Translating science into policy to improve ADPKD care in Europe

A report by the European ADPKD Forum

ADPKD, autosomal dominant polycystic kidney disease

This report is endorsed by

PKD International

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European ADPKD Forum

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European ADPKD Forum, January 2015

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European ADPKD Forum

Foreword

Prof. Norbert Lameire

It is with pleasure and admiration that the European Kidney Health Alliance (EKHA), an alliance of non-profit organisations representing the key stakeholders in kidney health in Europe, introduces this report on autosomal dominant polycystic kidney disease (ADPKD) by the European ADPKD Forum (EAF).

The aims of the EAF are in perfect harmony with the aims of the EKHA, i.e., among others, raising the awareness of the importance of overall kidney health and of the growing prevalence and societal burden of acute and chronic kidney diseases. In addition, both EKHA and the EAF will try to encourage the early detection and prevention of kidney diseases, and to influence future European Union research priorities and secure funding for innovation of care. Both EKHA and the EAF promote cooperation with other key stakeholders in the chronic disease arena and want to facilitate exchange of new information and provide expertise to the EU policy makers.

This report brings an up-to-date summary of the most important translational scientific aspects of ADPKD into policy to improve the care of patients with this dreadful disease in Europe.

As explained in this report, ADPKD is the most common hereditary kidney disease. Some patients with very few symptoms are not diagnosed during their lifetimes. This means that a family member may have the disease without knowing it. Signs of ADPKD often do not appear until adulthood, which is why this type of polycystic kidney disease is sometimes called 'adult PKD'. Not well known outside the renal community, ADPKD is an important cause of kidney failure, necessitating dialysis or transplantation in approximately 50,000 people across Europe. This likely represents only a small proportion of the total number of cases, as most patients living with ADPKD have yet to develop kidney failure. Many remain undiagnosed until they develop symptoms or undergo screening if there is a family history.

ADPKD is a systemic disorder, and people with ADPKD often have cysts in other organs, such as the liver. A subset of ADPKD patients have vascular complications, including intracranial and large-vessel aneurysms. The appearance of these extra-renal symptoms, like the kidney disease, is highly variable. Both renal and extra-renal manifestations are the cause of a lot of suffering. Despite extensive ongoing research, the molecular basis of cyst formation and cyst enlargement remains incompletely understood.

In addition, there are still important questions about the optimal care of people with cystic diseases. For example, hypertension is one of the earliest and most common manifestations and an important cause of morbidity and mortality in ADPKD. It has been associated with more rapid renal disease progression and is the focus of ongoing studies. Similarly, there is a high prevalence of systemic hypertension in children with ADPKD, and severe hypertension is often present in the first few months of life. Which BP goals are appropriate for ADPKD patients with incipient chronic kidney disease is still unknown.

Besides the scientific and purely medical aspects associated with ADPKD, this report also addresses a number of physical and psychological effects that can impair quality of life and wellbeing for not only the patient and his or her societal environment, but also their family. These aspects are often underestimated by healthcare professionals and other stakeholders.

EKHA sincerely congratulates the EAF for this initiative and hopes that with close cooperation between both organisations the care and wellbeing of all patients with kidney disease, including patients and families affected by ADPKD, will further improve in Europe in the future.

Prof. Norbert Lameire
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Chair, European Kidney Health Alliance

EKHA
EUROPEAN KIDNEY HEALTH ALLIANCE

Foreword

Mrs Soledad Cabezón Ruiz

First of all, I would like to thank the European ADPKD Forum (EAF) for giving me the opportunity of introducing this Report on autosomal dominant polycystic kidney disease (ADPKD), an inherited, chronic and incurable condition that is under-appreciated outside the nephrology field.

As a practitioner and a politician, I am fully aware of the need to raise awareness of chronic diseases and specifically those such as ADPKD which are little known outside the scientific community.

In Europe we face an enormous challenge: chronic diseases represent the major share of the burden of disease, and are responsible for 86% of all deaths in the region according to the World Health Organization (WHO). Translating this into economic data, the Organisation de coopération et de développement économiques (OCDE) estimates that 70% to 80% of healthcare costs are spent on chronic diseases. This corresponds to an estimated €700 billion in the European Union. However, 97% of this amount is spent on treatment whereas only 3% goes towards prevention.

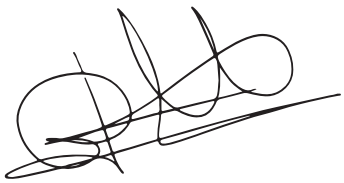
The European Union and WHO have recently promoted comprehensive, strategic approaches to tackling chronic diseases. The EU Reflection process on chronic diseases has been followed by the ongoing Joint Action on Chronic Diseases and Healthy Ageing across the Life Cycle. Central aspects of chronic disease strategies include: an integrated, collaborative approach involving all stakeholders, support for exchange of good practice on disease prevention and management, the adoption of innovative approaches and new technologies, and the empowerment of patients as a partner in decision-making about healthcare.

To date, kidney disease has not featured strongly in these strategies, despite accumulating evidence of its increasing contribution to the global disease burden. In the following Report, the EAF draws attention to the specific impact on patients and healthcare services of ADPKD, whose main challenges lie in: the need to raise awareness, the promotion of common guidelines and unified criteria for patients and practitioners, and improved research into specific treatments which would potentially slow the progression of the disease.

After defining the principal unmet needs in this setting, the EAF presents a short series of policy-focused recommendations to help address these needs, and to promote access to high-quality care for all patients with ADPKD in Europe.

These recommendations are well-aligned with the main tenets of the aforementioned chronic disease strategies. They aim to foster standardised care based on best practice and collaboration between stakeholders and health centres for the purposes of patient care and research, to support innovation in this field, and to help empower patients in decision-making in their own care and in driving system-wide improvements.

This Report touches on many health policy areas including initiatives on cross-border healthcare, health inequalities and access, genetic testing, kidney transplantation and healthcare technology assessment. Clearly the complex nature of ADPKD begs a targeted, strategic approach including collaboration between patients, healthcare professionals, healthcare managers, public health bodies and health ministries, as well as European-level decision makers. I commend this report and hope that it serves to progress such collaboration in this important disease area.



Mrs Soledad Cabezón Ruiz
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Executive summary

1. Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a chronic, progressive, inherited condition in which cysts grow in the kidneys and other organs. ADPKD is the most common inherited kidney disease, and one of the most common of all life-threatening inherited diseases. Current challenges in ADPKD include a lack of awareness among many health stakeholders, variations in ADPKD care, the absence of approved treatments, and challenges in translating advances in our understanding of ADPKD into clinical benefit for patients.

This report explains what ADPKD is, how it affects patients and their families, and the demands it places on healthcare systems, before proposing strategies to improve ADPKD across Europe in context with relevant European Union policy initiatives.

