

# European ADPKD Forum multidisciplinary position statement on autosomal dominant polycystic kidney disease care

## *European ADPKD Forum and Multispecialist Roundtable participants*

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## ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is a chronic, progressive condition characterized by the development and growth of cysts in the kidneys and other organs and by additional systemic manifestations. Individuals with ADPKD should have access to lifelong, multidisciplinary, specialist and patient-centred care involving: (i) a holistic and

comprehensive assessment of the manifestations, complications, prognosis and impact of the disease (in physical, psychological and social terms) on the patient and their family; (ii) access to treatment to relieve symptoms, manage complications, preserve kidney function, lower the risk of cardiovascular disease and maintain quality of life; and (iii) information and support to help patients and their families act as fully informed and

active partners in care, i.e. to maintain self-management approaches, deal with the impact of the condition and participate in decision-making regarding healthcare policies, services and research. Building on discussions at an international roundtable of specialists and patient advocates involved in ADPKD care, this article sets out (i) the principles for a patient-centred, holistic approach to the organization and delivery of ADPKD care in practice, with a focus on multispecialist collaboration and shared-decision making, and (ii) the rationale and knowledge base for a route map for ADPKD care intended to help patients navigate the services available to them and to help stakeholders and decision-makers take practical steps to ensure that all patients with ADPKD can access the comprehensive multispecialist care to which they are entitled. Further multispecialty collaboration is encouraged to design and implement these services, and to work with patient organizations to promote awareness building, education and research.

**Keywords:** ADPKD, CKD, clinical practice, multispecialist care, polycystic kidney disease

## INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is a chronic, progressive condition characterized by the development and growth of cysts in the kidneys and other organs and by additional systemic manifestations [1]. The renal cystic disease progresses throughout life, causing complications that include pain, cyst infections, bleeding and abdominal distention due to massive kidney enlargement. Kidney function may not be affected for many years, owing to compensatory renal mechanisms. However, most patients eventually develop end-stage renal disease (ESRD), typically before the age of 60 years, and require renal replacement therapy (RRT) by kidney transplantation or dialysis [2]. ADPKD accounts for approximately 1 in 10 of all patients needing RRT, corresponding to approximately 50 000 people across Europe [3]. Cysts also develop in the liver in most patients [4] and occur less commonly in the seminal vesicles, pancreas, arachnoid membrane and spinal meninges [1]. Patients with ADPKD are at increased risk of cardiovascular and cerebrovascular complications, including hypertension, cardiac valvular abnormalities and intracranial aneurysms [1, 5, 6]. The lifelong physical and psychological effects of ADPKD can impair quality of life (QoL) and interfere with social functioning and work [7–11]. These effects may be underappreciated by many physicians, including nephrologists, especially during the early stage of the disease [9]. Although ADPKD is typically diagnosed in adulthood, it may present in children (and even prenatally) and there have been calls for greater recognition of symptomatic paediatric disease to facilitate early diagnosis and appropriate care [12, 13].

Approaches to ADPKD care vary between and within European countries, with no widely accepted, evidence-based practice guidelines. A Kidney Disease: Improving Global Outcomes (KDIGO) initiative has begun the process toward international guidelines by assessing the current state of knowledge and best practice and proposing a research agenda [1].

National guidelines have been developed in some countries [14, 15], while European-level guidelines have been developed specifically regarding the therapeutic use of vasopressin V2 receptor antagonists [16]. Relatively little attention has been paid to the organization and delivery of ADPKD care and the means of overcoming barriers to the implementation of guidelines and patient-centred services. Practice patterns for ADPKD care are not well-documented across Europe. Many patients may not have coordinated access to the necessary range of specialists with expertise in ADPKD and to patient-centred, multidisciplinary care. Where specialized ADPKD centres exist, their roles, responsibilities and added value may be unclear among nephrologists in the local region. Patients and carers may also lack a clear understanding of the available services and how to navigate these optimally.

In 2015, the European ADPKD Forum (EAF) published policy-focused recommendations to help address unmet needs among patients with ADPKD [17]. These included the development of nationally coordinated approaches to ADPKD care and efforts to empower patients and carers. Such approaches require collaboration between all stakeholders. Building on discussions at a roundtable of clinical specialists and patient advocates, convened by the EAF, this article sets out (i) the principles for a holistic, patient-centred approach to the organization and delivery of ADPKD care in practice, with a focus on multispecialist collaboration and shared-decision making and (ii) the rationale and knowledge base for a route map for ADPKD care.

