Autosomal dominant polycystic kidney disease is the most common inherited kidney disease and accounts for 7–10% of all patients on renal replacement therapy worldwide. Although first reported 500 years ago, this disorder is still regarded as untreatable and its pathogenesis is poorly understood despite much study. During the past 40 years, however, remarkable advances have transformed our understanding of how the disease develops and have led to rapid changes in diagnosis, prognosis, and treatment, especially during the past decade. This Review will summarise the key findings, highlight recent developments, and look ahead to the changes in clinical practice that will likely arise from the adoption of a new management framework for this major kidney disease.

Epidemiology and economic burden

ADPKD affects all ethnic groups and is a major cause of chronic kidney disease, accounting for 7–10% of patients with end-stage renal disease. ADPKD is the fourth most common cause for renal replacement therapy (RRT) worldwide. The incidence rates for end-stage renal disease caused by ADPKD vary widely between countries, ranging from 4.8 (in Japan) to 7.9 (in USA) and from 3.9 to 15.3 (in Europe) cases per million population per year.

On the basis of landmark epidemiological studies performed in Copenhagen, Denmark, and in Olmsted County, MN, USA, the risk of developing ADPKD by the age of 80 years has been estimated to be between 1 in 400 and 1 in 1000. Subsequent studies have reported different prevalence rates, ranging from 1 in 543 to 1 in 4000 in European, Japanese, and other populations (appendix p 7). Differences in geographical area, duration of observation, sources of ascertainment, diagnostic criteria, family screening policy, population size studied, and health system characteristics probably explain such different results. The estimated prevalence numbers are much lower than those obtained from autopsy studies, which are less than 1 in 500 (1 in 339 to 1 in 492), suggesting that a significant number of affected individuals remain undiagnosed during life.

As in other causes of chronic kidney disease, the costs linked to ADPKD vary significantly according to baseline kidney function. In a retrospective US study the mean annual medical charges (unadjusted) increased from US$24 497 in patients with ADPKD and a baseline estimated glomerular filtration rate (eGFR) of greater than 90 mL/min to $134 784 in those with baseline eGFR of greater than 15 mL/min. According to the European Renal Association and European Dialysis and Transplant Association (ERA-EDTA) registry data, in 2010–2011 patients with ADPKD were receiving RRT in 12 European countries with 208 million inhabitants (representing about 40% of the total population of the 27 European Union [EU] countries). By extrapolation, an estimated 21 000 patients with ADPKD were receiving RRT in Europe, representing about 40% of the total population of the 27 European Union [EU] countries. By extrapolation, an estimated 21 000 patients with ADPKD were receiving RRT in Europe, representing about 40% of the total population of the 27 European Union [EU] countries.
The existence of re-analysis of purported cases. Genetic testing is not negative or equivocal scans, very early-onset cases in assessment of potential living related kidney donors with PKD1 challenges of analysing for 80–85% of patients and PKD2 accounts Mutations in two genes cause ADPKD. Diagnosis: how and when to test?

In clinical practice, genetic testing is restricted to the and, hence, the high cost. PKD1 to chromosome 16 PKD2 to chromosome 4 PKD1 (European PKD Consortium) PKD2 Identification of PKH1 Total kidney volume reported to be a marker of disease progression (CRISP consortium) First clinical trials in ADPKD with mammalian target of rapamycin inhibitors First successful trial in ADPKD with tolvaptan (TEMPO3/4 study) Second successful trial in ADPKD with octreotide (ALADIN study); completion of HALT-PKD trials estimated 50 000 patients with ADPKD were on RRT in the 27 EU countries, representing a cost of €1·5 billion per year. Additional costs not included in this analysis include the extra medical care needed for outpatient care and hospital admissions for common disease complications or associated comorbid disorders.

Diagnosis: how and when to test?

