compensatory glomerular hyperfiltration (14). However, once renal function declines, irreversible damage has already been established. Therefore, early identification of affected patients is important to allow anticipatory treatment such as stringent blood pressure control to reduce renal and cardiovascular morbidity; exclusion of disease in at-risk individuals; and enrolment into potential clinical trials of disease-modifying treatments and changes in treatment.

ADPKD is highly penetrant, and all individuals with an ADPKD gene mutation will develop ultrasound-detectable multiple simple renal cysts (Bosniak Class 1) during their lifetime. The onset is however progressive, insidious, age-dependent and potentially influenced by environmental factors. Cyst detection by imaging is difficult during childhood due to their microscopic size at that stage (15). Whilst molecular genotyping remains the gold standard for confirming diagnosis, this test is costly, time consuming and not always readily available (16, 17). Thus, renal ultrasound has been used to diagnose and screen for ADPKD amongst at-risk individuals for more than 40 years (18). Age-related criteria using cyst number to screen for ADPKD were developed, initially by Ravine in 1994 (19) and subsequently revised by Pei in 2009 (20), to assist in reducing the false-positive and false-negative rate during the screening of at-risk individuals.

The objective of this guideline is to review the evidence for imaging methodology, genetic testing and genetic counselling in ADPKD.

1a. DIAGNOSIS: IMAGING

Guideline Recommendations

a. We recommend ultrasound to be used as the first line imaging modality for diagnosis (1B)

b. We suggest using the age and genotype dependent criterion listed below for diagnosis in at risk individuals: (2B) (Table 1, Table 2)

c. We recommend when ultrasound findings are equivocal and absolute disease exclusion is required, such as in the case of potential kidney donors, that molecular genotyping be performed as the diagnostic gold standard (1A)

Ungraded suggestions for clinical care

1. Approach to individuals with equivocal ultrasound diagnosis:

Magnetic resonance imaging (MRI) can be considered as an alternative for disease exclusion in cases with an equivocal ultrasound diagnosis, or when molecular genotyping cannot be done. Gadolinium enhancement is preferable but not essential; and should be avoided in those with glomerular filtration rate (GFR) <60 ml/min/1.73m^2 due to risk of Nephrogenic Systemic Fibrosis (NSF) (21). Greater than 10 cysts in total can be used as a cut off for making a diagnosis using MRI, and a total of less than 5 cysts for disease exclusion. This is applicable for all individuals older than 15 years of age (Table 3) (22).

2. Approach to individuals with renal cysts without family history of APDKD: Due to lack of evidence for diagnostic criteria for an individual with findings of cystic renal disease and with no family history, a number of factors should be considered when making a diagnosis:

- Ultrasound imaging should be performed on the affected individual's parents to assess for asymptomatic *PKD2*;
- Ultrasound imaging for extra renal cystic diseases including liver and pancreatic cysts can aid with diagnosis;
- For less typical cases (borderline number of cysts, and absence of frank kidney enlargement), serial imaging studies to track cyst growth or genetic testing may be necessary to make a diagnosis of ADPKD;
- If an arbitrary number for renal cyst count is to be enforced, then 10 cysts in total detectable on ultrasound, is the general consensus.

1b. DIAGNOSIS: GENETIC TESTING

Guideline Recommendations

a. We recommend that the standard methodology for genetic diagnosis of ADPKD is polymerase chain reaction (PCR) amplification (including long-range PCR for the first 33 exons of *PKD1*) followed by Sanger sequencing (1A) or next generation sequencing where available (1D).

b. We suggest that individuals with a clinical diagnosis of ADPKD in whom a mutation is not found by PCR amplification and sequencing have *PKD1* and *PKD2* analysed for large genomic rearrangements (such as deletions) by Quantitative Fluorescent Multiplex-PCR or custom designed array Comparative genomic hybridization (CGH) (2B).

Ungraded suggestions for clinical care

- We suggest that next generation sequencing technologies will soon be the standard methodology for genetic diagnosis in ADPKD.

2. GENETICS AND GENETIC COUNSELLING

Guideline Recommendations

a. We recommend that adult patients diagnosed with ADPKD are referred to their regional genetics service for genetic counselling if they are interested in and would like to discuss (2B):

(i) Inheritance pattern and clarifying/communicating disease risk to family members;

(ii) Molecular genetic testing (role, indication, and interpretation);

(iii) Family planning and prenatal testing options (including preimplantation genetic diagnosis)

b. We recommend adults and children at-risk of ADPKD are referred to their regional genetics service for genetic counselling if they are interested in and would like to discuss (2A):

(i) Inheritance pattern and their risk of disease;

(ii) Predictive testing (via renal imaging and/or molecular genetic testing) and associated issues;

(iii) Family planning and prenatal testing options (including preimplantation genetic diagnosis).

Ungraded suggestions for clinical care

- We suggest all patients diagnosed with ADPKD be directed to relevant patient support groups, like the PKD Foundation of Australia.

3. SCREENING: CLINICAL AND IMAGING

Guideline Recommendations

a. We recommend prior to screening at-risk individuals that they should receive appropriate counselling regarding the potential benefits and risks of making the diagnosis of ADPKD from their general practitioner in consultation with a clinical geneticist or nephrologist (2A).

b. We recommend that screening of individuals who are at-risk (50% chance) be performed by renal ultrasound and that the Pei-Ravine unified diagnostic criteria for age-dependent cyst number is used to make and exclude the diagnosis of ADPKD (1B).

