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Autosomal dominant polycystic kidney disease: the changing face of clinical management

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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.

Introduction

The appearance and pathophysiology of polycystic kidneys have fascinated physicians and scientists alike since they were first described (panel). The first clear report of polycystic kidneys dates to the 16th century when anatomy was on the rise as a medical discipline.[1] At a time when liver hydatid disease was common, false hydatids of the kidney were recognised post mortem.[1] Early pathological descriptions of autosomal dominant polycystic kidney disease (ADPKD) as cystic degeneration or cystic transformation of the kidney led to many theories of cyst pathogenesis. The recognition of ADPKD as a familial disorder and of its clinical presentation were major milestones that led, in turn, to the eventual identification of *PKD1* and *PKD2* (panel).

Despite this progress, ADPKD is still regarded as untreatable, progressing relentlessly towards end-stage renal disease. This Review will focus on advances in diagnosis, prognosis, aetiology, and treatment in the study and management of this major kidney disease over the past decade. We believe that the time has come to revise current models for managing patients with ADPKD. Because of space limitations, the management of several important extrarenal complications is not discussed in detail and the reader is referred to other excellent reviews.[18–21]

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) world-wide.[18,19] 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,[3] and in Olmsted County, MN, USA,[22] 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),[3,23] 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.[24] According to the European Renal Association and European Dialysis and Trans-plant Association (ERA-EDTA) registry data, in 2010, 21 000 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

Search strategy and selection criteria

We searched PubMed and Medline for articles written in English with search terms that included but were not limited to "polycystic kidney disease", "ADPKD", and "cystic diseases". We considered reports published until Dec 1, 2014. We identified references from our own experience and those recommended by others in the specialty. Because of space limitations, we chose to select references within the past 5 years but did not exclude commonly referenced and highly regarded older publications. Review articles are cited to provide readers with more details and references than this Review has room for.

1585: Autopsy of Stefan Bathory, King of Poland (Zigulitz and Buccella)[1]

1757: Clinical descriptions of three patients (Galeazzi)[2]

1793: False hydatids of the kidney described (Baillie)[1]

1829: Cystic transformation reported (Cruveilheir)[1]

1841: Cystic degeneration recognised (Rayer)[1]

1888: Polycystic kidneys recognised as a clinical entity (Lejars)[1]

1899: Autosomal dominant transmission recognised in families (Steiner)[1]

1934: Autosomal recessive transmission recognised in children (Marquand)[1]

1957: Epidemiological study reveals incidence of one in 1000 (Dalgaard)[3]

1969: Human autosomal dominant polycystic kidney disease (ADPKD) cysts show active solute transport (Gardner)[4]

1985: Linkage of *PKD1* to chromosome 16[5]

1989: cAMP-dependent fluid secretion in human ADPKD cysts[6]

1993: Linkage of *PKD2* to chromosome 4[7]

1994: Identification of *PKD1* (European PKD Consortium)[8]

1996: Identification of *PKD2*[9]

2002: Identification of *PKHD1*[10]

2006: Total kidney volume reported to be a marker of disease progression (CRISP consortium)[11]

2010: First clinical trials in ADPKD with mammalian target of rapamycin inhibitors[12,13]

2012: First successful trial in ADPKD with tolvaptan (TEMPO3/4 study)[14]

2014: Second successful trial in ADPKD with octreotide (ALADIN study)[15]; completion of HALT-PKD trials[16,17]

estimated 50 000 patients with ADPKD were on RRT in the 27 EU countries, representing a cost of €1·5 billion per year.[25] 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%.[19] The existence of *PKD3* has been largely excluded after re-analysis of purported cases.[26] 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,[27] very early-onset cases in neonates (because of the high recurrence rate [45%] for subsequent pregnancies),[28] 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 patents with a positive family history and a clear genetic diagnosis of *PKD1* or *PKD2* mutations.[29] Advances in renal imaging (MRI and high-resolution ultrasound) might help with disease exclusion in at-risk individuals.[30]

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.[31] Second, clear genotype–phenotype correlations for the onset of end-stage renal disease have emerged.[32] 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.[33] Nonetheless, testing should always be done with adequate counselling, ideally with the involvement of clinical geneticists.[27] In 30% of patients with *PKD1* mutations, a non-truncating change will be identified that necessitates the careful assessment of its pathogenicity.[33] 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.[34,35] Conversely, hypomorphic alleles could be associated with mild or late-onset disease being misdiagnosed as simple cysts.[36] 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.[37] 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.[38] In these cases, full genetic assessment is advised. A wide range of clinical manifestations has been reported in affected children,[39] not necessarily linked to renal cyst burden.[40] 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.[41] Screening for hypertension in all at-risk children from the age of 5 years might be a pragmatic approach.[37] 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.[42]

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.[11] 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.[32,45] Patients with *PKD2* mutations have the best outlook, those with *PKD1* non-truncating mutations have an intermediate outcome, and patients with *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.[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.[47] Several environmental factors have been linked to disease progression from small cohort studies, but these need to be validated in larger populations.[43]