Genetics and imaging

Mutations in two genes cause ADPKD. PKD1 accounts for 80–85% of patients and PKD2 accounts for 15–20%. The existence of PKD3 has been largely excluded after re-analysis of purported cases. Genetic testing is not done as part of standard care because of the technical challenges of analysing PKD1 and, hence, the high cost. In clinical practice, genetic testing is restricted to the assessment of potential living related kidney donors with negative or equivocal scans, very early-onset cases in neonates (because of the high recurrence rate [45%] for subsequent pregnancies), and atypical presentations, especially in patients with a negative family history (6–8% are de-novo mutations). As a result, ADPKD is still diagnosed on the basis of ultrasound, with widely accepted age-banded diagnostic criteria derived from the analysis of patients with a positive family history and a clear genetic diagnosis of PKD1 or PKD2 mutations. Advances in renal imaging (MRI and high-resolution ultrasound) might help with disease exclusion in at-risk individuals. The availability and demand for genetic testing is likely to change for several reasons. First, technological advances in genome sequencing have resulted in the development of automated high-throughput tests, which are cheaper. Second, clear genotype–phenotype correlations for the onset of end-stage renal disease have emerged. A simple clinical scoring system based on genotype and phenotype could guide patient management by predicting individual risk. Third, the approval of new drugs for treatment of this disease might spur demand for testing if test results could guide decisions about who should be treated. Additionally, presymptomatic testing in younger at-risk individuals might be advocated especially if early treatment can be shown to be beneficial. Finally, demand for pre-implantation genetic diagnosis in family planning might increase to prevent disease transmission.

A clear genetic diagnosis is available in about 90% of patients tested. Nonetheless, testing should always be done with adequate counselling, ideally with the involvement of clinical geneticists. In 30% of patients with PKD1 mutations, a non-truncating change will be identified that necessitates the careful assessment of its pathogenicity. Compound heterozygous and digenic inheritance have been reported in children with very early-onset ADPKD, suggesting the need to screen for mutations in other cystic genes in addition to the familial mutation in these pedigrees. Conversely, hypomorphic alleles could be associated with mild or late-onset disease being misdiagnosed as simple cysts. Only more widespread adoption of genetic testing will reveal the full phenotypic spectrum of ADPKD in the general population.

ADPKD in children

In the absence of specific treatments, the screening of asymptomatic children with a positive family history is not recommended. Very early-onset ADPKD (under 2 years of age) is rare (occurring in 1–2% of affected children) and might phenocopy autosomal recessive polycystic kidney disease. In these cases, full genetic assessment is advised. A wide range of clinical manifestations has been reported in affected children, not necessarily linked to renal cyst burden. However, the early detection and treatment of hypertension, ideally with angiotensin-converting enzyme (ACE) inhibitors, is important because of increased left ventricular hypertrophy and lower kidney function in those with blood pressures above the 75th percentile. Screening for hypertension in all at-risk children from the age of 5 years might be a pragmatic approach. A clinical trial in 110 children and young adults (aged 8–22 years) with ADPKD taking lisinopril reported that the addition of pravastatin was associated with slower renal and cardiac disease progression.
Prognosis: identifying rapid and slow progressing patients

ADPKD usually develops over many decades with overall renal function remaining normal as a result of compensatory hyperfiltration by functioning nephrons despite the presence of thousands of microcysts. Progressive rapid deterioration characterised by fibrotic and inflammatory changes is seen in the later stages of the disease.\(^\text{13}\) Accurate risk prediction is an important goal because timely identification of patients with progressive disease could allow patients to receive new treatments early in the disease course and enable patients with early disease to enter clinical trials.