## PRINCIPLES OF ADPKD CARE: A MULTISPECIALIST, PATIENT-CENTRED APPROACH

Individuals with ADPKD should have access to lifelong, multidisciplinary, specialist and patient-centred care involving: (i) a holistic and comprehensive assessment of the manifestations, complications, prognosis and impact of the disease (in physical, psychological and social terms) on the patient and their family; (ii) access to treatment to relieve symptoms, manage complications, preserve kidney function, lower the risk of cardiovascular disease and maintain QoL; and (iii) information and support to help patients and their families maintain recommended self-management approaches and to deal with the impact of the condition [1, 17].

### Patient-centred approach

We define a ‘patient-centred’ approach to ADPKD as one in which patients and carers are empowered to act as fully informed and active partners in decision-making regarding their care and in healthcare policies, services and research directly or indirectly related to the disease [17, 18]. This requires patients and carers to have access to accurate, up-to-date information about ADPKD, their own clinical data and the opportunity to participate in decision-making. Survey evidence suggests the provision of written materials, and referrals to patient support groups, at the time of diagnosis are variable and suboptimal [19]. All stakeholders, including national governments and healthcare providers, should support efforts to better inform patients and families and, more widely, to include patient organizations

within strategic decision-making. Patients participated at the KDIGO Conference [1] and an expanded consultation regarding research priorities is underway among advocacy groups (T. Harris, personal communication). Researchers in Australia have also elicited the perspectives of patients and carers concerning clinical practice guidelines for ADPKD [20].

### Multidisciplinary coordination

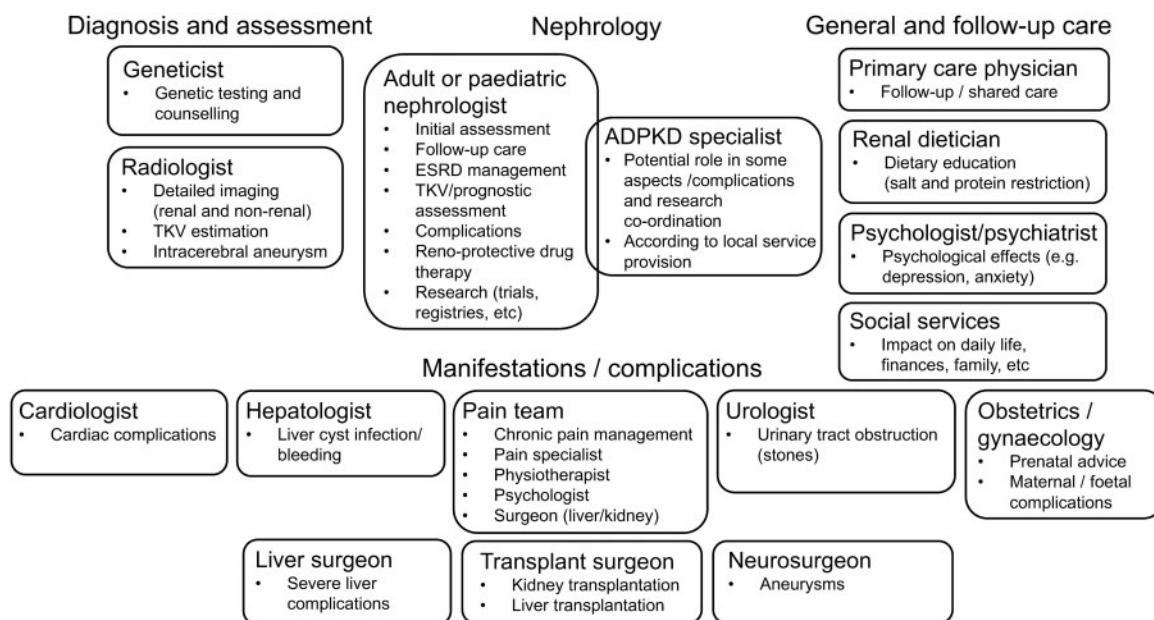
The complex and heterogeneous manifestations of ADPKD often necessitate access to specialized services. In order to establish strategies to detect complications and prevent progression of kidney failure, specialist care should start as soon as possible after diagnosis, ideally when kidney function is not yet impaired and protective measures can be taken. Some patients present with impaired renal function and require RRT soon after diagnosis, while others may have a low risk of progressing to ESRD. In all these cases, specialist care should still be considered.

All patients with ADPKD should have access to a nephrologist knowledgeable about the diverse aspects of the disease [1], including the multi-organ involvement, psychological and psychosocial issues, genetics, pain management and current treatment options, in addition to the ‘core’ management of renal function and RRT. Depending on local circumstances, referral to an adult or paediatric nephrologist with specialist ADPKD expertise may also be helpful in some cases for particular aspects of care according to the evolving best practice, such as prognostic assessment, kidney cyst infections [21, 22], specific reno-protective pharmacotherapy [16] and for clinical trials and other types of research. Patients should also have access to care from a range of other clinical specialists (e.g. hepatology, clinical genetics, neurosurgery and anaesthesiology or pain specialists) and healthcare professionals who also have specific expertise in ADPKD, according to clinical need in the event of other disease manifestations and complications (e.g. liver cyst

complications, intracranial aneurysms, lumbar pain; Figure 1). They may also require treatment for other chronic diseases (e.g. diabetes) based on a consensus among all practitioners involved.