Ungraded suggestions for clinical care

- We suggest that physicians inform index cases to notify first degree relatives to see their general practitioner to discuss screening.
- Second-degree and third-degree relatives should be screened on a case-by-case basis, due to the lower probability of ADPKD (25% and 12.5% respectively) and lack of diagnostic criteria for renal ultrasound.
- The screening assessment should include clinical evaluation and review for other features supporting a diagnosis of ADPKD such as kidney enlargement and extra-renal cysts.
- At-risk individuals under ≤40 years of age with renal cysts detected but do not meet the Pei-Ravine criteria for cyst number could have repeat ultrasound scanning in 12 months with further follow-up in 3-5 year intervals, depending on the clinical circumstances and discussion with the patient.
- A normal renal ultrasound in at-risk individuals under ≤40 years of age does not exclude the diagnosis of ADPKD. Annual blood pressure measurement and repeating the renal ultrasound at 5 year intervals (until the age of 40 years) may be considered. In contrast, a cautious approach in assigning a diagnosis of ADPKD should be undertaken in at-risk individuals >40 years of age who have equivocal ultrasound findings because of the increasing prevalence of simple age-related cysts.
- Presently, in the absence of a regulatory-approved disease-specific therapy, screening at-risk paediatric subjects (<18 years of age) may not be justified. The decision to screen should take into account clinical circumstances and parent/carer discussion regarding the potential benefits, risks, and limitations of ultrasound diagnosis in this population. In children, a tailored approach for screening may be appropriate, and include blood pressure measurement with or without renal ultrasound imaging.

- Screening of potential kidney donors who are at-risk of ADPKD requires comprehensive multidisciplinary clinical and radiological assessment. Renal CT is routinely performed during donor assessment but MRI has greater sensitivity in detecting cysts than ultrasound (US) and CT (0.3 vs. 0.5-1.0 vs. 0.5 cm diameter respectively). In at-risk individuals with a negative ultrasound, especially below the 40 years of age, the risk-benefit of kidney donation must be carefully considered, as ADPKD is not excluded entirely. Under these circumstances, renal MRI and molecular genetic testing may assist in the decision-making.
- Ultrasound transducers, more sensitive than that used in previous clinical studies of ADPKD (i.e. >5 MHz), increase the ability to detect renal cysts that are smaller than 1.0 cm in diameter. However, diagnostic criteria using these more sensitive transducers to differentiate ADPKD from age-related simple cysts are not defined.

PART II: MANAGEMENT OF ADPKD

The medical management of ADPKD is evolving rapidly. There is currently a greater need for precision in monitoring disease progression and predicting the life-time risk for chronic kidney disease (CKD), particularly in light of new disease-modifying drugs becoming available in the near future. Furthermore, current treatments to decrease the risk of progression of CKD through the early use of interventions (both pharmacological and non-pharmacological) are clearly focused on decreasing renal cyst growth as the therapeutic goal of treatment. The minimisation of cardiovascular morbidity and intraglomerular hypertension, through early treatment with angiotensin inhibitors, is perhaps, the most significant pharmacological achievement in ADPKD.

Finally, recognition and management of psychosocial aspects of care, is an important development.

ADPKD patients exhibit significant variability in the life-time risk for ESKD. Furthermore, patients at high-risk for ESKD develop extensive renal enlargement with the total kidney volume (TKV) being many times greater than normal, and occurring prior to CKD Stage 3. Thus, validation of clinical and surrogate biomarkers to reflect disease severity, progression and response to therapy are urgently required (23), and the challenges to effective clinical translation remain significant (24). The serial validation of TKV has so far only been studied in a single longitudinal cohort study and is likely to be the preferred biomarker of choice in the future. However, the relationship between TKV and renal function decline is non-linear and complex (25), and requires further study, and its role in routine clinical practice is not well established.

Over the last 30 years, the secondary extracellular and intracellular factors that mediate renal cyst growth have been defined. Elevation of intracellular levels of cyclic adenosine monophosphate (cAMP), in part stimulated by systemic levels of vasopressin, are a

characteristic of mutated epithelial cells lining the renal cysts. Vasopressin-cAMP signalling leads to cellular proliferation and transepithelial cystic fluid secretion, causing cyst growth. In the largest randomised control trial (RCT) conducted to date, vasopressin receptor antagonists reduced the rate of renal cyst growth, renal function decline and chronic pain. In addition, there is greater recognition that conventional treatments, such as angiotensin inhibitors and diet/lifestyle changes might influence vasopressin-cAMP signalling and attenuate renal cyst growth, in addition to their traditional role in blood pressure control and reducing cardiovascular risk. (26).

The need for constant medical monitoring, medications, and fear of renal replacement therapy (RRT) impose a significant treatment burden, and have a detrimental impact on the quality of life, psychosocial and social outcomes in patients with ADPKD (27-31). A systematic review on patient perspectives of living with ADPKD found that the erratic onset and intensity of pain disrupted daily living and prevented patients from developing long-term career and family goals. They experienced persisting uncertainties including perceived ambiguities surrounding the meaning and implications of their diagnosis, disempowerment in self-management, inability to plan ahead, and financial discrimination (32). A recent KDIGO Controversies conference identified additional issues such as impaired body-image, relationship strain, and limited participation in recreation and sport (33). Depression and anxiety have also been reported in patients with ADPKD (34). Thus the psychosocial care of patients with ADPKD is covered in this section of the Guidelines.