The major factors predicting disease progression in ADPKD are genotype, age, sex, kidney function (eGFR), and total kidney volume (TKV; measured by MRI or CT; figure 1). Several cohort studies have shown that genotype can predict the age of onset of end-stage renal disease, so patients could be stratified into three risk groups.\(^\text{12,35}\) Patients with \(\text{PKD2}\) mutations have the best outlook, those with \(\text{PKD1}\) non-truncating mutations have an intermediate outcome, and patients with \(\text{PKD1}\) truncating mutations have the worst outlook. Younger patients (<30 years) might benefit the most from information regarding their genotype but genotype alone cannot account for individual or intrafamilial variability.\(^\text{46}\) Studies of concordance in end-stage renal disease between identical twins and non-identical siblings have shown that genetic background has a key role.\(^\text{47}\) Several environmental factors have been linked to disease progression from small cohort studies, but these need to be validated in larger populations.\(^\text{48}\)

According to longitudinal studies from the Consortium for Radiologic Imaging Studies in Polycystic Kidney Disease (CRISP), TKV is an early and accurate measure of individual cystic burden and likely growth rate trajectory at a stage when eGFR is well preserved (>60 mL/min/1.73 m\(^3\)).\(^\text{39}\) Baseline TKV correlates with genotype and a height-adjusted TKV of at least 600 mL/m\(^3\) predicts progression to stage III chronic kidney disease within 8 years with 74% sensitivity and 75% specificity.\(^\text{39,49}\) On the basis of these results, the annual rate of change in TKV has been adopted as a surrogate endpoint for eGFR decline and as the primary outcome measure in several major clinical trials. Nevertheless, before TKV measurements become part of routine clinical care, a standardised protocol, ideally one that is rapid and semi-automated, needs to be developed and adopted internationally. A simple estimation of TKV based on the ellipsoid equation using measurements from MRI or CT has been proposed to help with the selection of patients for clinical trials or for treatment.\(^\text{49}\) However, this equation does not perform as well in patients with preserved eGFR, is insufficiently sensitive to measure longitudinal changes in TKV, and cannot be applied to patients with atypical cystic disease. An individual risk score combining genetic, clinical, and imaging information might prove the most accurate way of predicting long-term outcome.\(^\text{50}\)

Additional prognostic information might be gained from measurements of total cyst volume by gadolinium-enhanced MRI\(^\text{42}\) and hypo-enhanced non-cystic intermediate compartment volume on CT.\(^\text{13}\) However, their wider adoption could be limited by the need for contrast enhancement or radiation exposure.

Pathophysiology and treatment

Cystic cells are characterised by a complex cellular phenotype that includes changes in proliferation, apoptosis, fluid secretion, apico-basal polarity, directional cell migration, matrix abnormalities, and cilia or centrosomal fidelity (figure 2).\(^\text{44,50}\) Additionally, there are many aberrant signalling pathways that alter cyst growth (appendix p 2).\(^\text{50,55}\) Since, with some exceptions, a direct link between many phenotypic or signalling changes and polycystin dysfunction has not been shown, it remains unclear whether the changes detected are primary (cyst initiation) or secondary (cyst expansion). Here, we discuss evidence that ADPKD is a disease of primary cilia (ciliopathy) and highlight data for the mTOR and cAMP pathways—two pathways that have been studied in particular detail in ADPKD.

ADPKD as a ciliopathy

\(\text{PKD1}\) encodes polycystin-1 (PC1), which interacts with the \(\text{PKD2}\) gene product, polycystin-2 (PC2; also known as TRPP2), a non-selective calcium-permeable channel of the transient receptor potential (TRP) family.\(^\text{54}\) The extracellular domain of PC1 is cleaved at T\(_{3049}\), a G-protein-coupled receptor proteolytic cleavage site, yielding fragments that remain non-covalently attached to each other; mutations that prevent cleavage cause disease in mice and human beings.\(^\text{55,59}\) The C-terminal domain of PC1 can translocate to the nucleus, where it

![Figure 1: Factors relevant to the prediction of disease progression in autosomal dominant polycystic kidney disease](https://www.thelancet.com)