How multidisciplinary care is managed depends on the local, regional and national organization and resourcing of services. Where possible, a team approach with all specialties provided in one centre would be expected to benefit expert and patient networking, efficiency and patient outcomes [1]. Specialist centres also have a potential role in coordinating research efforts locally, nationally and internationally. This is not realistic for all patients, but most university hospitals should be able to provide most of the services required. Where this is the case, these services should be coordinated institutionally in a patient-centred manner. Not all patients are routinely cared for at university hospitals, of course, and some local nephrologists may not be able to offer all services necessary or may not have access within their hospital to colleagues from other specialties with appropriate ADPKD expertise. In these cases, managed coordination and networking of local, regional or national ADPKD specialist services, based on a common understanding of the multifaceted needs of patients and carers, is important to optimize care and to benefit research. Informal referral pathways often exist, but we argue that services should ideally be formally organized according to predefined pathways. Such coordination requires a consensus involving all practitioners, patients and providers.

To our knowledge, the relative cost-effectiveness of different delivery models of multidisciplinary ADPKD care have not been compared. Ongoing evaluation of the cost–benefit of care models is important, taking account of the ‘downstream’ increase in healthcare costs that occurs in later life among patients who require dialysis [23, 24]. However, managed coordination would be expected to facilitate prompt, accurate diagnosis, avoidance of duplication of tests, better management



**FIGURE 1:** Schematic overview of key specialties involved in care for ADPKD showing examples of indications that may warrant referral subject to individual circumstances and local care organization.

of disease complications and manifestations, and evidence-based access to specific reno-protective treatment, and ultimately to improve patient outcomes.

New technologies could facilitate interdisciplinary networking and research, and promote patient empowerment and self-care. These include telecommunication and information technologies ('telemedicine' or 'teleneephrology') that allow online consultation and videoconferencing, data and image sharing, education and biomarker development. Such modalities could have a particular role in supporting consultation between local nephrology services and distant specialist centres on specific aspects of care and research, reducing the need for patients to travel to the latter. These measures will be facilitated by the recent implementation of the European Rare Kidney Disease Reference Network (ERKNet), which aims to improve standards of diagnosis and treatment for rare and complex kidney diseases [25]. Polycystic liver disease will also be covered within the European Reference Network (ERN) on Hepatological Diseases (ERN RARE-LIVER) [26].

Patients' access to information also underpins their participation in shared decision-making. Regular monitoring may be important for some patients to improve their understanding and sense of control, to facilitate self-management and to allow them to prepare for RRT [20]. For example, the Renal PatientView system in the UK (<https://www.patientview.org/#/>; 15 November 2017, date last accessed) provides patients with web-based access to laboratory results and educational material [27, 28].

## ADPKD ROUTE MAP: CONCEPT AND AIMS

Route maps provide 'signposts' to health and social care for patients and their families in order to improve their access to information and to facilitate earlier diagnosis and improved care and support. Route maps can also help health and social care professionals to communicate, and work in partnership, with patients and families. Examples of route

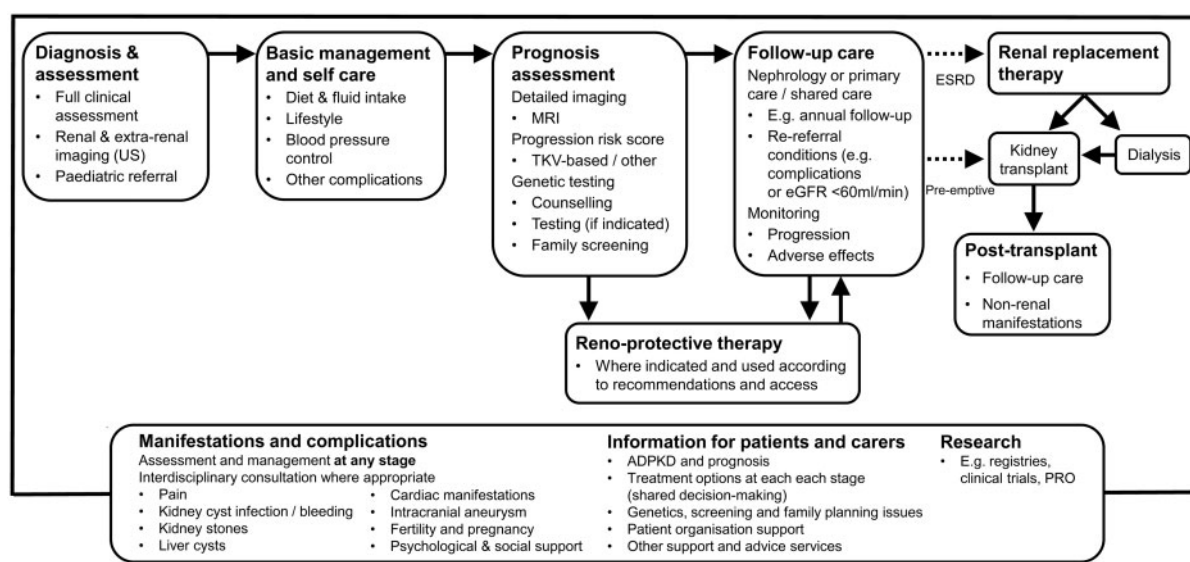
maps include those for arthritis [29] and spinal muscular atrophy [30].