4. MONITORING THE PROGRESSION OF ADPKD

Guideline Recommendations

a. We do not recommend performing serial ultrasound, renal CT or MRI for monitoring disease progression, unless there are other clinical reasons for repeating these tests (e.g. haematuria, pain, fever) (1B)

b. We suggest using renal function (i.e. estimated glomerular filtration rate and albuminuria) rather than imaging to monitor disease progression (2B)

c. We suggest when monitoring renal function by estimated glomerular filtration rate, to use the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (2B)

Ungraded suggestions for clinical care

- There is good level evidence supporting the use of TKV in MRI as a biomarker for disease progression and as a surrogate marker for disease response to therapeutic interventions in clinical trials. However, as there are no proven therapeutic interventions at this point in time, we suggest restricting the use of serial renal volume measurements in MRI [i.e. height adjusted total kidney volume (Ht-TKV), total cyst volume (TCV), parenchymal volume (PV) and fractional cyst volume (FCV)] for research purposes only.
- When measuring TKV, we suggest using non-gadolinium enhanced MRI sequence as opposed to ultrasound.
- Assessment of renal function by eGFR using CKD-EPI equation is reasonably accurate in monitoring the severity of functional decline below 90 ml/min/1.73m^2, and even more so for those with GFR between 60-90 ml/min/1.73m^2.

5. MANAGEMENT: DIET AND LIFESTYLE

Evidence summary

- No randomized controlled trials have investigated ADPKD-specific diet or lifestyle interventions. Findings from studies in the general CKD literature can be applied to this population, particularly in relation to blood pressure control.
- There is insufficient evidence, and potential harms associated with a low protein diet in the general CKD population, which is applicable to patients with progressive ADPKD.
- Increased fluid intake has been hypothesized to reduce the progression of ADPKD but the only available interventional data in humans is from a single non-randomised study (with methodological problems) which showed that fluid intake to 2.5-3.0 L accelerated renal disease, based on TKV and eGFR.
- Education programs for patients with ADPKD improved the level of awareness about the hypertension and understanding of clinical symptoms and outcomes, but no studies have focused on comorbidities such as pain, intracranial aneurysms and polycystic liver disease is lacking. Knowledge of the genetic aspects of the disease is variable. Studies also showed that quality of life is seriously affected and patients suffer pain and experience social and psychological changes, which affect their emotional state.

Guideline Recommendations

The following statements are modified from the KHA-CARI Early CKD guidelines on modification of lifestyle and nutrition interventions for management of early chronic kidney disease (36), as there is no evidence specific to ADPKD that would alter these recommendations:

(http://www.cari.org.au/CKD/CKD%20early/Modification_of_Llifestyle_Nutrition_ECKD.pdf)

a. We recommend that patients with progressive ADPKD, prior to advanced kidney disease (i.e. CKD stages 1 to 3), follow the recommendations from the National Health and Medical Research Council (NHMRC) Australian Dietary Guidelines (Adults), including to achieve and maintain a healthy weight, be physically active, and choose a wide variety of nutritious foods (35) (1D)

b. We recommend a moderate protein diet (0.75-1.0 g/kg/day) as a low protein diet (≤0.6 g/kg/day) has not been shown to slow the rate of ADPKD progression, and may increase the risk of malnutrition (1C).

c. We recommend that patients with ADPKD restrict their dietary sodium intake to 100 mmol/day (or 2.3 g sodium or 6 g salt per day) or less, as it reduces blood pressure and albuminuria in patients with CKD (1C).

d. We suggest that patients with ADPKD drink fluid to satisfy thirst, as there is no evidence that increasing fluid intake beyond thirst is beneficial for reducing cyst growth in ADPKD (2C).

e. We recommend that patients with ADPKD stop, or do not start active smoking (and avoid passive smoking) to reduce CKD progression and cardiovascular risk (1C)

f. We recommend that patients at high risk of ADPKD be provided with adequate genetic counselling and education regarding inheritance and future complications (Refer to Subtopic: *Genetic Counselling*) (1D)

g. We recommend that patients at high risk of ADPKD be educated regarding risk factors for disease progression, specifically hypertension (1D)

h. We suggest that all patients with ADPKD be taught self-management skills for blood pressure monitoring and low salt intake (2D)

i. We suggest that all patients with ADPKD undergo psychosocial counselling and support (2D)

Ungraded suggestions for clinical care

- Patients with progressive ADPKD chronic kidney disease (CKD) are likely to benefit from individualised diet intervention involving an appropriately qualified dietitian.
- There is no evidence to inform the level of fluid intake which may impact on cyst growth in ADPKD. Therefore, as a guide the recommendation is to drink fluid to thirst and vary this intake according to individual circumstances, such as physical activity/environment (e.g. exercise), states of excessive fluid loss (e.g. sweating, diarrhoea) or specific medical complications (e.g. renal calculi, CKD Stages 4-5).
- There is no evidence to date indicating that caffeine intake is associated with cyst growth in ADPKD. As a guide, up to 200 mg of caffeine intake per day (i.e. up to 2 cups of coffee or 4 cups of tea per day), is known to be safe for consumption for general cardiovascular health (37).
- Patients with ADPKD can continue to exercise and play sport. Although there is no evidence regarding the nature of sport, patients with progressive ADPKD undertaking

contact sports should be monitored for the potential impact on the kidneys increasing the risk of cyst rupture, bleeding and pain.