2. ADPKD: an overview

ADPKD is an important cause of chronic kidney failure, affecting hundreds of thousands of people in Europe. It is responsible for up to one in ten of all patients needing dialysis or transplantation, corresponding to approximately 50,000 people across Europe. Kidney cysts grow throughout life in patients with ADPKD, causing symptoms that include pain, cyst infections, bleeding and abdominal distention, and eventually resulting in kidney failure. ADPKD also causes liver cysts in most patients, and can affect many other organs. Patients with ADPKD are at risk of high blood pressure and cardiovascular disease. The disease can be diagnosed both in adults and in paediatric patients.

Patients require treatments for the various manifestations and complications of ADPKD throughout their lives, and ultimately most patients require either a kidney transplant or dialysis, known collectively as renal replacement therapy.

3. What does ADPKD mean for patients and families?

ADPKD has lifelong physical and psychological effects that can impair quality of life (QoL) and wellbeing, and interfere with functioning and work. Pain is perhaps the symptom that most affects patients' QoL. In the late stages of disease, dialysis has a major impact on daily lives of patients. ADPKD can detrimentally affect various other aspects of life, including employment, the obtainment of health or life insurance or mortgages, and family planning. The impact of ADPKD on affected patients and families is often underestimated by healthcare professionals and other stakeholders.

4. Impact of ADPKD on healthcare systems

Patients with ADPKD incur healthcare costs throughout life due to outpatient care and hospitalisations. The costs of ADPKD rise significantly when patients need dialysis or transplantation – ADPKD accounts for around one in 10 patients needing these treatments, at a cost of €1.5 billion/year across Europe. Research on the prevention of ADPKD-related complications could offer a tremendous return on investment.

Transplantation is highly cost-effective compared with dialysis and investments to increase transplantation rates and reduce waiting times are expected to be cost-saving.

5. Unmet needs in ADPKD care

Patterns of clinical practice for ADPKD diagnosis, assessment, treatment and support vary within and between European countries. There is an unmet need for all patients with ADPKD to have access to a nephrologist knowledgeable about the disease, and greater coordination of care policies and services is required. The optimisation and standardisation of ADPKD care in Europe is hampered by the lack of evidence-based consensus guidelines and standardised care pathways.

There is an urgent need for new medicines that delay the decline in kidney function due to ADPKD, thereby maintaining QoL and improving life expectancy among patients and reducing the impact on European health systems. Further efforts to promote kidney transplantation for patients with kidney failure are also necessary.

The total kidney volume is the most commonly used predictive factor to help identify patients likely to progress rapidly and hence to allow care to be individualised, although there is no consensus yet on the optimal way to predict prognosis.

6. Therapeutic innovation in ADPKD

Although our understanding of ADPKD has improved, challenges remain in translating these advances into new disease-modifying medicines available to patients. Collaborative multi-centre efforts are required to provide patient populations large enough for research. ADPKD research is also complicated by the chronic, progressive disease course affecting many parts of the body. Research is ongoing to refine and validate methods to predict disease prognosis for research and clinical purposes. At present there is no well-accepted patient-reported outcome of the impact of ADPKD.

7 Empowering patients with ADPKD

Patients and families affected by ADPKD need specific, comprehensive, accessible information about their disease in order to fully participate in decision-making.

Patients also have important roles in driving improvements in ADPKD diagnosis and care in partnership with healthcare professionals, researchers, healthcare system managers and health ministries. All stakeholders, including the European Commission, national governments and healthcare providers, should support efforts to better inform individual patients and families affected by ADPKD, and to include patient organisations within strategic and tactical aspects of healthcare planning and delivery, including the design of care services and research. Authorities responsible for assessing the effectiveness and value of ADPKD treatments and services should engage patients in their processes and use patient evidence to inform their decision-making.

8 EAF policy recommendations

The European ADPKD Forum (EAF) hereby provides a short series of policy-focused recommendations to help address the unmet needs identified in this Report and to promote access to high-quality care for all patients with ADPKD in Europe.

Recommendation 1: Governments should support the development of a nationally coordinated, tiered approach to ADPKD care in collaboration with experts, patient organisations and other stakeholders.

Recommendation 2: An expanded European network of ADPKD reference centres would facilitate further research and the establishment of harmonised, integrated, patient-centred care pathways.

Recommendation 3: The European Commission and national governments should support research to develop disease-modifying treatments for ADPKD with the potential to maintain QoL, delay renal decline and improve life expectancy among patients, and to reduce the economic impact on healthcare systems.

Recommendation 4: Governments and healthcare providers should support the implementation of methods to routinely assess prognosis in patients with ADPKD to inform clinical decision-making, research and innovation.

Recommendation 5: All stakeholders, including the European Commission, national governments and healthcare providers, should support efforts to better inform individual patients and families affected by ADPKD, and to involve patient organisations in policy making regarding healthcare planning and delivery related to ADPKD.

Recommendation 6: Health technology assessment (HTA) organisations should seek to engage patients and patient organisations in assessments to provide patients' unique knowledge about the impact of living with ADPKD, and their aspirations for new treatments, according to the HTA International Quality Standards for Patient Involvement in HTA.

1. Introduction

Key points

- **Autosomal dominant polycystic kidney disease (ADPKD) is a chronic, progressive, inherited condition in which cysts grow in the kidneys and other organs.**
- **ADPKD is the most common inherited kidney disease, and one of the most common of all life-threatening inherited ('monogenic') diseases.**
- **Current challenges in ADPKD include a lack of awareness among many health stakeholders, variations in ADPKD care, the absence of approved treatments, and challenges in translating advances in our understanding of ADPKD into clinical benefit for patients.**
- **This report explains what ADPKD is, how it affects patients and their families, and the demands it places on healthcare systems, before proposing strategies to improve ADPKD care across Europe in context with relevant European Union policy initiatives.**

1.1 Background

Autosomal dominant polycystic kidney disease (ADPKD) is a chronic, progressive condition in which fluid-filled sacs, or cysts, increase in number and size in the kidneys and other organs, notably the liver.[1] ADPKD is the most common inherited kidney disease, and one of the most common of all life-threatening inherited diseases.[1] Individuals with ADPKD commonly experience pain, bleeding and infections. Kidney failure occurs in most patients, on average before the age of 60 years.[2,3] Patients with ADPKD are also prone to high blood pressure and cardiovascular disease.[4]

Current challenges and unmet needs in ADPKD in Europe include:

