Children and young people with, or at risk of, Autosomal Dominant Polycystic Kidney Disease (ADPKD).

Paul Winyard,
UCL Great Ormond Street
Institute of Child Health.
Should children and young people at risk of ADPKD be tested for complications of the conditions?

A. Yes
B. No
C. Only if they have symptoms
D. Only if parents ask for it
Should children and young people at risk of ADPKD be tested for the condition?

A. Yes
B. No
C. Only if they have symptoms
D. Only if parents ask for it
Who should do the testing?

A. GP
B. Local paediatrician
C. Paediatric nephrologist
D. Parents or children
When should children and young people have a say?

A. Age 16 years
B. Age 18 years
C. When competent
D. Always
Classical view on children with ADPKD

a) 1-2% have early problems
b) 98-99% no problem until later
c) No point in upsetting people by talking about it or doing any tests until they can decide for themselves

Do we need to rethink this?
Two very distinct issues

Making the diagnosis

Knowing what to do then!
Specific attitudes:

1. Adult nephrologists
2. Paediatric nephrologists
3. Families and patients
1. Adult nephrologists

- Look of consternation
- Why do Paediatricians ‘baby’ their patients?
- ‘Never’ see proteinuria
- Rarely see major hypertension
- Waste of money doing frequent scans
ADPKD in children ..... the screening of asymptomatic children with a positive family history is not recommended. ..... the early detection and treatment of hypertension is important. Screening for hypertension in all at-risk children from the age of 5 years might be a pragmatic approach.
Diagnostic screening of asymptomatic children is not recommended. However, expert opinion advises screening for hypertension from 5 years of age in at-risk children, to identify and treat hypertension and prevent later cardiovascular complications.
2. Paediatric nephrologists

A survey of UK management of childhood ADPKD

Aim: To ascertain current attitudes amongst UK paediatric nephrologists
2. Paediatric nephrologists

There are no UK guidelines on management of ADPKD in Children and Young People

A survey of UK management of childhood ADPKD

• Aim
  – To ascertain current practice amongst UK paediatric nephrologists
• Method
  – Case based approach to identify practice
  – Questionnaire x 2 – 1 child, 1 young adult
Maanasa Polubothu
Amanda Richardson
Larissa Kerecuk
Manish Sinha
Paul Winyard
Tess Harris
Respondents

![Bar chart showing respondents from various locations.](chart.png)
Results

How often would you review?

Range, diversity but no consensus except recognition of high blood pressure
Autosomal dominant polycystic kidney disease in children
Screen now to save later?

Satyamaanasa Polubothu academic clinical fellow¹, Amanda Richardson paediatric nephrology specialist trainee², Larissa Kerecuk consultant paediatric nephrologist³, Manish D Sinha consultant paediatric nephrologist²
Blood pressure:
• 25% hypertensive as adolescents
• 67% hypertensive by age 30

Cysts progressively developing with age; corresponding loss of normal functioning tissues

GFR normal until age 40+
..... important shift from symptomatic to preventive treatment makes it a good time to question the current expectant approach to childhood ADPKD.

We propose an urgent national debate on an inclusive approach involving patients, families, clinicians, ethicists and commissioners. A few pounds spent now could save many thousands later
What is the evidence for raised blood pressure?
928 children across 14 studies, mean age 10 years. **One fifth (20%)** have high blood pressure
Grant to investigate blood pressure in children and young people with ADPKD

Evelina Children’s Hospital and Great Ormond Street
• Clinic, central and 24hr blood pressure measured
• Assessment of heart and blood vessel health
Central blood pressure and measures of early vascular disease in children with ADPKD

Matko Marlais, Sreedevi Rajalingam, Haotian Gu, Alexandra Savis, Manish D Sinha and Paul J D Winyard

Result deleted as results soon to be published
3. Families and patients

- Discussions with PKD Charity organisers
- Interactions at PKD information events
- Response to potential ADPKD in Children and Young People Study
ADPKD in children

This article is intended as a general guide for parents or carers who have children who are at risk of, or have been diagnosed with autosomal dominant polycystic kidney disease (ADPKD).

Find out here how ADPKD can affect children as well as how it is diagnosed, monitored and treated.

What is ADPKD?

Autosomal dominant polycystic kidney disease (ADPKD) is a relatively common inherited condition in which fluid-filled cysts develop in both kidneys.

The kidneys are normally filled with many thousands of thin, fine tubes called tubules that filter the blood and produce urine. In people with ADPKD, these tubules eventually become too big and fill up with fluid (like small balloons), forming cysts. The cysts press on the rest of the kidney and stop the kidney from working properly.

ADPKD is believed to affect one or two in every 1000 people. Although ADPKD causes progressive kidney failure, it very rarely causes major symptoms during childhood. If your child has ADPKD, they probably won't require treatment until later in life.

If my child is at risk of ADPKD, should they be tested?

You may know that your child is at risk of having ADPKD because you or their other parent has the condition.