Genotype (locus and allele), age, and sex are the major determinants of baseline total kidney volume, which, in turn, has high specificity and sensitivity in predicting long-term estimated glomerular filtration rate (eGFR) decline and ultimately end-stage renal disease.\(^\text{13}\) The effect of other gene modifiers,\(^\text{44}\) race, disease complications, environmental factors, or biological factors on total kidney volume or eGFR are shown by the dotted lines.
acts as a coactivator of gene transcription.60 Both PC1 and TRPP2 localise to primary cilia, which trigger intracellular Ca²⁺ transients upon mechanical stimulation.61 Although elimination of PC1/TRPP2 prevents these Ca²⁺ transients, PKD1L1/PKD2L1 complexes, but not PC1/TRPP2, mediate Ca²⁺ entry into the ciliary axoneme.62,63 However, deletion of the PKD1L1/PKD2L1 homologues in mice is not associated with cystic kidney disease, challenging the idea that cilia transmit Ca²⁺ signals via PC1/TRPP2 complexes to prevent cyst formation.

Considering the evolution of cilia alongside multicellular organisms, the association between cilia and long-range signalling networks that create tissues of defined architecture, including SHH64 and Wnt signalling, is unsurprising.65 Cilia have been implicated in cell cycle control,66 and loss of ciliary functions could contribute to the increased proliferation rates reported in animal cysts and human ADPKD.67 However, ciliary proteins including PC1/TRPP2 are also seen in cellular compartments outside the cilium and have been implicated in diverse functions, such as cell adhesion, DNA damage responses, and metabolism (figure 2).

Although cilia seem superfluous in differentiated adult tissues,69 ischaemic injury that requires proliferative repair responses triggers cyst formation in kidneys lacking cilia. Thus, cilia might have different roles at different developmental stages, organising tissues by directing cell division and migration during embryogenesis, while integrating metabolic states and damage responses to initiate cell-fate decisions in differentiated tissues.70,71

Figure 2: Concepts of cyst formation in autosomal dominant polycystic kidney disease

(A) Loss of heterozygosity with somatic mutation of the second allele (−/−), in addition to the inherited germline mutation (+/−), reduces the critical dose of polycystin-1/TRPP2. Non-autonomous effects might include normal cells with only the germline mutation (+/−) in cyst formation. De-differentiation with persistent cilia and reactive changes in the surrounding tissue were reported several decades ago.68 (B) G-protein-coupled receptor (GPCR)-dependent production of cAMP stimulated by antidiuretic hormone (ADH)/vasopressin-2-receptor and likely other GPCRs react to substances contained in the cyst fluid. Increased cAMP concentrations result in activation of protein kinase A (PKA)-dependent gene activation and cAMP-sensitive ion channels that secrete ions and enable cystic fluid accumulation. (C) Cilia cooperate with the non-canonical branch of the Wnt signalling cascade to orient tubular epithelial cell division and migration along the longitudinal axis (solid blue line) of the nephron, involving developmental programmes such as collective cell migration, cell intercalation and rosette formation, and oriented cell division. (D) PKD1/PKD2 mutations affect ciliary signalling and basolateral trafficking, leading to abnormal intracellular cargo transport, resulting in mislocalisation of growth receptors and ion channels and altered cell metabolism. A compromised Ca²⁺ homeostasis probably involving the endoplasmic reticulum (ER) and mitochondria might change the threshold for apoptotic and DNA damage responses and prevent tumour formation in ADPKD despite a heightened cellular activation. Whereas cell–cell contacts decrease, the integrin-dependent adhesion to the extracellular matrix increases. DDR=DNA damage response. TJ=tight junction.
mTOR pathway
An abnormality almost universally associated with different forms of cystic kidney disease is activation of the mTOR pathway, a protein kinase complex that promotes anabolic programmes in response to nutrients, growth factors, and cellular energy levels (appendix p 3). mTOR consists of two components, mTORC1 and mTORC2, which differ in their subunit composition and susceptibility to rapamycin. Extracellular stimuli trigger mTORC1 through two different pathways: the insulin receptor/insulin-like growth factor receptor pathway, which activates PI3K and Akt; or growth factors and G-protein-coupled receptors that converge on the Ras-Erk pathway (appendix p 3). Both pathways phosphorylate TSC2, which functions as a GTPase-activating protein and maintains Rheb in an inactive, GDP-bound state. Assembly of Rag GTPases on endosomal and lysosomal membranes and recruitment of the mTORC1 complex to this location suggests that aminoacids in late endosomes or lysosomes control mTORC1 activation.72 Cystic ADPKD cells have to display a so-called high nutrient state because in the absence of aminoacids overriding pathways block mTORC1.