An ADPKD Patient Route Map is in development to promote good practice in lifetime ADPKD care among all stakeholders. Specifically, the Route Map aims to:

- Inform patients and families about what they can expect from a good-quality service, engaging and supporting them to take a partnership role in their own care, thereby improving the dialogue between patients and physicians and helping patients to navigate available services
- Assist patient organizations in participating in the decision-making regarding the design, implementation and assessment of ADPKD services
- Support healthcare providers and policymakers to design, adapt or assess coordinated services to efficiently address current unmet needs and to take advantage of developments in knowledge, therapy and technology, taking into account local healthcare system conditions

The Route Map is being developed collaboratively by the EAF and PKD International, with input from member patient organizations across Europe. It is not a clinical practice guideline and is not intended to be prescriptive, nor a complete solution appropriate for all settings. Rather, it is intended to offer a practical, flexible, interactive and adaptable model that integrates, translates and stages key elements of good practice for patients and other stakeholders, according to the principles defined above and based on the latest knowledge base and good practice. It will be published as an open-access resource on the PKD International website for use and local adaptation by all stakeholders (e.g. patients, families, healthcare professionals and policymakers).

The Route Map is presented in terms of key assessments and interventions at distinct stages, together with considerations that apply to the different stages of the disease throughout a patient's lifetime (Figure 2). The following sections overview



ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate; MRI, magnetic resonance imaging; PRO, patient-reported outcomes; TKV, total kidney volume; US, ultrasound

FIGURE 2: Schematic illustration of a template patient Route Map for ADPKD care.

the main domains, highlighting key unmet needs and barriers and focusing on opportunities for inter-specialist co-operation for non-renal manifestations and complications.

## SCREENING AND DIAGNOSIS

A diagnosis of ADPKD can have important lifelong effects on patients, including psychosocial and financial consequences. The advantages and disadvantages of offering screening to a patient's family members should be carefully discussed. The offer of screening should be provided with appropriate counselling on the implications of a diagnosis for adults and children. Routine pre-symptomatic screening of ADPKD is not recommended for at-risk children, while it is usually thought that the benefits outweigh the risks in adults [1]. Ultrasound imaging is recommended for parents of children or adolescents in whom ADPKD is suspected and who have no previous family history of ADPKD [13].

ADPKD is diagnosed in adults and children mainly by ultrasound imaging [1]. Magnetic resonance imaging (MRI) may be useful to confirm or exclude the diagnosis. Both can be used for prognostic assessment. Specialist consultation is recommended for paediatric patients with renal cysts, as genetic testing is often required to confirm the diagnosis when clinical findings are equivocal [1, 13]. A detailed examination and additional investigations should be performed to identify extra-renal manifestations if appropriate.

## BLOOD PRESSURE CONTROL, LIFESTYLE AND SELF-CARE

Control of hypertension and other cardiovascular risk factors is a key aspect of early ADPKD management [1]. Cardiovascular disease is the leading cause of premature death in people with ADPKD [3] and yet risk management may be sub-optimal [31]. Up to 20% of paediatric patients with ADPKD may have hypertension [32]. In children and adults, 24-h ambulatory blood pressure monitoring can be helpful to detect prehypertension and any diminution of the normal fall in overnight blood pressure [1, 13].