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 m²).[11] Baseline TKV correlates with genotype and a height-adjusted TKV of at least 600 mL/m predicts progression to stage III chronic kidney disease within 8 years with 74% sensitivity and 75% specificity.[48,49] 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.[50] 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.[51]

Additional prognostic information might be gained from measurements of total cyst volume by gadolinium-enhanced MRI[52] and hypo-enhanced non-cystic intermediate compartment volume on CT.[53] 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).[54,55] Additionally, there are many aberrant signalling pathways that alter cyst growth (appendix p 2).[56,57] 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

PKD1 encodes polycystin-1 (PC1), which interacts with the *PKD2* gene product, polycystin-2 (PC2; also known as TRPP2), a non-selective calcium-permeable channel of the transient receptor potential (TRP) family.[54] The extracellular domain of PC1 is cleaved at T³⁰⁴⁹, 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.[58,59] The C-terminal domain of PC1 can translocate to the nucleus, where it
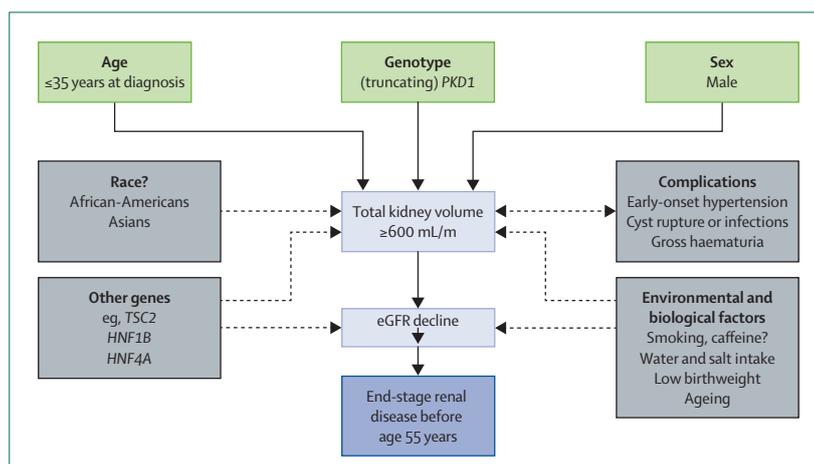

***Figure 1:* Factors relevant to the prediction of disease progression in autosomal dominant polycystic kidney disease**
Genotype (locus and allele), age, and sex are the major determinants of baseline total kidney volume, which, in turn, has high specificity and sensitivity in predicting long-term estimated glomerular filtration rate (eGFR) decline and ultimately end-stage renal disease.[43] The effect of other gene modifiers,[44] race, disease complications, environmental factors, or biological factors on total kidney volume or eGFR are shown by the dotted lines.
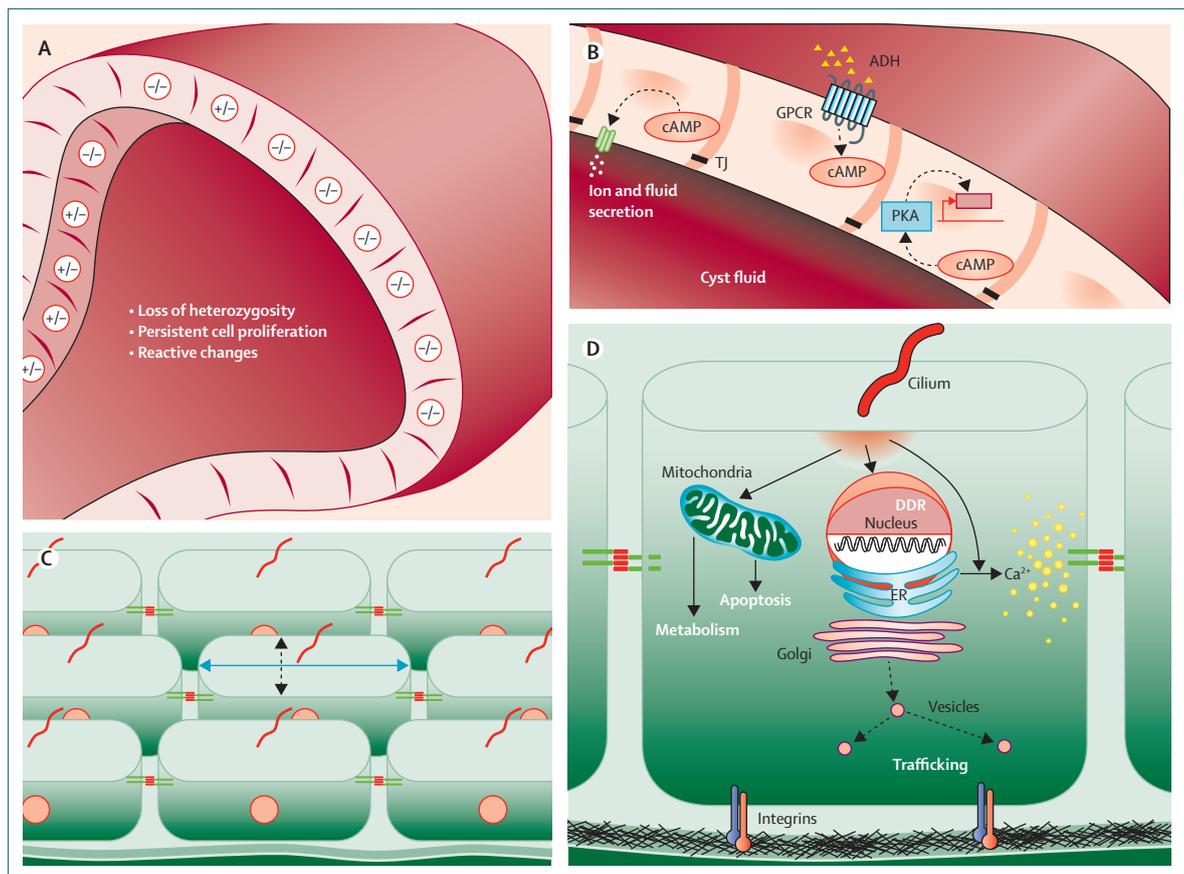
Figure 2: Concepts of cyst formation in autosomal dominant polycystic kidney disease