Inhibition of the mTORC1 complex by rapamycin or everolimus potently suppresses cyst growth in rodents with cystic kidney disease (appendix pp 8–11). Everolimus reduced TKV in patients with ADPKD but failed to improve renal function in patients with advanced disease. In patients with more preserved renal function, rapamycin did not affect TKV, but did improve eGFR.20 In 2014, a pilot study reported the improvement of renal function in patients given low-dose rapamycin.73

cAMP signalling
Increased concentrations of cAMP have been noted consistently in cell models of cystic kidney disease and animals with the disease. Although many different signalling pathways converge on cAMP production, vasopressin (also known as antidiuretic hormone) through activation of collecting duct vasopressin-2 (V2) receptors seems to be the major source of renal cAMP. This notion is supported by the beneficial effect of V2R antagonists in animals with cystic kidney disease (appendix pp 8–11). The TEMPO 3/4 trial15 compared the efficacy of the vasopressin V2 receptor inhibitor tolvaptan with placebo in ADPKD patients with a mean eGFR of 82 mL/min/1.73 m² and reported that tolvaptan reduced the increase in TKV and slowed the decline in renal function (eGFR; figure 3). A cost-effectiveness analysis calculated that tolvaptan could delay the onset of end-stage renal disease by 2·6 years.74 Tolvaptan was deferred by the end-stage renal disease by 6·5 years, and increase life expectancy by 2·6 years.74 Since both AC5 and AC6 are inhibited by cytoplasmic Ca²⁺, a decrease of intracellular Ca²⁺ would result in increased cAMP production. Although AC5 is only expressed in intercalated cells, AC6 is expressed in both intercalated and principal cells.8 Deletion of AC6 results in a substantial improvement of cyst growth and survival in Pkd1-deficient mice,7 suggesting that AC6 has a central role in ADPKD.8 Phosphodiesterases degrade cAMP and return cAMP concentrations to normal and a regulatory role for the calcium-inhibited isoform phosphodiesterase 1 in cyst growth has been reported.20 It is unclear which of the pathways promotes cAMP production and cAMP-mediated cyst growth (figure 2). Evidence that both mTORC1 activation and cAMP production can occur at endosomal membranes is intriguing because both pathways could be linked to abnormalities in cell polarity and vesicle trafficking.29 PKA has also been shown to activate PC2/TRPP2 directly in endosomes, a process regulated by PCl.80 Increased cAMP concentrations stimulate fluid secretion and promote actin depolymerisation at focal adhesions, resulting in abnormal polarisation and cellular de-differentiation.

Non-specific interventions to slow disease progression
Arterial hypertension occurs in more than 60% of patients with ADPKD before a noticeable loss in renal function. The probable cause of ADPKD-related hypertension is multifactorial, but the renin-angiotensin aldosterone system probably plays an important part.81 In the HALT PKD clinical trials,82,83 ACE inhibition (ACEI) was compared with combined ACEI/angiotensin receptor blockade. Although the trial did not identify statistically significant benefits on eGFR decline for an ACEI/angiotensin receptor blockade combination, lower target blood pressures (≤110/75 mm Hg) were associated with a slower increase in TKV and a greater reduction in left-ventricular mass and urinary albumin (figure 3A).84,85 The slower TKV increase in the lower blood pressure group was not associated with improved renal function, possibly because of a higher proportion of PKD2 mutations in this group (19·8% vs 13·1%). Additionally, HALT PKD noted that dual renin-angiotensin-aldosterone system blockade was safe in patients with ADPKD with an eGFR of 30 mL/min/1.73 m² or higher.