Parents in this situation often ask whether they should have their child tested for ADPKD. Until recently, specialists usually gave the answer of ‘No’, because very few children required any treatment and there were not many treatment options available. It was felt safe to wait until the child was old enough to decide about testing for themselves.

Some doctors now believe that it might be helpful to diagnose ADPKD earlier. This is so children can start...
### Should my child be tested for ADPKD?

<table>
<thead>
<tr>
<th>Advantages of testing in childhood</th>
<th>Disadvantages of testing in childhood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usually provides an answer as to whether or not your child has ADPKD, meaning less uncertainty.</td>
<td>Testing during childhood will stop your child being able to decide for themselves whether or not they want to be tested for ADPKD as an adult.</td>
</tr>
<tr>
<td>For your child, receiving a diagnosis of ADPKD when they are younger may be easier for them to come to terms with.</td>
<td>Some children won’t have any symptoms or signs during childhood, so knowing they have the disease earlier may not help.</td>
</tr>
<tr>
<td>If more treatments become available for children with ADPKD in the future, doctors may be able to offer these to your child if their ADPKD is confirmed.</td>
<td>Having a diagnosis of ADPKD confirmed may have implications for your child’s future life and health insurance.</td>
</tr>
</tbody>
</table>

It is also worth looking at ‘Talking to children and young people with ADPKD’ from the PKD Charity before making a decision about talking to your child about ADPKD.
## Estimated Number of children with ADPKD at each centre

<table>
<thead>
<tr>
<th>Centre</th>
<th>Lowest Estimate</th>
<th>Highest Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOSH</td>
<td>15</td>
<td>100</td>
</tr>
<tr>
<td>ECH</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Imperial</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Southampton</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Bristol</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Birmingham</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>CHERI</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Newcastle</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Manchester</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Liverpool</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>Leeds</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>Newcastle</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Glasgow</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>Belfast</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>SPIN</td>
<td>20 (258)</td>
<td>20 (493)</td>
</tr>
</tbody>
</table>

12 million UK children
1:1000 = 12,000 ADPKD
Currently missing ≥ 95%
Clinical Practice Guideline: Monitoring children and young people with, or at risk of developing Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Chair: Dr Jan Dudley
Clinical Leads: Prof Paul Winyard, Dr Matko Marlais
Co-Authors: Dr Oliver Cuthell, Ms Tess Harris, Dr Jiehan Chong, Prof John Sayer, Dr Daniel Gale, Mrs Lucy Moore, Mrs Kay Turner, Ms Sarah Borrows, Dr Richard Sandford
• Renal Association supported work to develop best practice guidance.
• Guideline development group included representation from:
  – Patients and families
  – Paediatric nephrology
  – General paediatrics
  – Clinical genetics
  – Adult nephrology
**Methods**

- Abstracts screened by 2 authors and those selected were critically appraised.

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (&lt;18) with a confirmed diagnosis of ADPKD or at risk of ADPKD due to their family history</td>
<td>Ultrasonography</td>
<td>Any intervention compared with any other or no intervention</td>
<td>Mortality</td>
<td>Randomised controlled trials (RCT)</td>
</tr>
<tr>
<td></td>
<td>Cranial imaging</td>
<td></td>
<td>Hospitalisations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blood Pressure monitoring</td>
<td></td>
<td>Chronic Kidney Disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Monitoring for albuminuria</td>
<td></td>
<td>Cardiovascular disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Genetic counselling</td>
<td></td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Non-randomised studies if adjusted for key confounders (age, health at baseline, co-morbidities).</td>
</tr>
</tbody>
</table>
Methods

• Where evidence was lacking, formal Delphi consensus methodology was employed.
• Delphi panel comprised of the following representatives:
  – Paediatric nephrologists (3)
  – Adult nephrologists (3)
  – Paediatricians with an interest in nephrology (3)
  – Lay members (3)
  – Clinical genetics (3)
  – General practitioners (3 invited, 2 responded)
• Consensus was deemed to be 80% agreement or disagreement with the statement.
• Three iterative rounds, with responses anonymised.
Guideline 1

• We recommend that parents or carers of children and young people at risk of developing ADPKD should be offered information on ADPKD inheritance and potential benefits and harms of testing for ADPKD, by health professionals with specialist knowledge in this area. (D)

• No relevant literature identified.
• 100% agreement with this statement in Delphi consensus.
• Health professionals providing information on testing should have a clear understanding of the benefits and challenges of USS or genetic testing for ADPKD.
Guideline 2

- We recommend that children and young people aged 5 years and above with, or at risk of developing ADPKD, should have an assessment of blood pressure (BP) at least once every 2 years. (B)

- Sufficient research evidence to make a recommendation.
- Prevalence of hypertension in children with ADPKD is estimated at 20%, with evidence of cardiac target organ damage in those with hypertension.
- Both those with known ADPKD and those ‘at risk’ who decline to be tested should have BP monitored.
- In the absence of other factors, BP rises slowly in ADPKD therefore every 2 years as a minimum is sufficient.
Guideline 3

- We recommend that the decision to test for ADPKD in asymptomatic children and young people (CYP) at risk of developing ADPKD, should be undertaken jointly between health professionals and parents or carers and, wherever possible, the young person. (D)