(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 cell proliferation 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⁺ homoeostasis 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.

acts as a coactivator of gene transcription.[60] Both PC1 and TRPP2 localise to primary cilia, which trigger intracellular Ca^{2+} transients upon mechanical stimulation.[61] Although elimination of PC1/TRPP2 prevents these Ca^{2+} transients, PKD1L1/PKD2L1 complexes, but not PC1/TRPP2, mediate Ca^{2+} 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 Ca^{2+} 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 SHH[64] 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]

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.[12] 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 (V_2) receptors seems to be the major source of renal cAMP. This notion is supported by the beneficial effect of V_2R antagonists in animals with cystic kidney disease (appendix pp 8–11). The TEMPO 3/4 trial[14] compared the efficacy of the vasopressin V_2 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 6·5 years, and increase life expectancy by 2·6 years.[74] Tolvaptan was deferred by the US Food and Drug Administration but is currently approved in Japan and recommended for approval by the regulatory agencies in Canada and Europe for the treatment of patients with ADPKD.

Increased cAMP concentrations in patients with ADPKD have consistently been linked to abnormal Ca^{2+} homoeostasis and reduced intracellular Ca^{2+} concentrations.[75] Since both AC5 and AC6 are inhibited by cytoplasmic Ca^{2+}, a decrease of intracellular Ca^{2+} would result in increased cAMP production. Although AC5 is only expressed in intercalated cells, AC6 is expressed in both intercalated and principal cells.[76] Deletion of AC6 results in a substantial improvement of cyst growth and survival in Pkd1-deficient mice,[77] suggesting that AC6 has a central role in ADPKD.[76] 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.[78] 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.[79] PKA has also been shown to activate PC2/TRPP2 directly in endosomes, a process regulated by PC1.[80] Increased cAMP concentrations stimulate fluid secretion[6] 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,[16,17] 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).[16,17] 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.[54] 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
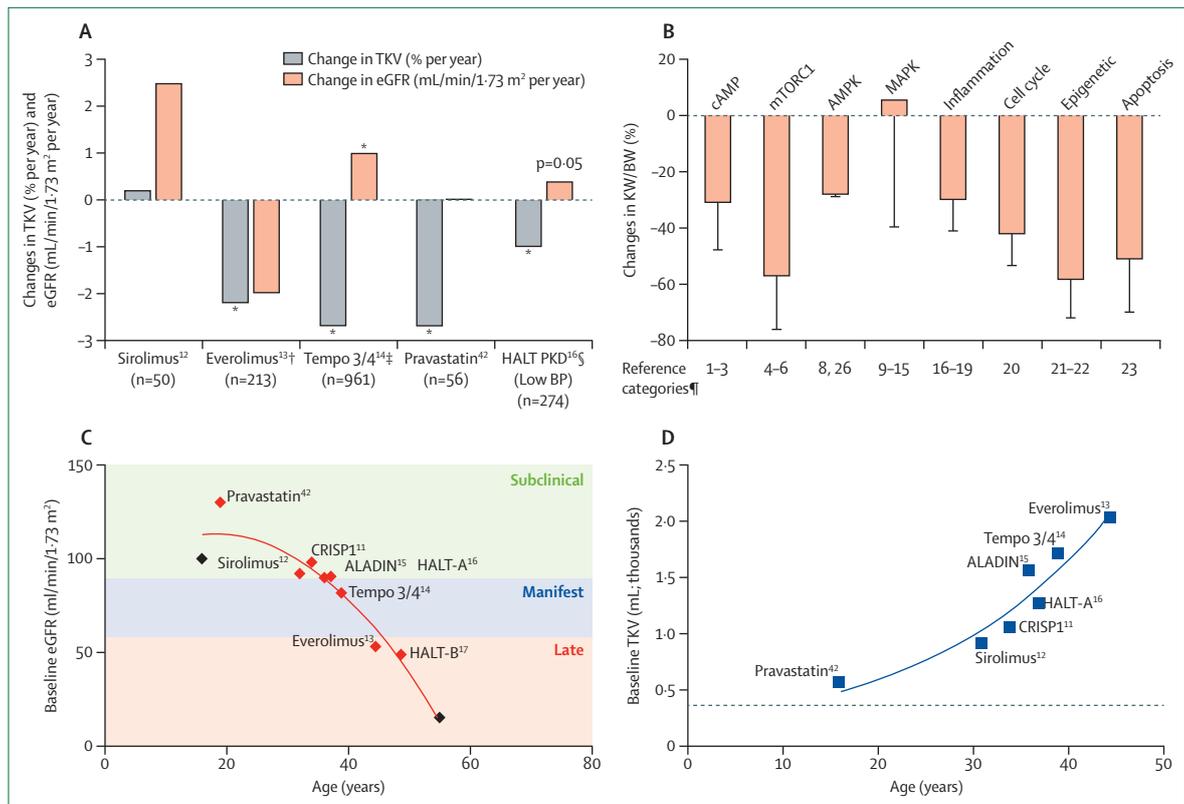
Figure 3: **Effect of therapeutic interventions on cyst progression in human trials and cystic kidney disease in rodents**
(A) Changes in total kidney volume (TKV) and improvement of renal function (gain in estimated glomerular filtration rate [eGFR] in mL/min/1·73 m² per year) of clinical trials involving 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.

