KHA-CARI Autosomal Dominant Polycystic Kidney Disease Guideline: Genetics and Genetic Counseling

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GUIDELINE RECOMMENDATIONS*

a. We recommend that adult patients diagnosed with autosomal dominant polycystic kidney disease are referred to their regional genetics service for genetic counseling if they are interested in and would like to discuss (2B) the following:
   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 autosomal dominant polycystic kidney disease are referred to their regional genetics service for genetic counseling if they are interested in and would like to discuss (2A) the following:
   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 autosomal dominant polycystic kidney disease be directed to relevant patient support groups, like the Polycystic Kidney Disease (PKD) Foundation of Australia (see the Links section).

IMPLEMENTATION AND AUDIT

In many countries it is not standard practice to refer autosomal dominant polycystic kidney disease (ADPKD) families for genetic counseling. A valuable future audit could evaluate the uptake of genetic counseling and the indications for and outcomes of referrals.

BACKGROUND

ADPKD is the most common genetic kidney disease, with a prevalence rate between 1:500 and 1:4,000.

*Criteria used for recommendations and levels of evidence (1,2A-D) are described in more detail in Tables 1 and 2 of Rangan G, Savige J. Introduction to the KHA-CARI Guidelines on ADPKD, Semin Nephrol.2015;35:521-3 in this issue.

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††††Financial support: KHA-CARI Guidelines is supported by Kidney Health Australia, the Australian and New Zealand Society of Nephrology, Amgen Australia, and Shire Australia Pty Ltd. Guideline members were not remunerated for their work.

Conflict of interest statement: Judy Savige is a board member of the Alport foundation of Australia, a not-for-profit organization; Andrew Mallett received financial support from Amgen to attend ASN 2013 and the 2014 Amgen symposium, and from Genzyme to attend the 2014 LSD symposium; and Gopala Rangan is a member of the advisory committee for the safety of Medicine, Therapeutic Goods Administration, and received financial support to attend the KDIGO Controversies on ADPKD meeting in 2014. Address reprint requests to Chirag Patel, MB BS, MD, FRACP, Genetic Health Queensland, 4th Floor, Building C28, Royal Brisbane and Women’s Hospital, Back Rd, Herston, Brisbane, Queensland, Australia, 4029. E-mail: chirag.patel2@health.qld.gov.au

0270-9295/ - see front matter
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http://dx.doi.org/10.1016/j.semnephrol.2015.10.003
based on studies in different populations.\textsuperscript{1–6} It is characterized by development and progressive enlargement of numerous bilateral renal cysts, resulting in end-stage kidney disease (ESKD) in mid- to late adulthood. It accounts for 5\% to 10\% of ESKD in the dialysis population of developed countries.\textsuperscript{7–11} There are also effects on other organ systems including extrarenal cysts (liver, pancreas, and arachnoid membrane), cardiac valvular defects, colonic diverticulosis, abdominal wall hernias, and intracranial arterial aneurysms.\textsuperscript{12} A diagnosis of ADPKD therefore has important implications for prognosis, management, renal transplantation, and genetic counseling. A list of Clinical Genetics service providers in Australasia can be found at www.genetics.edu.au

**SEARCH STRATEGY**

**Databases Searched**

Medical subject heading (MeSH) terms and text words for ADPKD were combined with the MeSH terms and text words for genetic counseling. This was then combined with further searches using the MeSH and text words for diagnosis and genetic counseling, animal studies were specifically excluded. The search was carried out in Ovid MEDLINE (1946 to June 2014), Embase (1974 to May 23, 2014), PsycINFO (1806 to June 2014), the Cochrane Database of Systematic Reviews and Cochrane Registry of Clinical Trials (inception to June 2014).

**Date of search:** June 2014.

**WHAT IS THE EVIDENCE?**

Supplementary evidence Tables are available online.