Preclinical models and novel targets
The use of models has contributed substantially to our understanding of polycystin function, cystic pathogenesis, and the identification of novel therapeutic compounds.86 However, rodent PKD models have been the mainstay for preclinical testing with an increasing focus on adult orthologous models, such as Pkd1 mice with homozygote deletions of hypomorphic alleles or an inducible Cre-Lox
system to delete Pkd1 in the kidney at different postnatal stages (appendix pp 8–11).82 The main endpoint used has been bilateral kidney weight normalised for bodyweight and few studies have compared overall survival. Differences in pharmacodynamics, the use of non-standardised readouts, the use of different animal models, and publication bias represent major obstacles in translating in-vivo preclinical results into ADPKD therapies.83 Standardisation of both animal models and readouts will be important. Another important issue to consider when transferring preclinical results into human trials is that most therapeutic interventions were initiated early in the disease before cyst formation and irreversible damage occur.84,85

A comparison across different treatment protocols suggests that modification of epigenetic and proapoptotic programmes, cell cycle progression, or inflammation could represent other important therapeutic targets (figure 3B). The dysregulation of common signalling pathways by very different gene mutations offers the opportunity to target common pathways despite genetic heterogeneity. Surprisingly, attempts to inhibit MAP kinase signalling have had mixed results and even caused an increase in cyst growth. These findings suggest that selective inhibition of one pathway could switch on other growth pathways, resembling the so-called bypass track that occurs after selective inhibition of oncogenic drivers in cancer.84,85 Since the incidence of renal cell carcinoma is not increased in ADPKD,86 stress responses, including DNA damage responses and initiation of proapoptotic programmes, seem to curtail tightly the cellular overactivity of cyst cells. In some instances, inhibitors that block cell cycle progression or promote apoptosis might initiate cell-fate decisions that are otherwise controlled by cilia. In view of the concurrent activation of various pathways or the release of negative feedback loops, or both, combinatorial or sequential drug regimens are likely to be better than single-drug regimens for controlling

Figure 3: Effect of therapeutic interventions on cyst progression in human trials and cystic kidney disease in rodents
(A) Changes in total kidney volume (TKV) and improvement of renal function (gain in estimated glomerular filtration rate [eGFR] in mL/min/1·73 m² per year) of clinical trials involving 100 or more patients with autosomal dominant polycystic kidney disease (ADPKD). Reductions in TKV and changes in eGFR that were significantly different from baseline values are denoted by an asterisk (p<0·05). (B) Mean changes in kidney weight (KW) corrected for bodyweight (BW) and SDs were calculated from published studies in rodents (appendix pp 8–11). (C) Baseline mean eGFR of the placebo group of recent trial ADPKD subgroups plotted against their mean age. The shaded areas show eGFR thresholds 60, and 90 mL/min/1·73 m² and the black diamonds show normal eGFR (100 mL/min/1·73 m² at age 16 years) and end-stage renal disease (<15 mL/min/1·73 m² at age 55 years). We define disease as subclinical (if eGFR >90 mL/min/1·73 m²), manifest (if eGFR >60 mL/min/1·73 m²), or late (if eGFR <60 mL/min/1·73 m²). (D) Baseline mean TKV of the placebo group of recent ADPKD trials plotted against their mean age shows that most patients already had substantial increases in TKV at baseline before treatment. The dashed horizontal line shows a mean TKV averaged for healthy males and females of 350 mL. n=number of patients exposed to the therapeutic interventions. BP=blood pressure. *p<0·05. †TKV changes were statistically different after 12 months but not after 24 months. ‡Patients received tolvaptan. §Patients received a combination of an angiotensin-converting-enzyme inhibitor (lisinopril) and an angiotensin receptor blocker (telmisartan). ¶Reference categories correspond to those in the table on appendix pp 8-11.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Baseline eGFR (mL/min/1·73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>40</td>
<td>100</td>
</tr>
<tr>
<td>60</td>
<td>150</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Change in TKV (% per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>-1</td>
</tr>
<tr>
<td>40</td>
<td>-2</td>
</tr>
<tr>
<td>60</td>
<td>-3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Change in eGFR (mL/min/1·73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>0.5</td>
</tr>
<tr>
<td>40</td>
<td>1</td>
</tr>
<tr>
<td>60</td>
<td>1.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Changes in KW/BW (% per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>-0.5</td>
</tr>
<tr>
<td>40</td>
<td>-1</td>
</tr>
<tr>
<td>60</td>
<td>-1.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Changes in TKV (% per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>-0.5</td>
</tr>
<tr>
<td>40</td>
<td>-1</td>
</tr>
<tr>
<td>60</td>
<td>-1.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Changes in KW/BW (% per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>-0.5</td>
</tr>
<tr>
<td>40</td>
<td>-1</td>
</tr>
<tr>
<td>60</td>
<td>-1.5</td>
</tr>
</tbody>
</table>