6. PHARMACOLOGICAL MANAGEMENT

Evidence summary

- *Reducing overall mortality:* Lipid lowering agent (LLA) therapies are indicated for mortality prevention via minimisation of cardiovascular risk, amongst those with CKD regardless of aetiology.
- *Reducing cardiovascular events*: LLA (statins) and antihypertensive agents most commonly consisting of ACEi, have been shown to decrease cardiovascular events.
- *Management of hypertension*: ACEi therapy has demonstrated safety and antihypertensive effectiveness with improvements in proteinuria and left ventricular mass index. There is no evidence of the benefit of dual ACEi and ARB therapy in ADPKD. Other agents that may be considered are ARBs, beta blockers (BBs), calcium channel blockers (CCBs) and diuretics though individualisation in the setting of comorbid illness, stage of renal disease and clinical circumstance is required. Targeting a low blood pressure target (96/60 to 110/75 mmHg) rather than a higher blood pressure target (120/70 to 130/80 mmHg) was beneficial in a trial of early stage renal disease (eGFR >60ml/min/1.73m^2)
- *Reduction of ESKD incidence*: No agents have been associated with differences in ESKD incidence
- *Reduction of TKV:* Targeting a lower blood pressure target in some patients may slow TKV progression. At present, there is insufficient evidence to recommend the use of vasopressin type 2 receptor antagonists, TORC1 inhibitors, somatostatin analogues or LLA in clinical practice to slow cyst growth and renal disease progression in

ADPKD.

- *Reducing the progression of renal function*: Tolvaptan, have been demonstrated to reduce the rate of increase in TKV and decline in eGFR (as well as improvement in chronic renal pain) in a single randomized control trial of early-stage ADPKD.
- *Adverse events of new agents:* TORC1 inhibitors are associated with stomatitis, anaemia, acne, dyslipidaemia, diarrhoea, ovarian cysts and increased risk of infection. Tolvaptan is associated with aquaresis related adverse events and liver function derangements. SSA are associated with diarrhoea, and injection site reactions.

Guideline Recommendations

a. We recommend the use of antihypertensive therapies to treat hypertension amongst those with ADPKD (1B) with a suggested blood pressure target of less than or equal to 130/80 mmHg (2B)

b. We recommend that angiotensin converting enzyme inhibitors be considered as first line antihypertensive therapy (1B) and if intolerant, that angiotensin receptor blockers be considered as second line antihypertensive therapy (1C)

c. We recommend the use of lipid lowering therapies such as 3-hydroxy-3-methyl-glutary-CoA reductase inhibitors as recommended for those with chronic kidney disease (1B)

Ungraded suggestions for clinical care

- Agents other than angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) can be used if ACEi/ARB are contraindicated, or added as stepwise therapy to ACEi/ARB for antihypertensive management.

- Targeting a low blood pressure target (96/60 to 110/75 mmHg) rather than a higher blood pressure target (120/70 to 130/80 mmHg) may be considered in selected patients with early stage renal disease (eGFR >60ml/min/1.73m^2) who are less likely to experience associated side effects or adverse events. This has been associated with the surrogate marker of slowed total kidney volume (TKV) expansion though not slowing of progression of renal dysfunction. It is also associated with greater reduction in left ventricular mass index (LVMI) providing potential cardiovascular benefit.
- All patients with ADPKD should be encouraged to enrol into clinical trials as appropriate and/or able, given the general uncertainty with regard to efficacy of new therapeutic agents.

7. PSYCHOSOCIAL CARE

Guideline Recommendations

a. We recommend that psychosocial issues are reviewed during clinical assessment and that patients should be offered multidisciplinary psychosocial support to address pain management, self-management, social challenges, psychological issues, and education and information. (1C)

Ungraded suggestions for clinical care

Management of chronic renal pain:

- Explore and validate patient concerns and frustrations about the unpredictability, volatility and intensity of chronic renal pain;
- Provide strategies and counselling on how to manage the psychological, emotional, and lifestyle impact of pain; and to limit its interference with lifestyle. Behavioural

therapy, peer support, emotional disclosure, and online programs have been found to be effective for managing chronic pain (38-42) but no studies of these interventions have been conducted in patients with ADPKD.

Self-management: *(Refer to Subtopic: 5. Management - Diet and Lifestyle)*

- Develop programs, resources, and individualised plans to equip patients with the capacity and confidence for their own self-care (including medicine-taking, lifestyle changes [diet, fluid intake, physical activity], self-monitoring, access to healthcare services); and to reduce the perceived treatment burden. Systematic reviews of self-management interventions in other chronic diseases suggest that they can improve knowledge and self-management behaviour (43-47).

Social work:

- Provide support to address potential or actual financial discrimination related to disclosure of the genetic test results and/or patient's diagnosis of ADPKD. Specific financial issues that have been identified in the literature and observed in clinical practice include: employment, obtaining personal insurance, applying for loans including mortgages, and additional expenses for medications.

Psychological support:

- Refer patients who may be at high-risk for or have indicators for depression and anxiety to psychological services;
- Identify ways to alleviate prognostic uncertainty regarding renal disease and extra-renal complications;
- Address body image and self-esteem;
- Patient support groups are also suggested for patients to reduce their sense of isolation and to learn practical and coping strategies from other patients with ADPKD.

Education and information for patients and providers (Refer to Subtopic: Management - Diet and Lifestyle)

- Provide patients and their families with comprehensive, comprehensible, and practical information about ADPKD, disease complications and prognosis, self-management and monitoring, medications, and dietary and fluid intake;
- Provide succinct information (e.g. printed leaflet) about ADPKD that are endorsed by experts and suitable for members of the public (e.g. employers, insurers, educational institutions)

Genetic screening and testing (Refer to Subtopics: 2. Genetic Counselling, and 3. Screening)

- Provide counselling to address self-blame and guilt because of genetic transmission;
- Address family planning;
- Discuss issues around genetic testing and disclosure.