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.

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

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 studies[12–14,16]) 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).[15] 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)
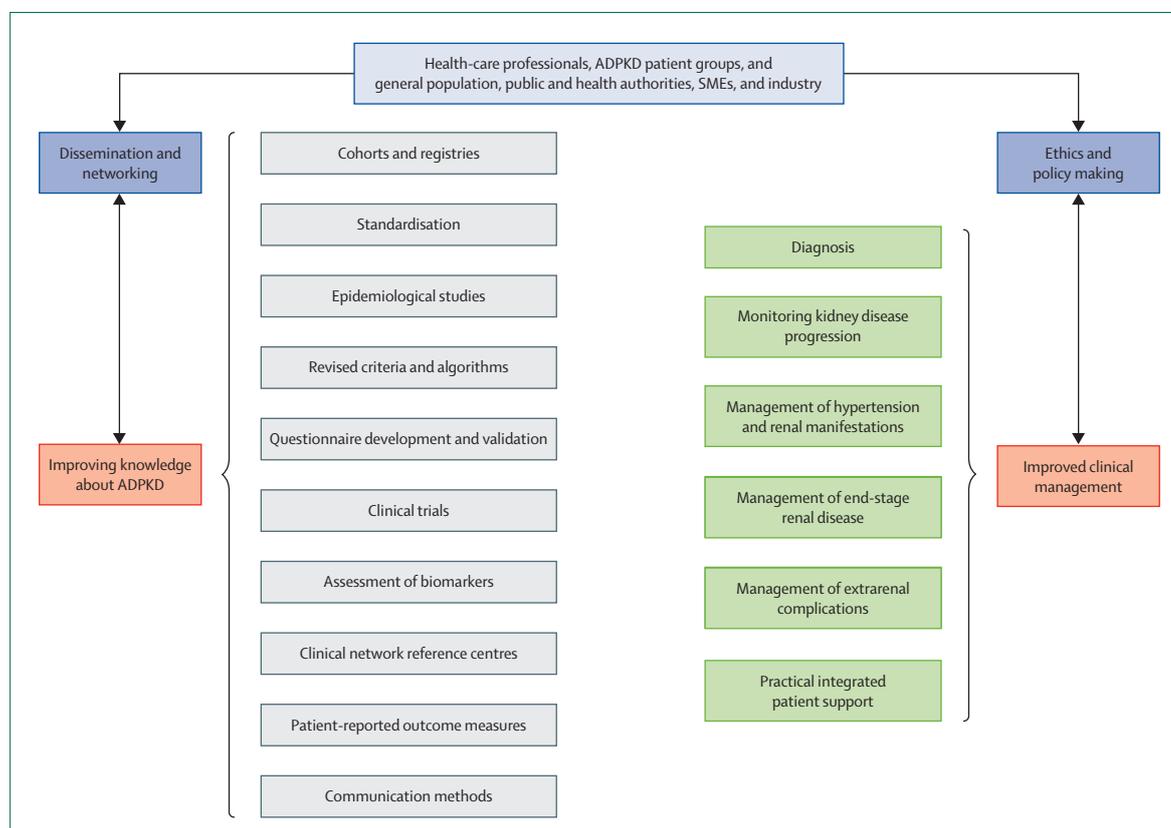

Figure 4: **Roadmap to improve clinical management in autosomal dominant polycystic kidney disease**
Specific action points are listed in appendix p 5. ADPKD=autosomal dominant polycystic kidney disease. SME=small or medium enterprise.