long-term cyst growth. Nonetheless, since any treatment is likely to be lifelong, the long-term safety and tolerability of a drug or regimen is an important consideration.56

Looking ahead

Future trial design

The correlation between eGFR, TKV, and age suggests that most clinical trials in ADPKD have been undertaken in patients with manifest or late disease (figure 3C, D). Thus, future clinical trials need to have a greater focus on patients with subclinical disease (ie, eGFR >90 mL/min/1·73 m²). The predicted loss in renal function depends largely on TKV, which probably captures other risk factors for rapid disease progression (figure 1).43 In a small series of patients with ADPKD, several serum and urinary proteins were reported to be raised and have been proposed as surrogate markers to assess ADPKD disease progression.43,87 Although most biomarkers correlate with eGFR, whether these markers can predict disease progression more accurately than serial serum creatinine measurements is unknown.

TKV has been the primary endpoint in recent clinical trials,12–17,42 but its value as a surrogate variable for renal function has been debated. The decline in eGFR in adults with ADPKD (as seen in control groups in some studies12–14,88) averaged 2·3–3·7 mL/min/1·73 m² per year, whereas the maximum statistically significant gain in renal function was 1·0 mL/min/1·73 m² per year. However, such apparently small benefits can translate into a meaningful extension of time to end-stage renal disease and overall survival (figure 3), and can help to ameliorate the disabling symptoms of nephromegaly. In manifest disease (eGFR 60–90 mL/min/1·73 m²), serially measured GFR by iohexol clearance could detect smaller changes in renal function requiring smaller sample sizes (eg, as shown by the ALADIN trial).5 In late disease (eGFR <60 mL/min/1·73 m²), the use of changes in eGFR as a primary endpoint will greatly simplify future ADPKD trials.88 In both instances, TKV measurements could be used to identify patients at risk of faster disease progression.50

Harmonising standards: what should be standard care?

Despite the scientific and medical advances in ADPKD research, significant differences between and within countries in terms of clinical care remain (ie, diagnostic modalities, initial assessment, models of care, treatment, and modalities of RRT). The absence of consensus and of internationally agreed best practice guidelines stimulated the organisation of the first KDIGO (Kidney Disease–Improving Global Outcomes)

---

**Figure 4:** Roadmap to improve clinical management in autosomal dominant polycystic kidney disease

Specific action points are listed in appendix p 5. ADPKD=autosomal dominant polycystic kidney disease. SME=small or medium enterprise.
Controversies Conference on ADPKD in 2014, which brought together a panel of multidisciplinary clinical experts and patients from 20 countries. Areas of consensus, gaps in knowledge and research, and health-care priorities related to ADPKD were identified and form the basis of a roadmap to improve the present and future management of ADPKD patients and of future research (figure 4). A model of how this could be delivered within a national health system (eg, the UK) is outlined, based on a hub and spoke framework (appendix p 4).