PART III: COMPLICATIONS

Complications of ADPKD include ESKD, nephrolithiasis, chronic pain, intra-cranial aneurysms and polycystic liver disease. This third section of the guideline outlines the evidence base for outcomes related to these complications.

8. MANAGEMENT OF END-STAGE KIDNEY DISEASE

Evidence Summary

- Outcomes in ESKD due to ADPKD appear to be better than those with non-ADPKD kidney disease, and these outcomes have improved compared to the older era.
- Despite theoretical reservations, continuous ambulatory peritoneal dialysis appears to be similar in terms of technique survival and peritonitis rates in patients with ADPKD compared to non-ADPKD ESKD individuals.

- The optimal timing of nephrectomy in relation to transplantation is not known - with no clear evidence favouring simultaneous or pre-transplantation nephrectomy.
- Anaemia is less likely in individuals being dialyzed with ADPKD compared to those with non-ADPKD related kidney disease and is linked with lower ESA use.
- There is no conclusive evidence supporting worse outcomes in terms of post-transplantation diabetes mellitus or bone loss in ADPKD transplant patients. Therefore immunosuppression in ADPKD individuals undergoing transplantation should not be approached any differently to a non-ADPKD individual.

Guideline Recommendations

a. We recommend that patients with ESKD due to ADPKD be considered for:

i. Kidney transplantation (refer to KHA-CARI Guideline: Recipient Assessment for Transplantation) (1C).

ii. Either haemodialysis or peritoneal dialysis where chronic dialysis is required (refer to KHA-CARI Guideline: Acceptance onto Dialysis) (1C).

b. We recommend that immunosuppression in kidney transplantation in ADPKD is managed in accordance with the KHA-CARI Adaption of the KDIGO Guideline for the Care of Kidney Transplant Recipients (1D).

c. We suggest that nephrectomy of a polycystic kidney for the purposes of transplantation to be evaluated before or at the time of transplantation (2C).

Ungraded suggestions for clinical care

- Preparation of patients with ADPKD for suitability for pre-emptive transplant presents unique challenges compared to preparation in patients with other types of kidney disease.

- Relatives of individuals with ADPKD, particularly those that are being considered as potential kidney donors, need to be carefully screened and excluded from having ADPKD (see Genetics, Imaging and screening subtopics), prior to living donor transplantation.
- Nephrectomy of a polycystic kidney prior to the time of transplantation may be required due to insufficient intra-abdominal space for the new allograft. Nephrectomy at the time of transplantation may be technically challenging for both procedures via a single incision. We acknowledge that these technical challenges may mean that pre-emptive native nephrectomy is preferred over simultaneous native nephrectomy.
- The need for nephrectomy requires clinical judgement by the transplant surgeon correlated with imaging studies (CT scan, MRI or ultrasound) in consultation with the nephrologist. Polycystic nephrectomy should be performed by the laparoscopic technique where possible due to less morbidity compared to an open approach.
- We suggest patients with ADPKD nearing end-stage kidney disease receive predialysis education as for any other patient with CKD (refer to KHA-CARI Acceptance onto dialysis, subtopic predialysis education).

9. **MANAGEMENT OF RENAL STONE DISEASE**

Guideline Recommendations

a. We recommend that unenhanced CT is the preferred imaging modality for the diagnosis of suspected nephrolithiasis in ADPKD (1B).

b. We suggest that patients with ADPKD complicated by nephrolithiasis should be investigated for predisposing urinary metabolic abnormalities (1C) and we suggest receive corrective therapy if an abnormality is identified (2D).

Ungraded suggestions for clinical care

- We suggest that for patients with ADPKD in whom a diagnosis of nephrolithiasis is considered, that the diagnostic performance of each imaging modality needs to be balanced against the relative risks of these different diagnostic tests, as does whether or not a contrast enhanced CT is required for other differential diagnoses or clinical indications.
- We suggest that in the early stages of cystic renal disease, screening for nephrolithiasis with ultrasound may be more useful.
- We suggest that the medical management of an acute presentation with suspected nephrolithiasis in a patient with ADPKD as well as the prevention of recurrent stone formation should follow general principles recommended for the general population, with exception that
    - Superimposed urinary tract infection should be considered in the acute presentation;
    - The differential diagnosis of the acute presentation should include ruling out other causes of acute loin pain (for example cyst infection or haemorrhage); and
    - Screening for underlying urinary metabolic abnormalities should be considered in ADPKD patients presenting with their first stone.
- We suggest that the indications for urological intervention for stone removal in ADPKD depend on the clinical circumstances. If required, Percutaneous Nephrolithotomy, Extracorporeal Shockwave Lithotripsy or Ureteroscopy with Laser Lithotripsy may be considered.

10. MANAGEMENT OF CHRONIC PAIN

Guideline Recommendations

a. We recommend that clinicians should include the evaluation of pain in patients with ADPKD during clinic visits (1D)

b. We recommend that patients be involved in the management of their pain, and that non-pharmacological treatments emphasised in the first instance (1D).

c. We suggest that surgical intervention may be warranted in individuals with severe ongoing pain (2C).