Controversies Conference on ADPKD in 2014, which brought together a panel of multidisciplinary clinical experts and patients from 20 countries.[37] 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.[89] 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,[90] the EU-funded Marie Curie Initial Training Network TranCYST, and the ERA-EDTA Working Group for Inherited Kidney Diseases.[91] 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.[25] An expanded role for the registry could help identify and monitor patients with ADPKD earlier in the disease process, facilitating longitudinal observational studies, enrolment into clinical trials, and post-trial monitoring.

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.

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References

1 Torres VE, Watson ML. Polycystic kidney disease: antiquity to the 20th century. *Nephrol Dial Transplant* 1998; **13**: 2690–96.

2 Fogazzi GB. The description of polycystic kidney by Domenico Gusmano Galeazzi. *Nephrol Dial Transplant* 1998; **13**: 1039–40.

3 Dalgaard OZ. Bilateral polycystic disease of the kidneys; a follow-up of two hundred and 80-four patients and their families. *Acta Med Scand* 1957; **158** (suppl 328): 1–255.

4 Gardner KD Jr. Composition of fluid in twelve cysts of a polycystic kidney. *N Engl J Med* 1969; **281**: 985–88.

5 Reeders ST, Breuning MH, Davies KE, et al. A highly polymorphic DNA marker linked to adult polycystic kidney disease on chromosome 16. *Nature* 1985; **317**: 542–44.

6 Mangoo-Karim R, Uchic ME, Grant M, et al. Renal epithelial fluid secretion and cyst growth: the role of cyclic AMP. *FASEB J* 1989; **3**: 2629–32.

7 Peters DJ, Spruit L, Saris JJ, et al. Chromosome 4 localization of a second gene for autosomal dominant polycystic kidney disease. *Nat Genet* 1993; **5**: 359–62.

8 Consortium TEPKD, and the The European Polycystic Kidney Disease Consortium. The polycystic kidney disease 1 gene encodes a 14 kb transcript and lies within a duplicated region on chromosome 16. *Cell* 1994; **77**: 881–94.

9 Mochizuki T, Wu G, Hayashi T, et al. PKD2, a gene for polycystic kidney disease that encodes an integral membrane protein. *Science* 1996; **272**: 1339–42.

10 Ward CJ, Hogan MC, Rossetti S, et al. The gene mutated in autosomal recessive polycystic kidney disease encodes a large, receptor-like protein. *Nat Genet* 2002; **30**: 259–69.

11 Grantham JJ, Torres VE, Chapman AB, et al, and the CRISP Investigators. Volume progression in polycystic kidney disease. *N Engl J Med* 2006; **354**: 2122–30.

12 Serra AL, Poster D, Kistler AD, et al. Sirolimus and kidney growth in autosomal dominant polycystic kidney disease. *N Engl J Med* 2010; **363**: 820–29.

13 Walz G, Budde K, Mannaa M, et al. Everolimus in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 2010; **363**: 830–40.

14 Torres VE, Chapman AB, Devuyst O, et al, and the TEMPO 3:4 Trial Investigators. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 2012; **367**: 2407–18.

15 Caroli A, Perico N, Perna A, et al, and the ALADIN study group. Effect of longacting somatostatin analogue on kidney and cyst growth in autosomal dominant polycystic kidney disease (ALADIN): a randomised, placebo-controlled, multicentre trial. *Lancet* 2013; **382**: 1485–95.

16 Schrier RW, Abebe KZ, Perrone RD, et al, and the HALT-PKD Trial Investigators. Blood pressure in early autosomal dominant polycystic kidney disease. *N Engl J Med* 2014; **371**: 2255–66.

17 Torres VE, Abebe KZ, Chapman AB, et al, and the HALT-PKD Trial Investigators. Angiotensin blockade in late autosomal dominant polycystic kidney disease. *N Engl J Med* 2014; **371:** 2267–76.

18 Grantham JJ. Clinical practice. Autosomal dominant polycystic kidney disease. *N Engl J Med* 2008; **359:** 1477–85.

19 Torres VE, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. *Lancet* 2007; **369:** 1287–301.

20 Gevers TJ, Drenth JP. Diagnosis and management of polycystic liver disease. *Nat Rev Gastroenterol Hepatol* 2013; **10:** 101–08.

21 Mao Z, Xie G, Ong AC. Metabolic abnormalities in autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant* 2015; **30:** 197–203.