- *A lack of awareness and recognition of the importance of ADPKD among healthcare policymakers, healthcare managers and some healthcare professionals*
- *A lack of awareness or understanding of ADPKD among the public, which can limit healthcare consultation and adherence to therapy*
- *Variations and inequities in ADPKD care, due in part to a lack of standardised care pathways and awareness of the impact of the disease on patients*
- *The absence of approved treatment options to slow disease progression, maintain patients' quality of life (QoL) and delay dialysis and transplantation*
- *Challenges in the development of innovative therapies and in their assessment by regulatory and reimbursement bodies.*

These challenges exist in the context of an increasing international recognition of the need to address the burden of chronic kidney disease in general.[5]

1.2 About the European ADPKD Forum report

This report, the first publication of the European ADPKD Forum (EAF; see panel overleaf), is based on the latest scientific knowledge about ADPKD and insights from leading experts and patient advocates. It also features results from a recent large survey of patients with the condition. It aims to:

- *Explain ADPKD and raise awareness of the disease and its implications for patients, health services and economies in Europe*
- *Recommend strategies to improve ADPKD care within the context of health policy development at the European and national levels*
- *Encourage and facilitate collaboration between the individuals and groups involved in the management of people with ADPKD, including health policy-makers, healthcare providers, payers, patients, caregivers and industry.*

The report is structured as follows:

Section 1 – Introduction

Section 2 – ADPKD: an overview Briefly explains the epidemiology and genetic basis of ADPKD, the signs and symptoms, how disease progression occurs, and approaches to its diagnosis, assessment and management.

European ADPKD Forum

The European ADPKD Forum (EAF) is a multidisciplinary, international faculty of ADPKD experts dedicated to improving the health and quality of life of people with ADPKD. The Forum comprises leading patient advocates together with practitioners and researchers from the fields of nephrology, hepatology and genetics. The EAF was initiated by, and is solely supported by, Otsuka Pharmaceutical Europe Ltd. Neither the Co-chairs of the EAF, nor the Faculty members, receive fees in respect of their roles in the initiative, and the opinions in this Report are those of the authors and not necessarily those of the sponsors. EAF Faculty members are listed in Section 9.

Section 3 – What does ADPKD mean for patients and families? Explains how ADPKD and its treatment negatively affects patients, including the impact on QoL, relationships and working lives, and how this is often under-recognised.

Section 4 – Impact of ADPKD on healthcare systems Presents recent data on the contribution of ADPKD to healthcare resource usage and costs.

Section 5 – Unmet needs in ADPKD care Identifies barriers to optimal diagnosis, assessment and treatment of ADPKD.

Section 6 – Therapeutic innovation in ADPKD Discusses challenges to research and innovation in ADPKD.

Section 7 – Empowering patients with ADPKD Explains why and how patients with ADPKD need to be empowered to help improve standards of care.

Section 8 – EAF policy recommendations Recommends strategies to improve ADPKD across Europe in context with relevant European Union policy initiatives.

Section 9 – European ADPKD Forum members

Section 10 – Polycystic kidney disease organisations

Section 11 – Glossary

Section 12 – References

This EAF report complements the 2014 Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference Report. Aiming toward the harmonisation and standardisation of ADPKD care, the KDIGO Report summarised the outstanding knowledge gaps and proposed a research agenda to resolve controversial issues.[6] The EAF Report has also been developed in alignment with the work of the Working Group on Inherited Kidney Disorders of the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA).[7]

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2. ADPKD: an overview

Key points

- **ADPKD is an important cause of chronic kidney disease and kidney failure, affecting hundreds of thousands of people in Europe. It is responsible for up to one in ten of all patients needing dialysis or transplantation, corresponding to approximately 50,000 people across Europe.**
- **Kidney cysts grow throughout life in patients with ADPKD, causing symptoms that include pain, cyst infections, bleeding and abdominal distention, and eventually resulting in kidney failure.**
- **ADPKD also causes liver cysts in most patients, and can affect many other organs of the body.**
- **Patients with ADPKD are at risk of high blood pressure and cardiovascular disease.**
- **Patients require treatments for the various manifestations and complications of ADPKD throughout their lives, and ultimately most patients require either a kidney transplant or dialysis, known collectively as renal replacement therapy.**

2.1 Introduction

ADPKD is a complex genetic condition affecting various parts of the body. An awareness and understanding of the disease process is vital to understanding the unmet needs among patients with ADPKD and within healthcare systems. Therefore, this section briefly explains:

- *How many people are affected by ADPKD*
- *The genetic basis of the disease*
- *How the disease affects the body and progresses over time*
- *Approaches to its diagnosis, assessment and management.*

2.2 How common is ADPKD, and what causes it?

ADPKD is an important cause of chronic kidney disease and kidney failure, affecting hundreds of thousands of people in Europe. It is responsible for up to one in ten of all patients needing dialysis or transplantation, corresponding to approximately 50,000 people across Europe.[1]

This figure represents only a proportion of the total number of cases as many patients living with ADPKD have yet to develop kidney failure or remain undiagnosed. Overall, ADPKD has conventionally been thought to affect around 1 in 1000 of the population.[2] This estimate requires further validation as divergent prevalence rates (as low as approximately 1 in 3000) have been reported in some European populations, reflecting variable screening strategies and health system characteristics.[3–4]

ADPKD affects both men and women from all ethnic groups, and can cause symptoms during childhood as well as in adults.

Why are the kidneys so important?

The kidneys have many essential functions. They filter the blood to remove waste products from the body's metabolism; these are excreted in the urine. They also reabsorb nutrients and adjust the balance of water and salts in the body, thereby regulating the blood pressure. The kidneys also produce several hormones important for the production of red blood cells, the absorption of calcium and the regulation of blood pressure.

ADPKD inheritance

The gene alterations that cause ADPKD are inherited in a 'dominant' pattern, meaning that the alteration need only be present in the inherited DNA from one parent for it to cause disease. Each person with ADPKD has a 50% (i.e. one in two) chance that any child he or she has will inherit the gene causing the disease. However, the severity and progression of ADPKD can vary greatly, even between family members.