Ungraded suggestions for clinical care

- An initial assessment (detailed history, psychosocial assessment and physical examination) should be performed to determine the most likely basis of chronic pain in patients with ADPKD. The initial evaluation should attempt to distinguish between acute pathology (often due to cyst infection, stones or bleeding) and chronic pathology (caused by cyst expansion or mechanical back pain from increased kidney mass). Thus, pain due to cyst infection, is typically localised and associated with fever, elevated inflammatory markers, and positive urine cultures, and positive MRI or FDG-PET imaging.
- The initial assessment, and ongoing monitoring, should indicate the appropriate management of chronic pain in ADPKD. Management should be stepwise, involving non-pharmacological, pharmacological and possibly invasive interventions for cyst decortication, and may require the involvement of multiple disciplines (radiology, urology, physiotherapy, chronic pain clinics).
- We suggest that treatment goals for patients with chronic pain in ADPKD should be individualised and patients should be made aware that the time required to treat

chronic pain is substantial (exercises for lumbar lordosis may require 3-6 months before any observed improvement).

- Pharmacological treatment of chronic pain in ADPKD should adhere to standard principles for managing chronic non-malignant pain, with the following exceptions:
  - Medication dose should be modified according to the level of renal function;
  - Chronic use of NSAID/COX-2 inhibitors should be discouraged;
  - A step wise approach should be used.
- We suggest that analgesic therapy adhere to the following principles:
  - A systemic, non-opioid analgesic (such as paracetamol) should be first-line treatment;
  - Severe acute-on-chronic pain, or pain that is refractory to non-opioid analgesics, may require escalation of analgesic therapy;
  - Analgesic adjuvants (such as tricyclic anti-depressants, gabapentin) may be useful.
  - Tramadol may be effective in the short-term management of acute-on-chronic pain;
  - Given the complexity, treatment of chronic pain with long-term opioids should involve a specialist chronic pain service (48).
- Invasive surgical interventions for cyst decortication to relieve chronic disease-related kidney pain may be considered if the pain is refractory to conservative medical management and can be attributed to a single dominant (>5 cm diameter) or a group of dominant cysts (3 cysts >4cm diameter). A simple test in attributing pain to a cyst is to confirm that maximal tenderness overlies a cyst demonstrated on ultrasound imaging.

- Surgical interventions can be divided into: minimally invasive procedures (simple renal cyst aspiration or renal cyst aspiration with sclerotherapy); and complex surgical interventions that have a greater risk of morbidity (laparoscopic cyst decortication, renal denervation and nephrectomy). The hierarchal approach and optimal choice of surgical intervention is not well described and depends on the clinical circumstances, and discussion with a surgeon/interventional radiologist. Thus chronic pain due to a single or multiple cysts may be amenable to aspiration and recurrent cysts to aspiration plus sclerotherapy and/or laparoscopic cyst decortication. Alternatively, patients with severe intractable pain who have end-stage kidney disease may be suited to laparoscopic nephrectomy.

11 – MANAGEMENT OF INTRACRANIAL ANEURYSM

Guideline Recommendations

a. We suggest screening for intracranial aneurysm (ICA) in high-risk individuals with ADPKD (that is, those with a positive family history of subarachnoid haemorrhage, intra-cerebral haemorrhage and/or unruptured ICA in at least one affected first degree relative) (2B)

b. We suggest performing the screening of individuals at high-risk of ICA at the time of diagnosis of ADPKD and preferably prior to the development of ESKD (2C)

c. We recommend intracranial imaging be performed urgently in patients with ADPKD who experience a sudden onset of severe headache or neurological symptoms of concern (1D)

d. We recommend that MR angiography or CT (Circle of Willis Angiography) be used for the screening and detection of ICAs in individuals with ADPKD (1B)

e. We recommend referral to a neurosurgeon if an ICA is detected (1D)

f. We suggest treatment of ICA in patients with ADPKD in centres which have expertise in endovascular coiling and microsurgery (2B)

Ungraded suggestions for clinical care

- The decision to screen for ICA in ADPKD needs to be made after careful discussion with the individual concerned. The potential benefits of screening (prevention of a catastrophic intracerebral event) need to be balanced against the risks of screening (morbidity potentially associated with radiation dose, the treatment if an ICA is detected [either endovascular coiling or craniotomy and clipping]) as well as anxiety to the individual and their carers/family.
- In addition to ADPKD patients with a family history of an ICA, we suggest considering screening for ICA in individuals at high risk of a poor outcome in the case of an ICA rupture (e.g. prior to renal transplantation or other major elective surgery; presence of uncontrolled hypertension, high-risk occupation, current or former smokers, concurrent treatment with anticoagulants).
- For individuals without significant renal impairment, the imaging modality for screening can be either MR angiography (MRA) or CT angiography (CTA). However, CTA provides better resolution and without blood flow artefact compared to MRA.
    - In those undergoing MRA, use of gadolinium is preferred as it enables better detection of small aneurysms.
    - If there is renal impairment (e.g. GFR $\leq$60 ml/min/1.73m^2), then the decision for gadolinium use should be carefully considered due to the risk of nephrogenic systemic fibrosis. In such cases, MRA without gadolinium is a reasonable choice of modality for screening and diagnosis, and avoids the risk of contrast-induced kidney injury with a CT angiogram (21).

- The optimal time-interval to repeat screening in individuals with ADPKD who are at high-risk of an ICA and who have a negative initial screening study, is not certain. Based on data from a single longitudinal study in ADPKD patients, repeat screening could be considered 5 to 10 years after an initial negative study (49). However, individual patient-specific factors should be considered in the frequency of follow-up (50), and repeat imaging should also be performed urgently in any ADPKD patient who experiences acute symptoms such as sudden onset of severe headache or neurological symptoms.
- In the general population, smoking increases the risk of unruptured ICA formation. Therefore the risk of an ICA provides another reason for patients with ADPKD to be counselled to avoid or cease smoking (51). Similarly, given that hypertension may promote the growth of unruptured ICAs, patients with ADPKD should have their blood pressure monitored regularly and treated appropriately (52).