22 Iglesias CG, Torres VE, Offord KP, Holley KE, Beard CM, Kurland LT. Epidemiology of adult polycystic kidney disease, Olmsted County, Minnesota: 1935–1980. *Am J Kidney Dis* 1983; **2:** 630–39.

23 Chan KW. Adult polycystic kidney disease in Hong Kong Chinese: an autopsy study. *Pathology* 1993; **25:** 229–32.

24 Lentine KL, Xiao H, Machnicki G, Gheorghian A, Schnitzler MA. Renal function and healthcare costs in patients with polycystic kidney disease. *Clin J Am Soc Nephrol* 2010; **5:** 1471–79.

25 Spithoven EM, Kramer A, Meijer E, et al. Renal replacement therapy for autosomal dominant polycystic kidney disease (ADPKD) in Europe: prevalence and survival-an analysis of data from the ERA-EDTA Registry. *Nephrol Dial Transplant* 2014; **29 (suppl 4):** iv15–25.

26 Paul BM, Consugar MB, Ryan Lee M, et al. Evidence of a third ADPKD locus is not supported by re-analysis of designated PKD3 families. *Kidney Int* 2014; **85:** 383–92.

27 Simms RJ, Travis DL, Durkie M, Wilson G, Dalton A, Ong AC. Genetic testing in the assessment of living related kidney donors at risk of autosomal dominant polycystic kidney disease. *Transplantation* 2014; published online Oct 21. DOI:10.1097/TP.0000000000000466.

28 Zerres K, Rudnik-Schöneborn S, Deget F. Childhood onset autosomal dominant polycystic kidney disease in sibs: clinical picture and recurrence risk. German Working Group on Paediatric Nephrology (Arbeitsgemeinschaft für Pädiatrische Nephrologie). *J Med Genet* 1993; **30:** 583–88.

29 Pei Y, Obaji J, Dupuis A, et al. Unified criteria for ultrasonographic diagnosis of ADPKD. *J Am Soc Nephrol* 2009; **20:** 205–12.

30 Pei Y, Hwang YH, Conklin J, et al. Imaging-based diagnosis of autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 2015; **26:** 746–53.

31 Rossetti S, Hopp K, Sikkink RA, et al. Identification of gene mutations in autosomal dominant polycystic kidney disease through targeted resequencing. *J Am Soc Nephrol* 2012; **23:** 915–33.

32 Cornec-Le Gall E, Audrézet MP, Chen JM, et al. Type of PKD1 mutation influences renal outcome in ADPKD. *J Am Soc Nephrol* 2013; **24:** 1006–13.

33 Rossetti S, Consugar MB, Chapman AB, et al, and the CRISP Consortium. Comprehensive molecular diagnostics in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 2007; **18:** 2143–60.

34 Rossetti S, Kubly VJ, Consugar MB, et al. Incompletely penetrant PKD1 alleles suggest a role for gene dosage in cyst initiation in polycystic kidney disease. *Kidney Int* 2009; **75:** 848–55.

35 Bergmann C, von Bothmer J, Ortiz Brüchle N, et al. Mutations in multiple PKD genes may explain early and severe polycystic kidney disease. *J Am Soc Nephrol* 2011; **22:** 2047–56.

36 Simms RJ, Ong AC. How simple are 'simple renal cysts'? *Nephrol Dial Transplant* 2014; **29 (suppl 4):** iv106–12.

37 Chapman AB, Devuyst O, Eckardt KU, et al, for Conference Participants. Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2015; published online March 18. DOI:10.1038/ki.2015.59.

38 Boyer O, Gagnadoux MF, Guest G, et al. Prognosis of autosomal dominant polycystic kidney disease diagnosed in utero or at birth. *Pediatr Nephrol* 2007; **22:** 380–88.

39 Shamshirsaz AA, Reza Bekheirnia M, Kamgar M, et al. Autosomal-dominant polycystic kidney disease in infancy and childhood: progression and outcome. *Kidney Int* 2005; **68:** 2218–24.

40 Ho TA, Godefroid N, Gruzon D, et al. Autosomal dominant polycystic kidney disease is associated with central and nephrogenic defects in osmoregulation. *Kidney Int* 2012; **82:** 1121–29.

41 Cadnapaphornchai MA, McFann K, Strain JD, Masoumi A, Schrier RW. Increased left ventricular mass in children with autosomal dominant polycystic kidney disease and borderline hypertension. *Kidney Int* 2008; **74:** 1192–96.

42 Cadnapaphornchai MA, George DM, McFann K, et al. Effect of pravastatin on total kidney volume, left ventricular mass index, and microalbuminuria in pediatric autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol* 2014; **9:** 889–96.

43 Schrier RW, Brosnahan G, Cadnapaphornchai MA, et al. Predictors of autosomal dominant polycystic kidney disease progression. *J Am Soc Nephrol* 2014; **25:** 2399–418.

44 Menezes LF, Zhou F, Patterson AD, et al. Network analysis of a Pkd1-mouse model of autosomal dominant polycystic kidney disease identifies HNF4α as a disease modifier. *PLoS Genet* 2012; **8:** e1003053.