ADPKD is caused by genetic alterations or 'mutations' in one of two genes, ***PKD1*** and ***PKD2***. Approximately 85% of cases with an identified cause are caused by ***PKD1*** mutations and 15% by ***PKD2*** mutations.[5,6] The ***PKD1*** and ***PKD2*** genes code for two proteins called polycystin-1 and polycystin-2, respectively. These proteins are found in hair-like structures called cilia that extend from the surface of cells. Although the exact function of the polycystin proteins are unclear, defects in the cilia are thought to be important in ADPKD and so the disease is regarded as a 'ciliopathy', i.e. a genetic disorder of the cell cilia.[7] How ***PKD1*** and ***PKD2*** mutations cause cysts and other features of ADPKD to develop is also not clear, and it appears that many complex cellular processes are involved.[7]

ADPKD caused by ***PKD1*** mutations is typically more severe than that caused by ***PKD2*** mutations, resulting in kidney failure up to 20 years earlier. However, both forms cause premature kidney failure and shorten life expectancy.[8]

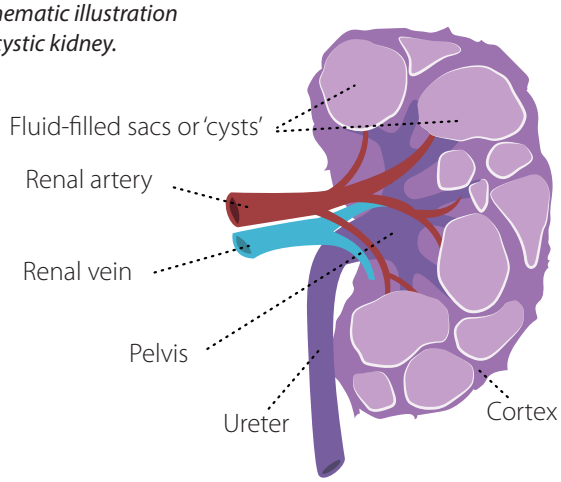
2.3 How does ADPKD affect the body?

ADPKD is a progressive disease that typically causes severe kidney damage in adult life, resulting in kidney failure in patients in their fifties or sixties. Many other organs may also be affected.

Cyst formation and progression

ADPKD causes fluid-filled cysts to develop from the tubules of both kidneys. These cysts appear continuously throughout life. This causes the kidneys themselves to grow, increasing on average by 5–6% each year.[9,10] The kidneys of a patient with ADPKD can become greatly enlarged, with inflammation and 'fibrotic' tissue (Fig. 1).

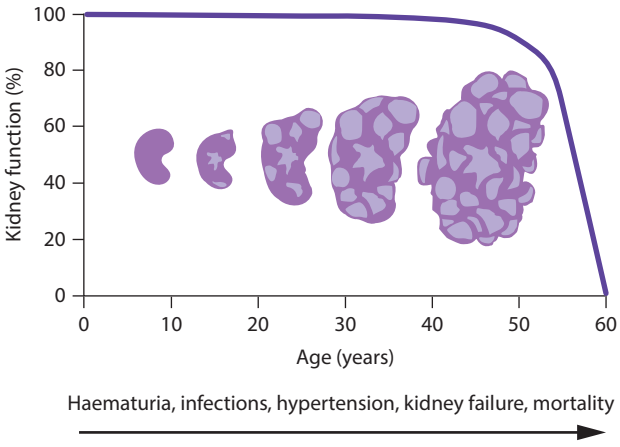
Fig. 1. Schematic illustration of a polycystic kidney.



Early in the disease, the healthy kidney tissue compensates for the damage caused by cysts. This means that the kidneys can appear to be working normally for many years. However, the damage accumulates until eventually kidney function declines and progresses to kidney failure (Fig. 2). On average, patients with ADPKD require a kidney transplant or dialysis between 55 and 60 years of age.[11,12]

ADPKD damage accumulates until kidney failure occurs later in life.

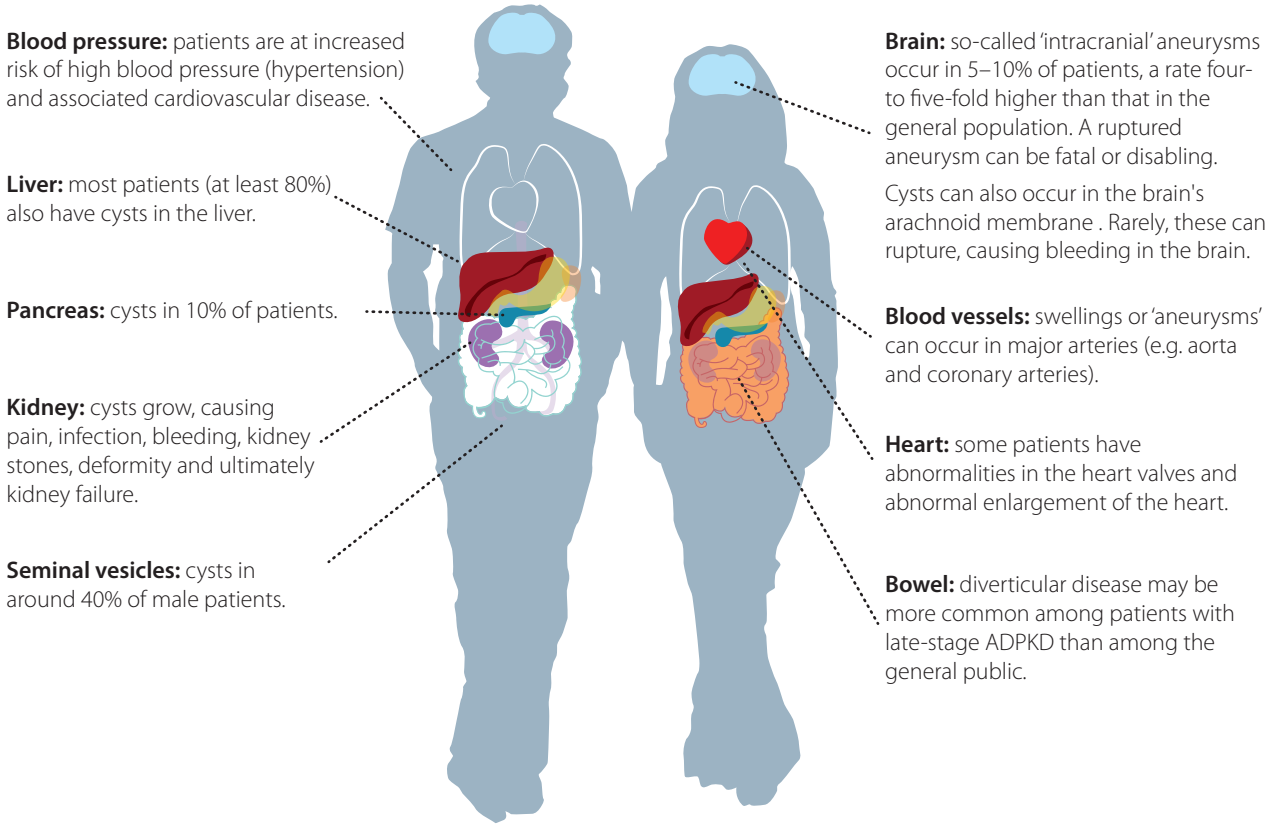
Fig. 2: Relationship between cyst and kidney growth, kidney function, symptoms and age in patients with ADPKD.



As well as damaging the function of the kidneys, kidney cysts cause other complications,[2,13] including:

- *Pain – the most common symptom experienced by people with ADPKD*
- *Infections of cysts and the urinary tract*
- *Kidney stones*
- *Bleeding into the cysts and the urine*
- *Abdominal deformation, causing stress and effects on lifestyle.*

Fig. 3. ADPKD affects many parts of the body.