12. MANAGEMENT OF POLYCYSTIC LIVER DISEASE

Guideline Recommendations

a. We recommend screening for polycystic liver disease in all patients diagnosed with ADPKD using abdominal ultrasound (1C).

b. We recommend that all female patients with ADPKD liver cysts undergo counselling regarding the risks of pregnancy and exogenous oestrogen exposure in worsening liver cyst growth (1C).

c. We recommend that females at risk of symptoms from hepatic cysts avoid oestrogen supplements. (1D)

d. We recommend that a multidisciplinary team (hepatologist, hepatobiliary surgeon, interventional radiologist and nephrologist) care for patients with severe polycystic liver disease associated with ADPKD (1D).

Ungraded suggestions for clinical care

- In some individuals with ADPKD, treatment with somatostatin analogues has been shown to decrease liver volume and reduce abdominal symptoms, but further clinical trials are required to substantiate their role in clinical practice. Disadvantages of somatostatin analogues include the need for parenteral administration, cost and risk of adverse effects.
- Rarely liver transplantation is required in patients with polycystic liver disease that has been complicated by severe hepatomegaly impairing quality of life.

CONFLICT OF INTEREST

G Rangan is a member of the Advisory Committee on the Safety of Medical Devices, Therapeutic Goods Administration, and received financial support to attend the KDIGO Controversies on ADPKD meeting in 2014.

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A Mallett received financial support from Amgen to attend ASN 2013, 2014 Amgen symposium and Genzyme to attend LSD symposium.

J Savige is a board member of the Alport foundation of Australia, a non-for profit organization.

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Table 1. Diagnostic criteria for at risk individual with positive family history†

Age (years)	Number of cysts
15-39	At least 3 (unilateral or bilateral)
40-59	At least 2 in each kidney
>60	At least 4 in each kidney

Table 2. Exclusion criteria for at risk individual with positive family history†

Age (years)	Number of cysts
<40	No recommendation
≥40	Less than 2 cysts in each kidney

† Source: Pei et al. (2009) (20)

Table 3.Suggested MRI criterion for at risk individual older than 15 years with positive family history

ADPKD	Number of renal cysts
Diagnosis	> 10 cysts in total
Exclusion	< 5 cysts in total

For those with equivocal ultrasound findings not fitting into the guidelines above, and who do not require immediate disease exclusion or confirmation, expert opinion suggests follow up imaging with ultrasound in 5-10 years.

Explanation of grades

The evidence and recommendations in this KHA-CARI guideline have been evaluated and graded following the approach detailed by the GRADE working group (www.gradeworkinggroup.org). A description of the grades and levels assigned to recommendations is provided in Tables 4 and 5.

Table 4. Final grade for overall quality of evidence*

Overall Evidence Grade	Description
A	*High quality of evidence.* We are confident that the true effect lies close to that of the estimate of the effect.
B	*Moderate quality of evidence*. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	*Low quality of evidence.* The true effect may be substantially different from the estimate of the effect.
D	*Very low quality of evidence.* The estimate of effect is very uncertain, and often will be far from the truth.

* Adapted from GRADE working group (www.gradeworkinggroup.org)

Table 5. Nomenclature and description for grading recommendations*

Grade	Implications		
	Patients	**Clinicians**	**Policy**
Level 1 "We recommend"	Most people in your situation would want the recommended course of action and only a small proportion would not	Most patients should receive the recommended course of action	The recommendation can be adopted as a policy in most situations
Level 2 "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences	The recommendation is likely to require debate and involvement of stakeholders before policy can be determined

* Adapted from GRADE working group (www.gradeworkinggroup.org)

Access to the full text version

For a full text version of the guideline, readers need to go to the KHA-CARI website [go to the Guidelines section (www.cari.org.au)]