45 Hateboer N, v Dijk MA, Bogdanova N, et al. Comparison of phenotypes of polycystic kidney disease types 1 and 2. European PKD1-PKD2 Study Group. *Lancet* 1999; **353:** 103–07.

46 Paterson AD, Magistroni R, He N, et al. Progressive loss of renal function is an age-dependent heritable trait in type 1 autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 2005; **16:** 755–62.

47 Persu A, Duyme M, Pirson Y, et al. Comparison between siblings and twins supports a role for modifier genes in ADPKD. *Kidney Int* 2004; **66:** 2132–36.

48 Harris PC, Bae KT, Rossetti S, et al. Cyst number but not the rate of cystic growth is associated with the mutated gene in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 2006; **17:** 3013–19.

49 Chapman AB, Bost JE, Torres VE, et al. Kidney volume and functional outcomes in autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol* 2012; **7:** 479–86.

50 Irazabal MV, Rangel LJ, Bergstralh EJ, et al, and the CRISP Investigators. Imaging classification of autosomal dominant polycystic kidney disease: a simple model for selecting patients for clinical trials. *J Am Soc Nephrol* 2015; **26:** 160–72.

51 Cornec-Le Gall E, Le Meur Y. Polycystic kidney disease: kidney volume—a crystal ball for ADPKD prognosis? *Nat Rev Nephrol* 2014; **10:** 485–86.

52 King BF, Torres VE, Brummer ME, et al, and the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP). Magnetic resonance measurements of renal blood flow as a marker of disease severity in autosomal-dominant polycystic kidney disease. *Kidney Int* 2003; **64:** 2214–21.

53 Caroli A, Antiga L, Conti S, et al. Intermediate volume on computed tomography imaging defines a fibrotic compartment that predicts glomerular filtration rate decline in autosomal dominant polycystic kidney disease patients. *Am J Pathol* 2011; **179:** 619–27.

54 Ong AC, Harris PC. Molecular pathogenesis of ADPKD: the polycystin complex gets complex. *Kidney Int* 2005; **67:** 1234–47.

55 Chapin HC, Caplan MJ. The cell biology of polycystic kidney disease. *J Cell Biol* 2010; **191:** 701–10.

56 Chang MY, Ong AC. New treatments for autosomal dominant polycystic kidney disease. *Br J Clin Pharmacol* 2013; **76:** 524–35.

57 Harris PC, Torres VE. Genetic mechanisms and signaling pathways in autosomal dominant polycystic kidney disease. *J Clin Invest* 2014; **124:** 2315–24.

58 Qian F, Boletta A, Bhunia AK, et al. Cleavage of polycystin-1 requires the receptor for egg jelly domain and is disrupted by human autosomal-dominant polycystic kidney disease 1-associated mutations. *Proc Natl Acad Sci USA* 2002; **99:** 16981–86.

59 Cai Y, Fedeles SV, Dong K, et al. Altered trafficking and stability of polycystins underlie polycystic kidney disease. *J Clin Invest* 2014; **124:** 5129–44.

60 Merrick D, Chapin H, Baggs JE, et al. The γ-secretase cleavage product of polycystin-1 regulates TCF and CHOP-mediated transcriptional activation through a p300-dependent mechanism. *Dev Cell* 2012; **22:** 197–210.

61 Nauli SM, Alenghat FJ, Luo Y, et al. Polycystins 1 and 2 mediate mechanosensation in the primary cilium of kidney cells. *Nat Genet* 2003; **33:** 129–37.

62 DeCaen PG, Delling M, Vien TN, Clapham DE. Direct recording and molecular identification of the calcium channel of primary cilia. *Nature* 2013; **504:** 315–18.

63 Delling M, DeCaen PG, Doerner JF, Febvay S, Clapham DE. Primary cilia are specialized calcium signalling organelles. *Nature* 2013; **504:** 311–14.

64 Goetz SC, Anderson KV. The primary cilium: a signalling centre during vertebrate development. *Nat Rev Genet* 2010; **11:** 331–44.

65 Lienkamp S, Ganner A, Walz G. Inversin, Wnt signaling and primary cilia. *Differentiation* 2012; **83:** S49–55.

66 Goto H, Inoko A, Inagaki M. Cell cycle progression by the repression of primary cilia formation in proliferating cells. *Cell Mol Life Sci* 2013; **70:** 3893–905.

67 Chang MY, Parker E, Ibrahim S, et al. Haploinsufficiency of Pkd2 is associated with increased tubular cell proliferation and interstitial fibrosis in two murine Pkd2 models. *Nephrol Dial Transplant* 2006; **21:** 2078–84.