Effects on other parts of the body

Cysts can also occur in other parts of the body (Fig. 3). Overall, at least eight out of 10 patients with ADPKD have cysts in the liver.[14] Liver enlargement is common even in the early stages of ADPKD.[15] Like kidney cysts, these can become very numerous and large, and can cause complications related to massive abdominal distension. Like kidney cysts, liver cysts can also be complicated by infection or bleeding.[16]

Patients with ADPKD often report other symptoms, such as fatigue, breathlessness, weakness and general malaise.[17]

Liver cysts are the most common ADPKD manifestation outside the kidneys.

Importantly, people with ADPKD are also at high risk of developing high blood pressure (or 'hypertension') and cardiovascular disease, as compared with the general population.[18] Around 50–70% of patients have hypertension before substantial kidney impairment occurs. Hypertension is common even in children with ADPKD. Hypertension is associated with faster progression to kidney failure, as well as an increased risk of cardiovascular disease and stroke.[18] Cardiovascular disease is the main cause of death among patients with ADPKD.[1]

2.4 Diagnosis

ADPKD is most often diagnosed when patients present with signs or symptoms such as abdominal pain, blood in the urine or high blood pressure. Alternatively, it may be identified during a medical examination performed for other reasons. In some cases patients may not be diagnosed until late in life and remain symptom-free. As ADPKD is inherited, people who have a parent with ADPKD may consider screening before they develop symptoms.

Defining chronic kidney disease

Chronic kidney disease is defined as abnormalities of kidney structure or function, present for more than 3 months, with implications for health.[19] The principle measure of kidney function is called the glomerular filtration rate (GFR). A measure of how much fluid is being filtered by the kidneys, the GFR falls as the kidney function declines. GFR is used to define five stages of increasing severity of chronic kidney disease, from Stage 1 (when GFR is normal or high) to Stage 5, known as kidney failure.

Aspects of ADPKD management[2,13,21,22]

- *Blood pressure control – protects against cardiovascular disease and slows kidney growth*
- *Increased water intake – **may** protect kidney function*
- *Dietary salt restriction – to help control blood pressure and possibly may help protect the kidneys*
- *Dietary protein restriction (at Stage 4 chronic kidney disease with severe decline in kidney function) – to avoid waste products of metabolism accumulating in the blood*
- *Avoid high caffeine intake (which **may** promote cyst growth)*
- *Weight control, including exercise*
- *Symptom management: e.g. pain*
- *Management of kidney complications: infection, kidney stones, bleeding into cysts*
- *Avoidance of activities that risk injuring the kidneys, such as contact sports*
- *Management of other manifestations: e.g. liver cysts*
- *Management of other cardiovascular risk factors, e.g. cholesterol*
- *Renal replacement therapy: transplantation or dialysis*

Imaging of the kidneys should be performed as an initial evaluation of a patient with ADPKD.[13] Ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) can all be used to examine the kidneys for cysts, subject to clinical indications and local availability.[13,20] Genetic testing to detect the DNA mutations that cause ADPKD may be used to confirm the diagnosis in some situations, particularly in children.[13]

2.5 Management

Typically, ADPKD management involves various measures with unproven effects on disease progression and treatments for the various manifestations and complications of the disease (see Panel). However, there are no evidence-based, European-level guidelines for ADPKD management (Section 5).

Slowing ADPKD progression

ADPKD cannot be cured and in Europe there is currently no approved treatment to delay its progression. Some studies suggest that disease progression may be slower in patients with lower blood pressure.[23] Recently, a large, landmark study in patients with early stage ADPKD and high blood pressure confirmed that aggressive blood pressure control (to a target 95-110/60-75 mmHg) slows kidney growth compared with standard blood pressure control (target 120-130/70-80 mmHg).[24] Aggressive blood pressure control did not significantly affect the decline in kidney function (as measured by the GFR; see panel on page 11), however, meaning that other approaches to slowing disease progression are needed. Widely used medicines called angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are recommended for use in people with ADPKD.[13] Blood pressure can be well controlled using an ACE inhibitor, in combination with other medications if necessary; adding an ARB does not alter the progression of the disease.[24]

Several measures (see Panel) are commonly used in an attempt to protect the kidneys, but there is no good evidence that they work (Section 5). New medicines for ADPKD are in development, but innovation in this disease is challenging (Section 6).

Cardiovascular risk management

Controlling high blood pressure by weight loss, lifestyle modification or medical treatment is very important to reduce the risk of cardiovascular disease.[13,18] Indeed, aggressive blood pressure control is more beneficial than standard blood pressure control even in young patients with early ADPKD.[24]

Other risk factors should also be addressed, including high cholesterol levels (e.g. by treatment with medicines known as 'statins'). Patients also are advised to limit their salt intake, stop smoking, eat a healthy diet, moderate their alcohol intake and to take exercise.[13] However, despite their importance, cardiovascular risk factors are often not properly controlled in patients with ADPKD.[25]

Managing symptoms and complications

Patients with ADPKD commonly require treatment for pain, other symptoms and complications such as cyst infections, kidney stones and bleeding within cysts.[2,13,21,22]

Renal replacement therapy

Most patients with ADPKD eventually need a kidney transplant or dialysis, known collectively as renal replacement therapy (RRT). ADPKD accounts for around one in 10 of all people undergoing a kidney transplant or dialysis.[1] The choice between transplantation and dialysis depends on factors such as patient choice, physicians' advice and local resource availability.

Transplantation: When possible, kidney transplantation is the treatment of choice and gives excellent outcomes.[26] The ideal approach involves a 'pre-emptive' transplant (i.e. before resorting to dialysis) from a living donor.[13,21] Given the predictable evolution of renal function deterioration in patients with ADPKD, it is important to perform a transplant evaluation before patients need dialysis. This can allow patients to be placed on a waiting list for a cadaveric donor, in case the option of a living donor is not available.

Dialysis: This is used if transplantation is not possible, or while patients are waiting for a transplant. Dialysis involves artificially filtering the blood to remove waste products and excess water. There are two forms of dialysis: haemodialysis and peritoneal dialysis. Haemodialysis filters the blood through a dialysis machine outside of the body. Peritoneal dialysis filters the blood using a membrane within the patient's own abdomen. Either method can be used in ADPKD, although haemodialysis is used most often.[1,11]

Without dialysis or transplantation, kidney failure due to ADPKD is life-threatening. However, neither dialysis nor transplantation is a cure for ADPKD.

2.6 Conclusions

ADPKD causes a progressive decline in kidney function and the development of kidney failure. Patients require treatments for its various manifestations and complications throughout their lives, but no European-level, evidence-based guidelines for ADPKD management exist. Ultimately, most patients require either a kidney transplant or dialysis. In the next section we review the impact that ADPKD has on patients themselves.