- No relevant literature identified.
- 88% agreement with this statement in Delphi consensus.
- Emphasis on patient choice and avoiding paternalism.
- Testing can reduce psychological burden in some families.
- It is entirely reasonable to decide against testing, provided that blood pressure is monitored regularly in those who remain ‘at risk’ through their family history.
Guideline 4

- If testing is decided on, we suggest that either kidney ultrasound or genetic testing may be offered to asymptomatic children and young people at risk of ADPKD, where testing has been agreed by parents or carers (and, wherever possible, the young person) and health professionals. (D)

- No relevant literature identified.
- 70% agreement with this statement in Delphi consensus.
- There is a lack of clear evidence for superiority of either modality for testing, so the emphasis remains on individual choice after full explanation of benefits and harms.
Guideline 5

• We suggest that, if asymptomatic children at risk of ADPKD do not have cysts on ultrasound, further ultrasound testing should be deferred until adolescence (15-18 years), or later if preferred by the young person.(D)

• No relevant studies identified.
• 70% agreement with this statement in Delphi consensus.
• Serial ultrasound scanning may reduce or increase anxiety.
• No evidence of benefit from regular ultrasound scans.
• Adult practice is not to support regular ultrasound.
• Resource implications.
Guideline 6

- We recommend that if genetic testing is planned in children and young people at risk of ADPKD, identification of the mutation in the affected adult family member (if not already known) should be undertaken prior to testing the child or young person. (D)

- No relevant literature identified.
- 88% agreement with this statement in Delphi consensus.
- ADPKD is associated with a wide range of mutations in PKD1 and PKD2, it can be difficult to determine pathogenicity if a mutation is not previously described.
- Testing affected family members allows analysis to help assign pathogenicity in mutation identified in the child.
Audit Measures

1: Proportion of parents or carers of children at risk of developing ADPKD offered information on ADPKD inheritance and potential benefits and harms of testing for ADPKD

2: Proportion of children and young people aged 5 years and above with, or at risk of developing ADPKD, having an assessment of blood pressure (BP) at least once every 2 years

3: Proportion of asymptomatic children and young people at risk of developing ADPKD offered testing for ADPKD

4: Proportion of asymptomatic children and young people at risk of developing ADPKD offered either genetic or ultrasound testing testing for ADPKD

5: Proportion of asymptomatic children at risk of ADPKD who do not have cysts on ultrasound, having repeated ultrasound testing prior to adolescence (15-18 years)

6: Proportion of asymptomatic children at risk of ADPKD whose parents have been tested for a genetic mutation prior to the child being tested
Research Recommendation 1

- In children and young people with ADPKD does regular (e.g. yearly or every 2 years) urine albumin: creatinine monitoring and treatment improve outcome?
  - No consensus after two Delphi rounds.
  - 20% of children with ADPKD are reported to have proteinuria, but there is a lack of studies assessing outcomes in children with proteinuria.
  - Studies have failed to show a relationship between hypertension and proteinuria in children with ADPKD.
Research Recommendations 2 and 3

- In children and young people with ADPKD what is a) the incidence of sub-arachnoid haemorrhage and b) the prevalence of intracranial aneurysm?
- In adults, children and young people with ADPKD with a family history of intracranial aneurysm or sub-arachnoid haemorrhage does Intracranial Magnetic Resonance (MR) imaging reduce the risk of intracranial events?

- No consensus after two Delphi rounds.
- Literature limited to 3 case reports in children.
- Adult practice is to screen those with a family history of ICA or SAH every 5 years.
- Threshold for intervention in childhood is unclear.
Personal ADPKD conclusions

• Blood pressure seems the prime issue
• There is a large variation in practice in ADPKD, which may disadvantage affected families and children
• Guidelines should help but will clinicians adopt these, with the major ethical and financial implications of changing practice?

✓ What we need is ….. a definitive unbiased study of ADPKD in undiagnosed children and young people
New potential study submitted – how common is high blood pressure really?

- 200 UK Children and young people at risk of ADPKD, but not yet diagnosed
- Advertise by internet, social media, meetings
- Birmingham, Cambridge, London (GOSH and Evelina), Manchester, Newcastle and Nottingham
- Half day visit - blood pressure, blood tests, MRI of kidneys (and heart) and genetics
So what are the right answers ..... ?

In children and young people:

Should those at risk of ADPKD be tested for complications ... ?
Yes / No / Only if they have symptoms / Only if parents ask for it

Should those at risk of ADPKD be tested for the condition?
Yes / No / Only if they have symptoms / Only if parents ask for it

Who should do the testing?
GP / Local Paediatrician / Paediatric Nephrologist / Parents

When should children and young people have a say?
Age 16 / age 18 / When ‘competent’ / always
Thank you

Satymaanasa, Matko, Manish, Tess

Members of the guideline working group

Delphi panellists

Renal Association

Royal College of Paediatrics and Child Health

PKD Charity (UK)

p.winyard@ucl.ac.uk