i) Genetics and Inheritance

ADPKD is inherited in an autosomal dominant manner and is a genetically heterogeneous condition. Around 85\% of cases are due to mutations in the \textit{PKD1} gene (MIM 601313) located on chromosome 16, with the remaining 15\% due to mutations in the \textit{PKD2} gene (MIM 173910) located on chromosome 4.\textsuperscript{13,14} About 90\% of affected individuals have an affected parent, with the remaining 10\% being due to a de novo mutation. Parents and siblings of an affected individual have a 50\% chance of being affected with the disease, unless it has occurred \textit{de novo}. Every offspring of an affected individual with ADPKD has a 50\% chance of inheriting the disease. If renal imaging (and/or genetic testing) suggests that the proband has a \textit{de novo} mutation, then the risk to siblings is low; however, gonadal mosaicism may play a role in a minority of families.\textsuperscript{15} There is marked intrafamilial and interfamilial variability in both the age of clinical onset and disease severity. Penetrance is considered complete for cyst development and all older adults with a \textit{PKD1} or \textit{PKD2} mutation develop multiple bilateral cysts.\textsuperscript{16} As the disease is progressive, few cysts may be evident during childhood or young adulthood, especially for \textit{PKD2}-associated disease.\textsuperscript{16} Penetrance is reduced, however, for ESKD, and while the majority of individuals with a \textit{PKD1} mutation develop ESKD during their lifetime, many individuals with \textit{PKD2} have adequate renal function into old age.

ii) Family History and Communication

Taking a family history is very important to identify other affected and at-risk individuals. The family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. A detailed family history, especially of renal disease severity, may also provide important prognostic information and/or determine the underlying genotype. The presence of at least one family member with ESKD at or before age 55 years is highly predictive of \textit{PKD1}, and the presence of at least one family member with ESKD at or after age 70 years is highly predictive of \textit{PKD2}.\textsuperscript{17} The family history should also be used to identify other disease-related complications such as cerebral aneurysms, which may support more widespread family screening (KHA-CARI ADPKD Guideline: Intracranial Aneurysms in ADPKD). In addition, other comorbidities may suggest alternative diagnoses and modes of inheritance such as tuberous sclerosis, renal cysts and diabetes, and oral-facial-digital syndrome type 1.

A systematic review of studies looking at patient perspectives of living with ADPKD identified a number of themes pertinent to genetic counseling: a) genetic guilt and resentment (blaming parents and/or self, constant burden of guilt); b) precariousness in pursuing parenthood (prognostic uncertainty, owning the decision, needing directive counseling); and c) defining parental responsibility for genetic testing and disclosure (preserving normality, doubting necessity of genetic testing, respecting the child’s autonomy, and hope in future technologies)\textsuperscript{18} (KHA-CARI ADPKD Guideline: Psychosocial Care).

For individuals living with ADPKD, genetic counseling is recommended to allow education on the inheritance pattern, support in sharing this information to increase the awareness of genetic risks for family members, and to address many of the psychosocial and ethical issues. A survey of over 300 individuals at 50\% risk of developing ADPKD (due to the family history) showed that around 6\% of them had an incorrect or poor understanding of their genetic risk.\textsuperscript{19} For those with an opinion about their risk, the most important source of information (both correct and incorrect) came from family members. A clinician treating an ADPKD patient is in an important
position to educate the family correctly. They can try to understand the family dynamics of their patient, and the family’s approach to communication about ADPKD. This will aid the clinician to promote effective family communication about risk of disease and the benefits/risks of knowing one’s genetic risk.

iii) Predictive Testing in Asymptomatic At-Risk Relatives

Screening or testing for the disease in the absence of definite symptoms is termed predictive testing, and in the context of ADPKD that may be via renal imaging or molecular genetic testing (see section on Evaluation of Asymptomatic At-Risk Relatives).

Adult (> 18 years)

At present, in asymptomatic individuals, there are no proven therapies to delay cyst progression, and complications like hypertension are managed as they arise (KHA-CARI ADPKD Guideline: Pharmacological Management). This aspect of ADPKD management is evolving and there may be therapies applicable to asymptomatic individuals in the future. It is recommended that at-risk, asymptomatic adult family members who are seeking predictive testing (renal imaging/genetic testing) should be referred to a Clinical Genetics service for genetic counseling. This would include assessing and improving the individual’s knowledge of ADPKD, determining the motives for requesting predictive testing, and assessing the possible impact of positive and negative test results.

Advantages of predictive testing include:

- Reducing the uncertainty and anxiety associated with at-risk status
- Early diagnosis permitting early detection and treatment of complications
- Decisions regarding lifestyle, health, retirement, and employment
- Discussions on reproductive options
- Sharing the information with family members
- Identifying potential unaffected living-related kidney donors

Disadvantages of predictive testing include:

- Age-dependent, false-negative renal imaging
- Financial discrimination, especially obtaining insurance coverage (health, life, and disability)
- Employment discrimination
- Changes in social and family interactions
- Psychological impact (especially anxiety) of the test and disease development, with its complications in the future

Child (< 18 years)

Predictive testing in children for adult-onset conditions remains a controversial topic. Families who are seeking predictive testing (renal imaging/genetic testing) in children should be referred to a Clinical Genetics service for genetic counseling and further discussions of the ethical, legal, and psychosocial implications of genetic testing in children and adolescents. In general, the broad consensus is that it is not considered appropriate to test asymptomatic at-risk children for adult-onset conditions in which there are no childhood treatments or compelling medical benefits at that age. The main rationale for deferring predictive testing in asymptomatic children is to preserve the child’s ability to consent to the test until they reach maturity, when they can better understand the various issues of predictive testing (as discussed for adults).