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3. What does ADPKD mean for patients and families?

Key points

- **ADPKD has lifelong physical and psychological effects that can impair quality of life (QoL) and wellbeing, and interfere with functioning and work. However, little formal research has been conducted.**
- **Pain is perhaps the symptom that most affects patients' QoL, while in the late stages of disease, dialysis has a major impact on daily lives of patients.**
- **ADPKD can detrimentally affect various other aspects of life, including employment, the obtainment of health or life insurance or mortgages, and family planning.**
- **The impact of ADPKD on affected patients and families is often under-estimated by healthcare professionals and other stakeholders.**

3.1 Introduction

Chronic kidney disease substantially decreases health-related quality of life (QoL) and its impact worsens as kidney function deteriorates.[1–3] Little formal research has been conducted into the specific impact of ADPKD on patients. However, there is accumulating evidence of its lifelong effects on QoL and wellbeing.

This section explains how ADPKD affects patients' QoL, relationships and working lives and presents new insights from recent surveys of patients in Europe.

3.2 Physical impact

Most patients with ADPKD experience symptoms even at early stages of the disease when kidney function is normal,[4] and these symptoms worsen throughout life. Interviews conducted with 80 patients in Denmark, Finland, France, Germany, Italy, Norway, Spain, Sweden and the UK revealed that most individuals with early stage ADPKD experienced symptoms that were severe enough to interfere with work and physical activity or exercise.[4]

ADPKD often affects patients' working lives. In another survey, 730 patients in the aforementioned countries completed an online questionnaire about the effect of ADPKD on their lives.[5] The patients had an average age of 45 years. Almost a fifth (19%) were on dialysis and 9% had received a kidney transplantation. According to their responses:

- *A quarter (26%) of patients who had told their employer about their ADPKD stated that it had a negative impact.*
- *65% of patients (chronic kidney disease Stage 3–5) in full or part-time employment took time off due to ADPKD.*

"ADPKD is a condition that my employers don't seem to understand. It's been quite frustrating trying to explain the condition and the effects it's had on me. I find it difficult to explain the tiredness and especially the amount of pain I've had. I had to take a lot of time off to recover from the pain. My bosses don't quite understand what I've had to go through to try and get back to work. They seem to think it's a condition that can be fixed and once you've recovered they don't expect it to happen again. So that's frustrating, trying to explain again and again. It's frustrating because my kidney function is okay, so physically I should be okay and I should feel normal. Even when dealing with doctors at the emergency department it can be a bit difficult for them to understand the condition, because a lot of them haven't even heard of polycystic kidney disease since medical school. It's even worse with my son because he wants to have a dad who can run around in the park with him, and when you don't feel up to it and you've got to take the painkillers it's almost heart-breaking, in that you feel like you're letting him down."
Justin, UK

These patients took a median of 7.5 days' (mean 12 days) sick leave each year due to ADPKD. Overall, among all patients with stage 3–5 chronic kidney disease, the median number of sick leave days taken due to ADPKD was 5 days (mean 7.6 days).

- *Self-employed patients reported often having to make changes to their working life, especially by reducing working hours. This mainly occurred in later stages of the disease.*
- *One-third of patients (33%) stated that ADPKD had a negative impact on their social life – this increased to 53% at Stages 3–5.*

3.3 Psychological impact

ADPKD can have a profound emotional impact, expressed by patients in terms of:[4]

- *Loss (of their future, their roles and self-concept, and their valued activities)*
- *Uncertainty (certainty of their decline and outcome but uncertainty about when and how bad this will be)*
- *Fear, for example of dialysis or transplantation, or of the rupture of a brain aneurysm.*

Together, these aspects may often result in anxiety or depression.[6,7] For example, in Brazil, 61% of 38 patients with ADPKD (diagnosed for an average of 6 years) had depression, although none were being treated for this. Patients most commonly commented on a loss of libido, concerns about physical health, sleep disturbance, fatigue, and difficulty working. Patients with ADPKD also showed some evidence of anxiety. The worst affected aspects of QoL were those relating to general health and emotional aspects.[6]

A recent study in Poland showed that patients who have ADPKD, but who have no symptoms, still tend to suppress anxiety and depression, reflecting the high psychological costs of the disease. Patients also had lower life satisfaction levels, as compared with healthy individuals.[8]

Feelings such as anxiety and depression may reduce adherence to treatment among patients with ADPKD. A lack of adherence to treatments for high blood pressure, in particular, could place patients at risk of cardiovascular disease.

ADPKD can have a profound emotional impact, which can result in depression and anxiety.

Around two-fifths of patients completing the aforementioned online survey reported that APDKD had affected their relationships.[5] A similar proportion reported negative effects on their sexual relationships, mainly due to the psychological impact of ADPKD. Around three-quarters (77%) thought that their family had been affected, and were often concerned and worried about this.

Importantly, the impact of ADPKD on QoL cannot be accurately assessed at present because no suitable questionnaire has been fully validated (see Section 6.2).

"ADPKD is like living on a knife-edge, on the edge of a precipice, and you're walking towards it and one day you know you will fall down it. It's always at the back of your head, something that you wake up in the middle of the night and think about occasionally, that you cry about occasionally. It's a silent killer and too few people know about ADPKD and understand and appreciate the impact it has on the individuals affected and their families. ADPKD is an ever present feature of my life and the lives of my family. I had an older sister who died last year of complications from the disease. I don't expect to be an old, frail lady. I do expect to die sooner than most people would expect to die."
Tess, UK

3.4 Pain – a particular problem

Pain is perhaps the symptom that most affects patients' QoL. ADPKD causes various different kinds of acute and chronic pain.[9,10–14] In recent studies, around half of patients suffered from kidney pain or back pain, while over a quarter reported abdominal pain.[12,15] In an earlier study, almost two-thirds of patients with all forms of polycystic kidney disease reported having back pain daily or constantly, while a quarter had daily or constant abdominal pain.[9] Patients report chronic dull pain, acute 'stabbing' pain, and abdominal fullness or discomfort, as well as more generalised pain.[10,11]

Patients often report that the pain associated with ADPKD can affect their mood and interfere with their sleep, relationships, daily activities and their enjoyment of life.[10–13]

Pain can occur even in the early stages of ADPKD, and indeed for many patients it is the symptom leading to diagnosis.[9] Generally, however, patients are more likely to report that pain affects their daily lives, and have worse QoL scores, as their kidney function worsens.[6,12]

Other symptoms – such as fatigue, heartburn, fever, bleeding into the urine, abdominal distension, anorexia and cyst infection – may also worsen QoL. Liver cysts,

the most common manifestation of ADPKD outside the kidneys, also impair QoL, even during the early stages of the disease.[16–18]