Patients should be provided with comprehensive, up-to-date written information on recommended lifestyle and self-care aspects (Table 1). Although evidence specifically in ADPKD is

lacking, patients should be advised on the expected antihypertensive benefits of lifestyle adaptation, such as weight control, exercise and a low-salt diet. There is no good evidence that protein-limited diets slow the progression of ADPKD [33]. Others have advised a moderate protein intake (0.75–1.0 g/kg/day) for adults with ADPKD, commensurate with that in the general population [34]. KDIGO guidelines for general chronic kidney disease (CKD) care in adults recommend moderate protein limitation (to 0.8 g/kg/day) when estimated glomerular filtration rate (eGFR) is <30 mL/min/1.73 m<sup>2</sup>, along with the avoidance of high protein intake (>1.3 g/kg/day) in those at risk of CKD progression [35]. Where protein restriction is applied, it should preferably involve education by a renal dietician and monitoring for malnutrition, especially those patients with high total kidney and liver volumes whose nutritional intake may become insufficient. A recent Cochrane review has drawn attention to the limitations in the evidence base for dietary interventions for adults with CKD [36].

Peer-to-peer support from patient organizations may aid adherence to lifestyle and diet measures, together with regular reinforcement by healthcare practitioners.

Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are the first-line antihypertensives in ADPKD. The KDIGO CKD blood pressure target of ≤140/90 mmHg is recommended for individualized use, taking comorbidities into account [1]. Data from the HALT PKD study suggest that a lower target might benefit young hypertensive ADPKD patients (15–49 years) at CKD Stages 1 or 2 and without diabetes mellitus or significant cardiovascular comorbidities [37]. In this group, a target of 95/60–110/75 mmHg was associated with a slower increase in total kidney volume (TKV), though no overall change in the eGFR, together with a greater decline in the left-ventricular-mass index and a greater reduction in urinary albumin excretion, as compared with a target of 120/70–130/80 mmHg [37]. A cardiology referral is needed if signs or symptoms of cardiac disease are evident.

## LIVER CYSTS

Liver cysts are the most common extra-renal manifestation of ADPKD and a recent case series suggested that biliary disease is

**Table 1. Information for patients, carers and families affected by autosomal dominant polycystic kidney disease (ADPKD)**

Disease information	Explanation of the disease and its potential course and manifestations Details of ADPKD patient organizations
Basic management and self-care	Self-management: water intake, low-salt diet, low-protein diet (where appropriate), weight control, lifestyle (e.g. exercise), smoking cessation, caffeine intake Cardiovascular risk management: importance, antihypertensive therapy, cholesterol-lowering therapy Situations for contacting clinic (e.g. pain, complications)
Prognostic assessment	Rationale, interpretation and implications of prognostic risk score
Specific reno-protective pharmacotherapy	Indication, rationale/benefit, adverse effects, monitoring requirements Clinical trial opportunities
Managing disease impact	Potential impact of the disease on activity (e.g. work and lifestyle) Psychological impact and support available Discussing ADPKD with employers Issues regarding health insurance and mortgage applications Family planning, including genetic counselling and pre-implantation genetic diagnosis, contraception and pregnancy issues
Renal replacement therapy	Dialysis and transplantation options (according to clinical situation and availability)
Research	Registry entry, clinical trials, patient-reported outcome data collection

also a frequent complication in ADPKD [38]. Liver cysts can occur at any disease stage (irrespective of marked progression of CKD) and affect women in particular. Liver cysts can contribute significantly to pain, gastrointestinal symptoms and QoL impairment [4, 11, 39–41]. All patients with ADPKD should be assessed for polycystic liver disease, and those with liver cyst complications should be referred to a hepatologist as necessary. Liver symptoms can be assessed using the polycystic liver disease questionnaire (PLD-Q) [40]. Current guidelines suggest that patients with moderate-to-severe polycystic liver disease should avoid oestrogens [42], in view of the evidence that exogenous oestrogen increases liver (but not renal) volume in postmenopausal ADPKD patients [43].

## INTRACRANIAL ANEURYSMS

Intracranial aneurysms are an uncommon but important manifestation of particular concern to patients. One survey in patients with ADPKD found a self-reported prevalence rate of 5.0% for brain aneurysm and 7.5% for stroke or cerebral bleeding [6]. A recent systematic review reported that unruptured intracranial aneurysms occur in around 11% of patients with ADPKD [44], as compared with around 3% in the general population [45]. The rate of rupture among patients with ADPKD appears similar to that in the general population: a rupture rate of 0.4%/patient-year was reported among ADPKD patients with conservatively treated aneurysms [44]. In the general population, the rupture rate depends strongly on the size and location of the aneurysm.

Systematic screening for intracranial aneurysms is not recommended for all patients with ADPKD, but is recommended in certain groups at elevated risk [1, 46]. Consultation with a neurosurgeon and neurovascular radiologist is needed in the management of identified aneurysms [1, 5, 46].