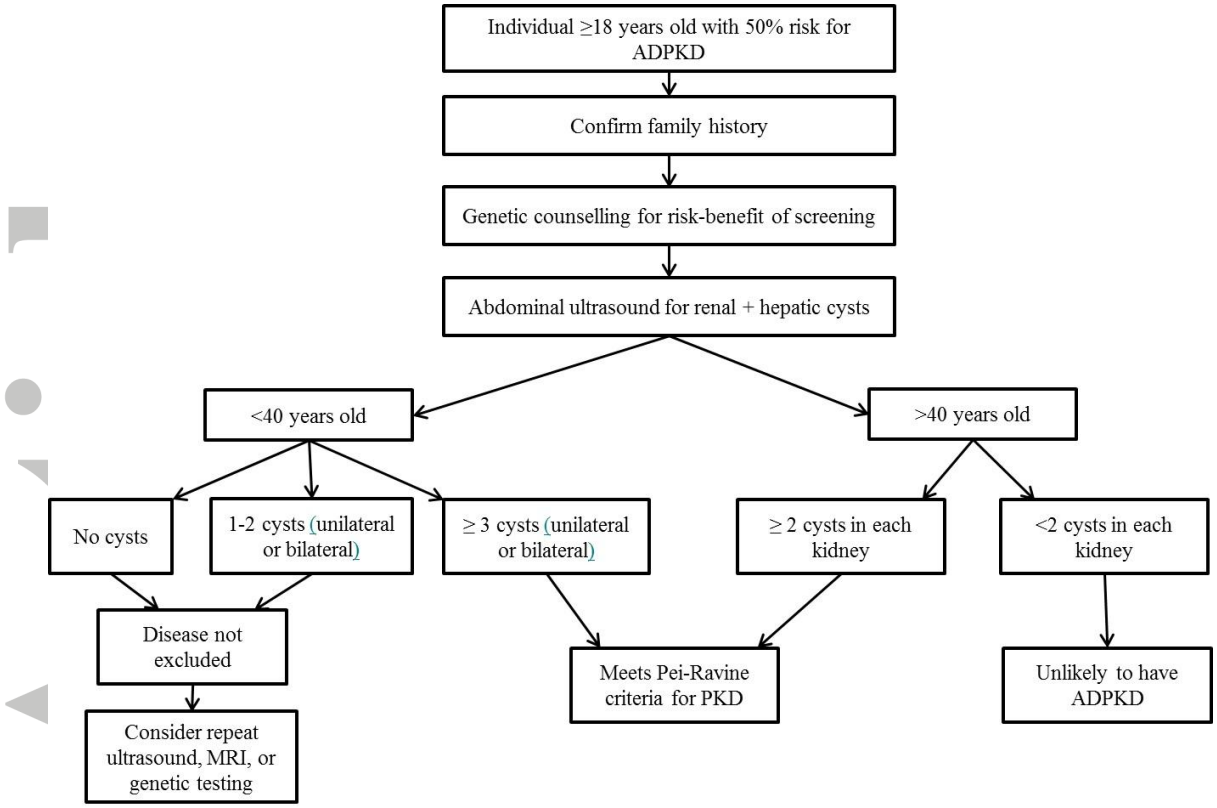

Figure 1. Screening for ADPKD in at risk individuals.

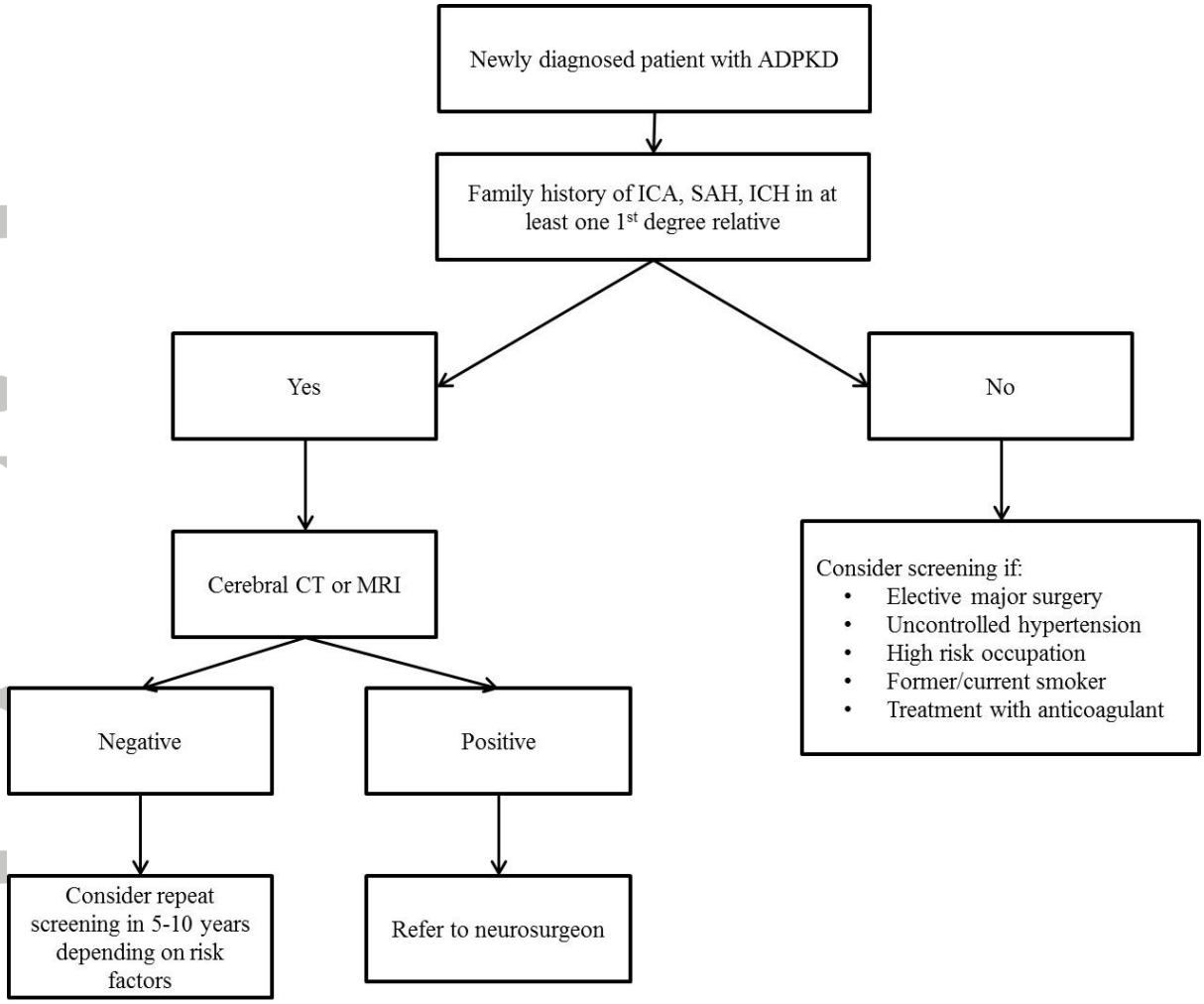

Figure 2. Screening for intracranial aneurysms in newly diagnosed patients with ADPKD.

Abbreviations: ICA= intracranial aneurysm, SAH= subarachnoid haemorrhage, ICH= intracerebral haemorrhage