"What I fear the most is to see my daughter going on dialysis one day. Dialysis represents death for me in a way because my father died on dialysis and this is obviously a fear that everybody who has ADPKD has."
Corinne, France

3.5 Impact of renal replacement therapy

Dialysis has a major impact on the daily lives of all patients with all forms of chronic kidney disease. Many patients spend considerable time on dialysis while they await transplantation. In the UK, for example, the average waiting time for a kidney transplant (across all forms of chronic kidney disease) is 1,100 days.[19]

The principal frustrations of patients with ADPKD include the need for dialysis (20%) or transplantation (12%), and the progression of the disease (15%).[5]

Surveyed patients with ADPKD reported that their three biggest frustrations are dialysis and disease progression and, later in the course of the disease, the delay in transplantation. Overall, dialysis took an average of 11–15 hours per week (including travel), although some patients in Denmark, Germany and the UK spent over 20 hours per week on dialysis.[5] Among surveyed patients with ADPKD who had received or were waiting for a transplant, approximately half had waited between 1 and 3 years. Germany and the UK had the longest waiting time of more than 5 years.

3.6 ADPKD in paediatric patients

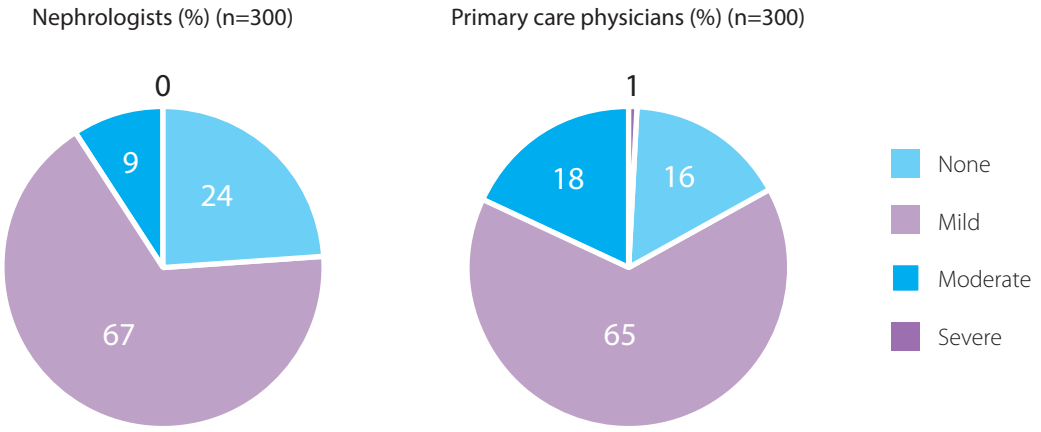
ADPKD is an inherited disease and hence is present from birth. ADPKD can be diagnosed in infants, children and adolescents, for example following investigations for urine infections, pain, high blood pressure or as a chance finding during other tests. Children and adolescents with ADPKD may experience various psychological, social and economic repercussions due to the diagnosis, although this has been little studied. In light of these issues, paediatric patients and their parents need particular support.[20]

3.7 Under-recognition of impact

Healthcare professionals may often underestimate the impact of ADPKD on patients. According to a recent survey (Fig. 4):[4]

- *Approximately two-thirds of nephrologists and primary care physicians from across Europe believed that patients with early stage ADPKD had only mild physical symptoms.*
- *A further quarter of nephrologists believed that such patients had no symptoms at all, in contradiction with patients' own reports (Section 3.2).*

Fig. 4. Perceptions of nephrologists and primary care physicians regarding the severity of physical symptoms among patients with early stage ADPKD. In total, 300 nephrologists and 300 primary care physicians from Denmark, Finland, France, Germany, Italy, Norway, Spain, Sweden and the UK completed an online survey.[4] The pie charts show the percentages of physicians who perceived that patients had no symptoms or symptoms that were mild, moderate or severe.



- *Approximately half of both groups (52%) believed that early stage ADPKD was not associated with any emotional symptoms, or with only mild ones.*
- *Perceptions of the impact varied between countries with up to 78% of nephrologists and 62% of primary care physicians believing that early stage ADPKD had no impact on daily activities.*

The under-recognition of symptoms could lead physicians to ignore or discount symptoms, causing distress and poor care for patients.

3.8 Health insurance and family planning

Health insurance: Patients diagnosed with ADPKD may have problems obtaining health or life insurance or mortgages. Patients may be reluctant to inform an employer about their disease if insurance is employer-provided.[21] Generally, a lack of health insurance among people at risk of kidney disease is independently associated with an increased risk of early death and kidney failure.[22]

Insurers' algorithms may not take account of recent improvements in life expectancy among patients with ADPKD, linked in particular with cardiovascular disease prevention. Accordingly, the KDIGO ADPKD Conference Report recommends that an updated, standardised and endorsed statement should be developed to help patients deal with healthcare insurance organisations, banks, employers and health payers.[20]

Family planning: Patients with ADPKD face a one in two (50%) chance of passing the disease to every child. Attitudes among patients with regard to family planning issues vary.[5,23] In the aforementioned European survey of 730 patients, over one in three (35%) reported that they would not, or probably would not, have children (or any more children) because of their ADPKD.[5] Family planning counselling should be available to all adults with ADPKD.

According to a recent survey, 59% of 58 patients with ADPKD in the UK would have opted for pre-implantation genetic diagnosis (PGD) (or might consider it in the future) if it were available on the National Health Service.[23] The majority (69%) patients believed that PGD should be offered to patients with ADPKD, as has been recently recommended by experts.[20]

3.9 Conclusions

A progressive, lifelong and incurable condition, ADPKD has a profound physical and psychological impact on patients. Negative emotions, such as anxiety and depression, are common. Improving and maintaining patients' QoL is among the goals of treatment for ADPKD. Importantly, many healthcare stakeholders have a limited appreciation of its major negative effects on patients and their families – a burden that increases as the disease progresses.

A better understanding of the effects of ADPKD is important to inform future public health strategies. Therefore, health providers need to:

- *Recognise the psychological, functional and economic effects of the disease on patients and their relatives*
- *Ensure that procedures are in place to assess these effects routinely during consultations and*
- *Support patients and relatives to help manage this burden.*

Crucially, existing questionnaires are not suitable for assessing QoL among patients with ADPKD, either for routine clinical purposes or for research. ADPKD-specific questionnaires are therefore needed (Section 6).