In general, very few children present with ADPKD-related disease, although occasionally there are families with in utero and/or severe childhood presentations. The proportion of children who have inherited ADPKD and are asymptomatic but have treatable complications, like hypertension, by age 18 years is low, although not well defined. At present, for ADPKD, there are no indications for predictive testing of asymptomatic at-risk children. This may, however, change in the future, if and when effective therapies are found to be beneficial in young asymptomatic at-risk individuals. An alternative measure for at-risk children can be to monitor their blood pressure annually, thereby ensuring they do not miss out from the benefits of early intervention if required. Any individuals who become symptomatic during childhood, however, should be referred for appropriate diagnostic testing and medical management.

iv) Evaluation of Asymptomatic At-Risk Relatives

For those individuals who still wish to pursue predictive testing, after genetic counseling, either renal imaging and/or molecular genetic testing may be utilized.

Renal imaging

Imaging ultrasound examination should be considered as the first means to test for ADPKD. Age-specific ultrasound criteria to confirm a diagnosis of ADPKD have been proposed for individuals who are at 50% risk for ADPKD because they have an affected first-degree relative. The absence of renal cysts by ultrasound examination virtually excludes a diagnosis of ADPKD caused by a mutation in PKD1 in an at-risk person age 30 years or older, but not in persons

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younger than age 40 years who are at risk for ADPKD caused by a mutation in \textit{PKD2} or ADPKD of unknown genotype. Therefore, at-risk individuals (from an unknown genotyped family) who have normal renal imaging under age 40 years could be falsely reassured of disease status (false negatives).

\textbf{Molecular genetic testing}

Molecular genetic predictive testing requires prior identification of the disease-causing mutation in \textit{PKD1} or \textit{PKD2} in an affected family member. This should be considered for predictive testing, especially when renal imaging is equivocal and/or when a definitive diagnosis is required in a younger individual (eg, reproductive planning or potential renal transplant donor). As some generalizations can be made about the phenotype expected in individuals with mutations in \textit{PKD1} versus \textit{PKD2}, knowledge of the causative gene mutation may provide some information on likely disease severity in asymptomatic individuals. However, disease progression tools using genetic test results or renal volumes remain to be validated in the clinical setting. Informed consent should be obtained prior to predictive genetic testing, and individuals with a positive test result should have arrangements for long-term renal follow-up and evaluations.

\textbf{v) Family Planning and Prenatal Testing}

Differences in perspective may exist among medical professionals and in families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Two surveys of over 100 ADPKD individuals have suggested that a minority of individuals changed their reproductive behavior as a result of ADPKD. The majority felt a prenatal test should be available, but only 4\% would terminate a pregnancy for ADPKD.\textsuperscript{30,31}

The decision to pursue prenatal testing avenues may depend on: a) personal experience of the disease; b) family history of the disease (especially if in utero and/or severe childhood presentations); c) fertility issues; and d) social circumstances. Prenatal diagnosis (by amniocentesis or chorionic villus sampling) and pre-implantation genetic diagnosis for at-risk ADPKD pregnancies is available, but does require prior identification of the disease-causing mutation in an affected family member.\textsuperscript{32}

Most centers would consider decisions about prenatal testing to be the choice of the parents, so discussion of these issues is appropriate. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before a pregnancy. It is recommended to refer young adults who are affected (or at-risk) to a Clinical Genetics service to offer genetic counseling (including discussion of potential reproductive options).

\textbf{SUMMARY OF THE EVIDENCE}

ADPKD is an autosomal dominant condition. Obtaining a detailed family history and referring patients/families for genetic counseling allows them to be more informed of the inheritance of the condition, identifies those at risk of the condition, and guides them on communicating genetic risks to family members. It can also address many of the genetic psychosocial issues associated with the disease and issues surrounding predictive testing in asymptomatic individuals (adults and children), as well as facilitate discussions and decisions regarding family planning.