68 Grantham JJ. Pathogenesis of renal cyst expansion: opportunities for therapy. *Am J Kidney Dis* 1994; **23:** 210–18.

69 Kim E, Walz G. Sensitive cilia set up the kidney. *Nat Med* 2007; **13:** 1409–11.

70 Chaki M, Airik R, Ghosh AK, et al. Exome capture reveals ZNF423 and CEP164 mutations, linking renal ciliopathies to DNA damage response signaling. *Cell* 2012; **150:** 533–48.

71 Slaats GG, Ghosh AK, Falke LL, et al. Nephronophthisis-associated CEP164 regulates cell cycle progression, apoptosis and epithelial-to-mesenchymal transition. *PLoS Genet* 2014; **10:** e1004594.

72 Dibble CC, Manning BD. Signal integration by mTORC1 coordinates nutrient input with biosynthetic output. *Nat Cell Biol* 2013; **15:** 555–64.

73 Braun WE, Schold JD, Stephany BR, Spirko RA, Herts BR. Low-dose rapamycin (sirolimus) effects in autosomal dominant polycystic kidney disease: an open-label randomized controlled pilot study. *Clin J Am Soc Nephrol* 2014; **9:** 881–88.

74 Erickson KF, Chertow GM, Goldhaber-Fiebert JD. Cost-effectiveness of tolvaptan in autosomal dominant polycystic kidney disease. *Ann Intern Med* 2013; **159:** 382–89.

75 Torres VE, Harris PC. Strategies targeting cAMP signaling in the treatment of polycystic kidney disease. *J Am Soc Nephrol* 2014; **25:** 18–32.

76 Héliès-Toussaint C, Aarab L, Gasc JM, Verbavatz JM, Chabardès D. Cellular localization of type 5 and type 6 ACs in collecting duct and regulation of cAMP synthesis. *Am J Physiol Renal Physiol* 2000; **279:** F185–94.

77 Rees S, Kittikulsuth W, Roos K, Strait KA, Van Hoek A, Kohan DE. Adenylyl cyclase 6 deficiency ameliorates polycystic kidney disease. *J Am Soc Nephrol* 2014; **25:** 232–37.

78 Sussman CR, Ward CJ, Leightner AC, et al. Phosphodiesterase 1A modulates cystogenesis in zebrafish. *J Am Soc Nephrol* 2014; **25:** 2222–30.

79 Wilson PD. Apico-basal polarity in polycystic kidney disease epithelia. *Biochim Biophys Acta* 2011; **1812:** 1239–48.

80 Streets AJ, Wessely O, Peters DJ, Ong AC. Hyperphosphorylation of polycystin-2 at a critical residue in disease reveals an essential role for polycystin-1-regulated dephosphorylation. *Hum Mol Genet* 2013; **22:** 1924–39.

81 Ecder T, Schrier RW. Cardiovascular abnormalities in autosomal-dominant polycystic kidney disease. *Nat Rev Nephrol* 2009; **5:** 221–28.

82 Happé H, Peters DJ. Translational research in ADPKD: lessons from animal models. *Nat Rev Nephrol* 2014; **10:** 587–601.

83 Devuyst O, Wang X, Serra A. Vasopressin-2 receptor antagonists in autosomal dominant polycystic kidney disease: from man to mouse and back. *Nephrol Dial Transplant* 2011; **26:** 2423–25.

84 Crystal AS, Shaw AT, Sequist LV, et al. Patient-derived models of acquired resistance can identify effective drug combinations for cancer. *Science* 2014; **346:** 1480–86.

85 Niederst MJ, Engelman JA. Bypass mechanisms of resistance to receptor tyrosine kinase inhibition in lung cancer. *Sci Signal* 2013; **6:** re6.

86 Wetmore JB, Calvet JP, Yu AS, et al. Polycystic kidney disease and cancer after renal transplantation. *J Am Soc Nephrol* 2014; **25:** 2335–41.

87 Corradi V, Gastaldon F, Virzi GM, Caprara C, Martino F, Ronco C. Clinical and laboratory markers of autosomal dominant polycystic kidney disease (adpkd) progression: an overview. *Minerva Med* 2015; **105:** 53–64.

88 Rosansky SJ, Glassock RJ. Is a decline in estimated GFR an appropriate surrogate end point for renoprotection drug trials? *Kidney Int* 2014; **85:** 723–27.

89 Devuyst O, Knoers NV, Remuzzi G, Schaefer F, and the Board of the Working Group for Inherited Kidney Diseases of the European Renal Association and European Dialysis and Transplant Association. Rare inherited kidney diseases: challenges, opportunities, and perspectives. *Lancet* 2014; **383:** 1844–59.

90 Petzold K, Gansevoort RT, Ong AC, et al. Building a network of ADPKD reference centres across Europe: the EuroCYST initiative. *Nephrol Dial Transplant* 2014; **29** (suppl 4)**:** iv26–32.

91 Devuyst O, Antignac C, Bindels RJ, et al. The ERA-EDTA Working Group on inherited kidney disorders. *Nephrol Dial Transplant* 2012; **27:** 67–69.