## PAIN

Pain is a principal symptom of ADPKD. Even in early disease stages, patients can experience acute or chronic pain that can interfere with daily activities and cause distress [7, 9, 47]. ADPKD-specific causes of pain include kidney and liver cyst haemorrhage and infection and urinary stones. Pain may be under-assessed in the clinic and under-recognized by physicians, leading to inadequate management and feelings of powerlessness among patients [9, 20, 47].

Physicians should carefully ascertain and assess patients' pain at each clinic visit and discuss management options according to current best practice. Chronic pain in ADPKD is often refractory, and may necessitate referral, e.g. involving radiologists, physical therapists and pain specialists [1]. A multidisciplinary, stepwise protocol in the Netherlands has recently shown promising results [48].

## PSYCHOSOCIAL SUPPORT

ADPKD can significantly impair QoL and psychosocial well-being, and can be associated with depression and anxiety [9, 10, 11, 49]. Typical issues include worry and fear (associated, for example with pain, unpredictability of symptoms, the effect of

the disease on work and finances, future need for dialysis or the diagnosis of intracranial aneurysm), confusion (which might be linked with a lack of correct information), as well as anger and guilt.

Physicians should recognize the potential psychological, social and functional effects of ADPKD at all disease stages. Measurement of patient-reported outcomes, such as health-related QoL, is important. ADPKD-specific instruments are more sensitive than generic ones, especially in early disease. Recently developed disease-specific tools include the ADPKD Genetic Psychosocial Risk Instrument (GPRI-ADPKD) [10] and the ADPKD Impact Scale (ADPKD-IS) [50], along with the aforementioned PLD-Q [40]. Ideally, patient-reported outcomes should be measured routinely during consultations, although further research is required to define clinically significant changes in scores. The UK Renal Registry is evaluating routine QoL data collection within its Transforming Participation in Chronic Kidney Disease initiative, which aims to help patients manage their own condition and plan future services [51]. The collection of patient-reported outcomes is also a potential role for reference networks at national and European levels.

Patients and carers should have access to psychological and social support services, according to need. Patients and carers should also receive information on managing the impact of ADPKD on employment, mortgages and other financial aspects, and health insurance. Patient organizations play an important role in this respect. Other relevant educational topics for patients and parents include contraception, pregnancy and medication adverse effects [1, 20]. The role of complementary medicines is a topic of interest to some patients [20] and on which nephrologists and other healthcare professionals may need to offer advice. There is no evidence that any complementary or alternative therapy helps to protect the kidneys or to slow the progression of ADPKD. Patients should be encouraged to ask their doctor before using any complementary therapy and should never stop a treatment prescribed by a doctor on the advice of a complementary practitioner without discussing it with their doctor.

## PROGNOSTIC ASSESSMENT

### Progression risk scoring

Prognostic assessment during the early stages of ADPKD has become increasingly important to identify patients with rapidly progressing disease who may be eligible for new renoprotective therapies or clinical trials [1, 16, 52]. It warrants associated investment, awareness building and training and support by healthcare policymakers and providers [17].

The height-adjusted TKV is the gold-standard image biomarker for early ADPKD progression [53]. Classical volumetry to measure TKV from MRI images is laborious and expensive and may not be viewed as an efficient use of time by some radiologists. New, automated methods should allow faster, less labour-intensive imaging at lower costs and thereby facilitate repeat TKV measurement in routine practice [54, 55]. In addition, estimating TKV using MRI images and the ellipsoid

equation is an easy to use and quick surrogate for classical TKV measurement, and seems to perform sufficiently well to be used in clinical practice [56]. Improving the uptake and implementation of such methods, and access to repeat MRI imaging, should be a target for collaboration between nephrologists and radiologists. An image classification of ADPKD based on height-adjusted TKV and age has been proposed to optimize patient selection for enrolment into clinical trials or treatment [57]. Other approaches to prognostic risk scoring include the PROPKD score, which predicts the risk of progression to ESRD using four factors: gender, presence of hypertension before 35 years of age, first urologic event before 35 years of age and genotype [58]. A recent study has demonstrated the prognostic value of fasting urine osmolality (Uosm) to predict disease progression and response to treatment in ADPKD [59]. Determination of Uosm is non-invasive, affordable and valued as an integrative marker of renal function that could improve or complement the existing scores to predict renal outcome in patients with ADPKD.

### Genetic testing

Although diagnostic genetic testing for ADPKD mutations is not required for most patients, it can be important where clinical findings are equivocal or atypical, especially in children [1, 13]. Where possible, patients should have access to testing via clinical geneticists with ADPKD expertise. Access to genetic testing varies across Europe with key barriers including the cost of tests, resourcing of services, diverse reimbursement policies and a lack of clear, reliable information in some countries. Although data are lacking, the European Expert Group on Rare Diseases (EUCERD) have observed that genetic testing may offer economic advantages by avoiding unnecessary diagnostic and therapeutic procedures [60]. Next-generation sequencing technologies offer increasingly cost-efficient diagnostic strategies [61]. The ERKNet aims to develop standard criteria for genetic testing for inherited rare and complex kidney diseases [25].