\textbf{LINKS}

\textbf{The Centre for Genetics Education:} http://www.genetics.edu.au

\begin{itemize}
\item Genetic counseling services in Australia http://www.genetics.edu.au/Genetics-Services/genetic-counselling-services
\item Prenatal testing: CVS and amniocentesis http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets/prenatal-testing-cvs-amniocentesis
\end{itemize}


\textbf{PKD Foundation of Australia} Available: http://pkdaustralia.org

\textbf{GLOSSARY}

\textbf{Allele:} there are usually two copies of a gene. These two copies are called alleles. In ADPKD one allele of \textit{PKD1} or \textit{PKD2} carries a mutation, the other allele is normal.

\textbf{Autosomal dominant mutation:} a dominant mutation in a gene that is carried on an autosome (see chromosome).

\textbf{Chromosome:} physical structure consisting of DNA and supporting proteins called chromatin.
Human cells normally contain 46 chromosomes identified as 23 pairs; 22 pairs are autosomes and one pair is the sex chromosomes, XX in females and XY in males.

Clinical genetics: A specialty of medicine concerned with the diagnosis and provision for risks of developing an illness with a genetic basis in individuals and families.

De novo: an alteration in a gene that is present for the first time in one family member as a result of a mutation only in a germ cell (egg or sperm) of one of the parents or in the fertilized egg itself.

Diagnostic test: a term used to describe particular tests that are able to identify (diagnose) a recognized condition.

DNA sequencing: determining the pattern or order in which the nucleotide bases occur in a piece of DNA. This sequence is the genetic code.

Expressivity: the degree to which an inherited characteristic is expressed in a person. “Variable expressivity” refers to the variation in expression and severity of particular characteristics or severity of a condition.

Gene: the basic unit of heredity; a segment of DNA that contains the information for a specific characteristic or function.

Genetic counseling: the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. This is provided by a team of health professionals with specialized training in genetics and counseling.

Genetic heterogeneity: mutations in different genes causing the same condition.

Genetic testing: analysis of an individual’s genetic make-up to determine predisposition to a particular health condition or to confirm a diagnosis of a genetic condition.

Genotype: the genetic constitution of an individual.

Germline/gonadal mosaicism: when the germ cells (sperm or egg cells) have a different genetic make-up than the cells in the rest of the body.

Hypomorphic allele: a mutation that reduces but does not eliminate a gene’s functionality is hypomorphic.

Linkage: the tendency for genes or segments of DNA that are located close together on the same chromosome to be inherited together.

Molecular genetics: the branch of genetics that studies the function and structure of genes at the molecular level.

Mutation: this is a permanent change of the nucleotide sequence of the genome. A mutation can result in several different types of change in sequences (eg, point mutations, insertions, deletions, duplications, and rearrangements). Mutations in genes can have no effect, alter the product of a gene, or prevent the gene from functioning properly or completely. If the mutation occurs in the germ line cells, it is then able to be inherited. Mutations in somatic cells cannot be inherited. Mutations can occur naturally and spontaneously or they may be due to exposure to mutagens.

Polymerase chain reaction (PCR): the polymerase chain reaction is a technology in molecular biology used to amplify a single copy or a few copies of a piece of DNA across several orders of magnitude, generating thousands to millions of copies of a particular DNA sequence.

Penetrance: the probability of detecting the presence or clinical expression of a gene or combination of genes when they are present. If the penetrance of a particular condition is less than 100%, not all individuals who carry a mutation in the gene or genes responsible for the condition will develop symptoms of the condition it causes. Such a genetic condition is said to have reduced or incomplete penetrance.

Phenotype: the physical and/or biochemical characteristics of a person that are determined by their genetic make-up and/or environment.

Predictive testing: a form of genetic testing performed on a person with a family history of a particular genetic condition, but who does not have any symptoms of the condition at the time of testing. This testing determines if that person has inherited the mutation (present in their family). If testing for this mutation reveals that it is present in the person, then they have an increased predisposition to developing the condition that was tested for. The detection of a specific mutation does not necessarily mean the individual will definitely develop the condition (see penetrance).

Preimplantation genetic diagnosis (PGD): an adjunct to the In Vitro Fertilization (IVF) process where the embryo undergoes genetic testing before it is transferred (implanted) into the uterus.

Proband: usually the first affected family member who seeks medical attention for a genetic disorder.