**Improving care: what do patients want?**

The development and expansion of the role of patient advocates and patient organisations in the prioritisation, organisation, and delivery of health care and research is gaining importance on health agendas. Increasingly, the question being asked is, what do patients want? For ADPKD, the work of the PKD Foundation and PKD International are models for positive patient–physician partnerships in initiating patient support groups, fundraising, and lobbying for the disease within major health-care systems. Other potential benefits of greater patient involvement are the development of more effective educational materials, better measures of patient-reported outcomes, increased participation in clinical studies, and improved individual outcomes through peer support, ownership, and self-care.

**Integrating research across borders: working together**

Within the EU, initial attempts to harmonise research efforts between different member states have begun with the creation of both clinical and scientific networks to promote ADPKD research—eg, the ERA-EDTA EuroCYST initiative, the EU-funded Marie Curie Initial Training Network TranCYST, and the ERA-EDTA Working Group for Inherited Kidney Diseases. The ERA-EDTA has an established patient registry that offers the opportunity to collect data from all patients receiving RRT in the EU, a total population of 500 million. An expanded role for the registry could offer the opportunity to collect data from all patients receiving RRT in the EU, a total population of 500 million. An expanded role for the registry could offer the opportunity to collect data from all patients receiving RRT in the EU, a total population of 500 million. An expanded role for the registry could offer the opportunity to collect data from all patients receiving RRT in the EU, a total population of 500 million. An expanded role for the registry could offer the opportunity to collect data from all patients receiving RRT in the EU, a total population of 500 million. An expanded role for the registry could offer the opportunity to collect data from all patients receiving RRT in the EU, a total population of 500 million. An expanded role for the registry could offer the opportunity to collect data from all patients receiving RRT in the EU, a total population of 500 million. An expanded role for the registry could offer the opportunity to collect data from all patients receiving RRT in the EU, a total population of 500 million.

**Contributors**

All authors discussed the overall plan of the Review. OD wrote the section about epidemiology and economic burden and harmonising standards; ACMO wrote the section about diagnosis, prognosis, and looking ahead; and GW wrote the section about pathophysiology and treatment. ACMO initiated the proposal and was responsible for putting together the final submission. All authors participated in the revision and approved the final draft.

**Members of the Board of the ERA-EDTA Working Group for Inherited Kidney Diseases**

Rene Bindels, Carsten Boeger, Olivier Devuyst (President), Francesco Emma (Secretary), Nina V Knors, Ron T Gansevoort, Patrick H Maxwell, Albert C M Ong, Giuseppe Remuzzi, Franz Schaefer, and Roser Torra.

**Declaration of interests**

The authors have received consultancy fees from Otsuka Corporation (ACMO, OD, BX, GW), Pfizer (ACMO), Raptor (BX), Roche (BX), Amgen (BX), Genzyme (BX), and Advicenne (BX). ACMO, OD, and GW are steering group members of the EuroCYST Consortium; ACMO and OD are board members of TranCYST; and OD is a member of the Rare Disease Initiative Zürich (radiZ) KFSP of the University of Zurich. Research in the authors’ laboratories is supported by the ERA-EDTA (EuroCYST to ACMO, OD, GW); European Union (EU-FP7/2007–2013 grant agreement number 317246 and TranCYST [ACMO and OD]; FP7/2007–2013 grant agreement number 305608 and EURenOmics [OD]); Kidney Research UK (ACMO); Medical Research Council (ACMO); Fonds National de la Recherche Scientifique and the Fonds de la Recherche Scientifique Médicale (OD); the Swiss National Science Foundation project grant 310030–146490 (OD); Association pour l’Information et la Recherche sur les Maladies Rénales Génétiques (BX); Fondation Maladies Rares (BX); and Deutsche Forschungsgemeinschaft SFB 1140 (GW).

**Acknowledgments**

We thank Vicente Torres and board members of the Working Group for Inherited Kidney Diseases, EuroCYST Consortium, and TranCYST Network for advice and helpful discussions.

**References**


2002