Patients should have access to family planning services, including pre-implantation genetic diagnosis (PGD). PGD is used in reproductive medicine to screen for DNA mutations that cause inherited diseases in embryos created by *in vitro* fertilization. Anecdotally, PGD is of interest within the ADPKD patient community (T. Harris, personal communication). A UK survey suggested that many patients with ADPKD would seek PGD if it were available and that a majority believed it should be offered [62]. Currently, access to PGD varies for reasons that include regulatory, ethical and legal policies, cost, reimbursement policies, and attitudes among doctors and society [63]. Regarding cost issues, the potential for significant societal cost savings by avoiding ADPKD cases should be considered [1], although data are lacking. Other barriers may include low awareness of the method among patients. Nephrologists, geneticists and patient organizations have roles in collaboratively advocating for governments to formulate national policies on PGD.

All forms of genetic testing must be accompanied by access to accurate, personalized information and to counselling, preferably by clinical geneticists with ADPKD expertise [1, 13, 63].

## SPECIFIC RENO-PROTECTIVE PHARMACOTHERAPY

In Europe, a vasopressin V2 receptor antagonist (tolvaptan) is indicated to slow the progression of cyst development and renal insufficiency in ADPKD in adults with CKD Stage 1–3 at initiation of treatment with evidence of rapidly progressing disease [64]. European experts have published a decision algorithm to assess whether treatment is warranted, taking into account the adverse event profile and costs of treatment [14]. This guidance is expected to also help set the indications for other future therapies. Currently, patients' access to treatment, and its deployment within nephrology services, varies across Europe and national guidelines have been developed in some countries [65, 66]. Shared decision-making with patients is advocated: issues to be discussed with patients include the mechanism of drug action, expected adverse events, and need for precautions and lifestyle modifications [16]. Due to its mode of action, tolvaptan causes class effects of thirst, polydipsia, dry mouth, nocturia, pollakisuria and polyuria. Patients must be counselled to avoid dehydration [64]. In the TEMPO 3:4 trial, idiosyncratic increases [ $>3\times$  the upper limit of normal (ULN)] in alanine transaminase (ALT) and aspartate transaminase (AST) were observed in 4.4% and 3.1% of tolvaptan-treated patients, respectively, compared with 1.0% and 0.8% of placebo recipients. Two (0.2%) tolvaptan treated-patients, and a third patient treated in the TEMPO 4:4 extension trial, showed increases in hepatic enzymes ( $>3\times$  ULN) with concomitant elevations in total bilirubin ( $>2\times$  ULN) [64, 67]. Blood testing for transaminases and bilirubin is therefore required prior to initiation of tolvaptan, continuing monthly for 18 months and at regular 3-monthly intervals thereafter [64].

Other novel pharmacological approaches to slowing ADPKD progression are currently under investigation [52].

## FOLLOW-UP CARE

Life-long follow-up care for patients with ADPKD requires coordination between nephrologists (locally and at specialist centres, where relevant), other secondary care specialists and primary care physicians. Patients referred to specialist centres for particular assessments or interventions would typically be expected to return to the care of their local nephrologist for ongoing care, pending the need for any further consultation. The frequency of scheduled nephrology follow-up visits depends on CKD stage, blood pressure, specific monitoring requirements (e.g. associated with specific reno-protective therapy), complications and other clinical factors. An annual follow-up for adults without renal failure and with controlled blood pressure has been recommended [14, 52].

Primary care physicians may see relatively few patients with ADPKD but should be alert to the impact that the condition can have throughout its course and to current approaches to treatment, monitoring and support. Patients with suspected

ADPKD should be referred to a nephrologist, at least for a first visit, to establish the diagnosis, assess the rate of progression and the potential indication for specific reno-protective treatment, and to evaluate the presence of possible complications. Re-referral procedures should be established according to clinical need and the evolving standards of good practice.

For example, nephrology re-referral has been recommended in the event of complications or if eGFR falls below 60 mL/min [52]. Patients should be clearly informed regarding the roles of the healthcare professionals and appropriate contact procedures and actions if they experience complications. Special considerations for paediatric patients include the coordination of transitional care between paediatric and adult specialist nephrologists.