Risk: “genetic risk” refers to the likelihood or probability that a genetic characteristic or condition will occur or recur in a family, based on an understanding of the pattern of inheritance.
Working group on Inherited Kidney Diseases within the Spanish Society of Nephrology

i. The patient with a secure or likely diagnosis of ADPKD should be advised to inform first-degree adult relatives of the diagnosis, and screening should be offered to them (D).

ii. Genetic counseling should always be provided (C).

SUGGESTIONS FOR FUTURE RESEARCH

Determine the effect of genetic counseling by assessing ADPKD patients/families (pregenetic and postgenetic counseling):

1) Knowledge and understanding of inheritance/risks to family members, role of genetic testing/prenatal options;
2) Issues of predictive screening/testing in adults and children; and
3) Psychosocial issues around ADPKD.

The KDIGO 2014 controversy conference report identified gaps in knowledge and suggested a relevant research agenda on:

- Production of a standardized diagnostic care pathway
- Production of comprehensive family planning guide, with research on outcomes and the role of peer-to-peer support networks and youth counselors for children and adolescents
- Development of communication tools and observational studies to evaluate the effectiveness of such interventions
- Development of specific tools to measure the psychosocial impact of ADPKD. Studies to test the efficacy of strategies to manage anxiety and depression.

APPENDIX A. SUPPLEMENTARY INFORMATION

Supplementary data associated with this article can be found in the online version at 10.1016/j.semnephrol.2015.10.003.

REFERENCES


APPENDIX

GENETICS AND GENETIC COUNSELLING

Date written: May 2015
Authors: Chirag Patel, Michel Tchan, Judy Savige, Andrew Mallett, Allison Tong, David J Tunnicliffe, Gopala Rangan,

Table 1 Evidence tables of included studies.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>N</th>
<th>Study Design/ Setting</th>
<th>Participants</th>
<th>Methods</th>
<th>Results</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barua et al. 2009 [17]</td>
<td>484</td>
<td>Cross section, single center, Canada</td>
<td>484 affected individuals from 90 families</td>
<td>132 patients presented to hereditary disease clinic in Toronto, all key spouses and at risk family members were recruited as well as 14 individuals from the Newfoundland study.</td>
<td>• Medical records reviews • Ultrasound scan • Genotyping for PKD1/PKD2</td>
<td>Having at least one family member with early onset ESRD at before age 55-58 yrs. of age had a positive predictive value (PPV) of 100% and sensitivity of 72-75% for PKD1.</td>
</tr>
<tr>
<td>Hodgkinson et al. 1990 [30]</td>
<td>190</td>
<td>Interview study/ cross-sectional</td>
<td>Adult patients with ADPKD (n=100), and families on North Western Regional Genetic Register (n=90), who had previously received genetic counseling All age 18-45 years old.</td>
<td>Semi-structured interviews, For interview topics: knowledge and understanding of clinical aspects and available therapies, and knowledge of mode of inheritance. The responses were scored using weighted lists of facts. Scores where then classified as excellent, good, fair, poor and absent.</td>
<td>• 56% of patients with ADPKD indicated that the disease did not influence their childbearing • 75% of patients with ADPKD indicated that prenatal testing was desirable.</td>
<td>Very low (no quality appraisal available)</td>
</tr>
<tr>
<td>Ravine et al. 1991 [19]</td>
<td>321</td>
<td>Qualitative-survey/ cross-sectional</td>
<td>46 families with two or more members with ADPKD were identified</td>
<td>Participants were clinical assessed and asked about their knowledge of genetic risks through open-ended discussion.</td>
<td>• 91% were aware the disease is hereditary • 30% knew the risk was one in two • 41% were aware that ADPKD was inherited but had no opinion of their personal risk • 22% (67/304) were diagnosed through ultrasound.</td>
<td>Very low (no quality appraisal available)</td>
</tr>
<tr>
<td>Sujansky et al. 1990 [31]</td>
<td>278</td>
<td>Qualitative-survey/ cross-sectional</td>
<td>Patients with ADPKD (n=141), at-risk individuals (n=137) from 107 kindreds</td>
<td>Questionnaire regarding knowledge and attitudes about ADPKD and use of genetic testing for pre and postnatal presymptomatic diagnosis.</td>
<td>• High level of knowledge • 87% of patients with ADPKD considered recurrence rates high • 11% of patients with ADPKD did not have children because of recurrence rates. • 88% of patients and 85% of at-risk individuals would test offspring • 4% of patients and 8% of at-risk individuals would terminate pregnancy due to ADPKD.</td>
<td>Very low (no quality appraisal available)</td>
</tr>
</tbody>
</table>