## ESRD

### Dialysis and transplantation

Kidney transplantation is the optimal RRT modality [1, 68], resulting in excellent patient and graft survival, improved QoL and lower healthcare costs compared with dialysis [3, 69–71]. Patients with ESRD due to ADPKD should be offered the opportunity to join a kidney transplant waiting list, if no contraindications exist. Pre-emptive transplantation from a living donor gives the best outcomes [68, 72], and this is facilitated in ADPKD by the relatively predictable decline in renal function. Pre-transplant nephrectomy is not routinely performed, but may be appropriate in selected individuals [1, 68]. Patients with symptomatic massive polycystic liver disease may be evaluated for isolated liver transplant or combined liver and kidney transplant, depending on kidney function. Importantly, even after a successful kidney transplant, patients require ongoing monitoring, care and support with respect to non-renal manifestations and complications.

Across Europe, fewer than 1 in 10 patients with ADPKD undergo kidney transplant as their first mode of RRT. Around 7 out of 10 of these transplants come from living donors [2]. Rates of kidney transplantation overall, and living donation, vary considerably between countries. In the Netherlands, 52% of all kidney transplants in 2015 came from living donors, while in some European countries this figure was <10% [73]. The autosomal dominant nature of ADPKD necessitates screening of potential related donors to exclude the disease. However, this need not be an obstacle to living donation: across Europe, the proportion of patients with ADPKD who receive a living donor kidney transplant as their first mode of RRT is more than twice as high as that in non-ADPKD CKD [2]. The main limitation is a shortage of available kidneys, while other barriers result from infrastructure, funding, legal frameworks, and attitudes among physicians and the public. Collaborative efforts are needed to improve access to transplantation in line with EU initiatives. In March 2016, the European Commission Working Group on Living Donation published a Toolbox to help Member States establish or optimize living donor programmes [74].

Haemodialysis and peritoneal dialysis are both suitable for most patients with ADPKD who cannot undergo a transplant or who are awaiting a transplant, and the choice between them should be made according to the individual circumstances [1].

Peritoneal dialysis is often not considered for use in patients with ADPKD owing to a lack of knowledge or experience of its use in this indication. However, it can be an adequate mode of RRT in most ADPKD patients [75–77]. Nephrologists and patients should therefore be fully informed on the potential use, and limitations, of this modality in ADPKD.

Evidence suggests that there is room for improvement in the information on RRT options provided to patients with all forms of CKD, and in the involvement of patients in decision-making [78, 79]. A European Commission-funded study, titled the ‘Effect of Differing Kidney Disease Treatment Modalities and Organ Donation and Transplantation Practices on Health Expenditure and Patient Outcomes’ (EDITH) pilot study is underway to assess the different treatment modalities for CKD in Europe and the factors influencing the treatment choices [80]. This study also aims to further develop and establish registries to follow-up living donors and transplant recipients.

## RESEARCH

Further research is needed to improve our understanding of ADPKD and to improve patient outcomes [1, 20]. Patients should be informed of opportunities to join registries and clinical trials. Paediatric patients with ADPKD should be included in research projects, as early disease detection and application of novel therapies at early disease stages might significantly improve the long-term outcome.

Local or national ADPKD registries provide valuable data, but these exist only in few European countries. Further, international, multispecialist collaboration is necessary to address the challenges of ADPKD research [17]. The ERKNet and ERN RARE-LIVER are valuable developments in this regard.

## CARE QUALITY CHECKLISTS

No widely accepted care quality standards exist for ADPKD, reflecting the lack of international evidence-based guidelines and pathways. The KDIGO Conference recommended that consultation checklists are needed for both patients and physicians and that these should include the patient’s experience of care and the impact of the disease, as well as the management of renal and extra-renal complications. A Quality Improvement Tool, comprising checklists at each Route Map stage, is being developed in conjunction with patients to help them, and other stakeholders, assess care quality.

## CONCLUSIONS

While healthcare delivery is the responsibility of national governments and providers, European-level bodies have an important role in fostering greater harmony in the approach to ADPKD. Individuals with ADPKD should have access to coordinated, patient-centred, multispecialist care according to the principles defined herein. Collaboration between the various specialists involved in ADPKD care is encouraged to design and implement these services, and to work with patient organizations to promote awareness building, education and research. All stakeholders, including national governments and healthcare providers, should support efforts to better inform patients and families and



to empower them to act as fully informed and active partners in care, i.e. to maintain self-management approaches, deal with the impact of the condition, and participate in decision-making regarding healthcare policies, services and research. The ADPKD Route Map, developed collaboratively by multidisciplinary ADPKD experts and patients, is a new tool to help patients navigate the services available to them and to help stakeholders and decision-makers take practical steps to ensure that all patients with ADPKD can access the comprehensive multispecialist care to which they are entitled.

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## CONFLICT OF INTEREST STATEMENT

### EAF Faculty:

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### Multispecialist participants

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