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4. Impact of ADPKD on healthcare systems

Key points

- **Patients with ADPKD incur healthcare costs throughout life due to outpatient care and hospitalisations.**
- **The costs of ADPKD rise significantly when patients need dialysis or transplantation – ADPKD accounts for around one in 10 patients needing these treatments, at a cost of €1.5 billion/year across Europe.**
- **Research on the prevention of ADPKD-related complications could offer a tremendous return on investment.**
- **Transplantation is highly cost-effective compared with dialysis and investments to increase transplantation rates and reduce waiting times are expected to be cost-saving.**

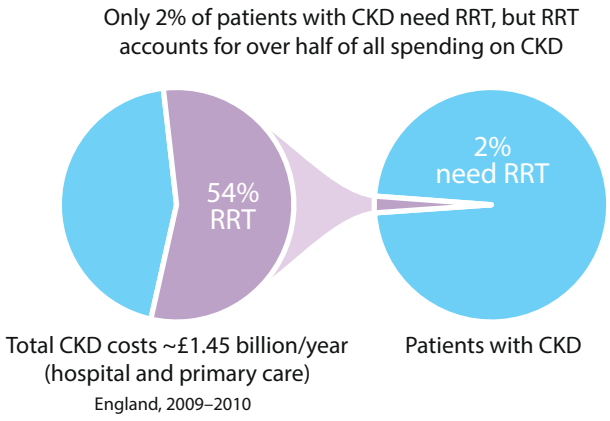
4.1. Introduction

Non-communicable diseases are acknowledged as the leading healthcare challenge worldwide.[1] While chronic kidney disease is not among the major non-communicable diseases listed by the World Health Organization,[1] its substantial and increasing contribution to global morbidity and mortality is now recognised.[2–5] Worldwide, the number of deaths caused by chronic kidney disease almost doubled between 1990 and 2010.[2] It can be argued that chronic kidney disease should be included in national non-communicable disease strategies.[6]

Costs associated with chronic kidney disease increase with worsening kidney function owing to the need for costly dialysis or transplantation.[7] Patients with kidney failure therefore account for a disproportionate level of health costs. For example, approximately 3% of the entire UK health service budget is spent on kidney failure services.[8] In England, the total cost of chronic kidney disease to the health system in 2009–10 was estimated at £1.44–1.45 billion. More than half of this was spent on dialysis or transplantation provided to only 2% of patients with chronic kidney disease (Fig 5).[7] In the USA, the 1.4% of Medicare patients with end stage kidney disease account for 7.2% (US$25.6 billion; 2011 values) of the total Medicare budget (US$355 billion).[9] Chronic kidney disease is therefore an important target for improvements in healthcare quality and spending.

ADPKD is the fourth most common reason for patients requiring dialysis or transplantation, accounting for one in 10 of all patients receiving these treatments in Europe.[10] This section reviews the important and increasing contribution made by ADPKD to healthcare costs in order to inform strategic approaches to addressing them.

Fig. 5. Proportion of total healthcare costs of chronic kidney disease (CKD) spent in England on dialysis or transplantation (known as renal replacement therapy; RRT). Adapted from Kerr et al.[7]

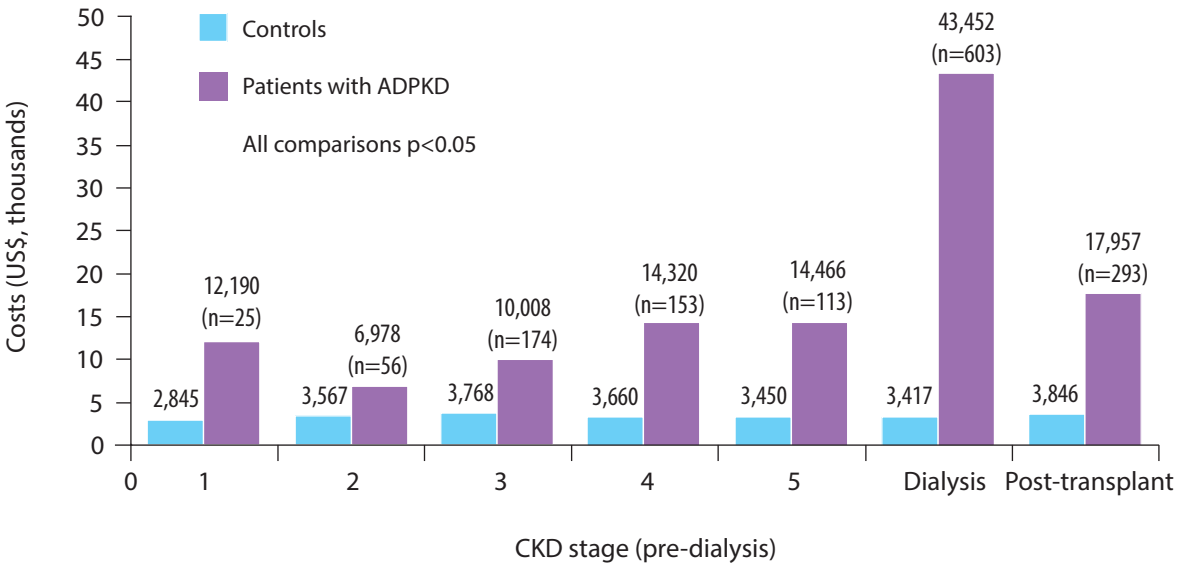


4.2 What does ADPKD cost?

Early stage disease: healthcare use increased

Patients with ADPKD require decades of outpatient care and sometimes hospital admissions for the treatment of complications of the disease. According to a US study, 21% of patients with early (Stage 2) chronic kidney disease due to ADPKD had at least one hospitalisation over a 6-month period – this rose to 44% at Stage 4, 51% of patients post-transplant and 74% in those undergoing dialysis. Thus, even at the early disease

Fig. 6. Healthcare costs over 6 months among patients with ADPKD according to chronic kidney disease stage, compared with age/sex-matched controls without ADPKD (not matched for disease stage). Adapted from Knight et al.[11] CKD, chronic kidney disease.



stages, patients with ADPKD had healthcare costs two- to four-times higher than age- and sex-matched people without the disease (Fig. 6).[11]

'Precipitous' costs of kidney failure

The costs of ADPKD, as for other forms of chronic kidney disease, rise precipitously in the later stages of the disease when dialysis or transplantation is required.[11,12] US researchers estimated the total healthcare costs over 6 months in patients undergoing dialysis for ADPKD at US$43,452 (Fig. 6).[11]

Data from the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Registry (see Section 6) have been used to estimate the costs of dialysis and transplantation per patient with ADPKD in Europe (Fig. 7).[10] Haemodialysis, by far the most common form of renal replacement therapy (RRT), is estimated to cost €55,500 per patient per year. Extrapolating these data to the 27 countries of the European Union, it is estimated that approximately 50,000 patients with ADPKD received RRT in 2010 at a cost of €1.5 billion (95% confidence interval: €1.1–2.0 billion).[10]

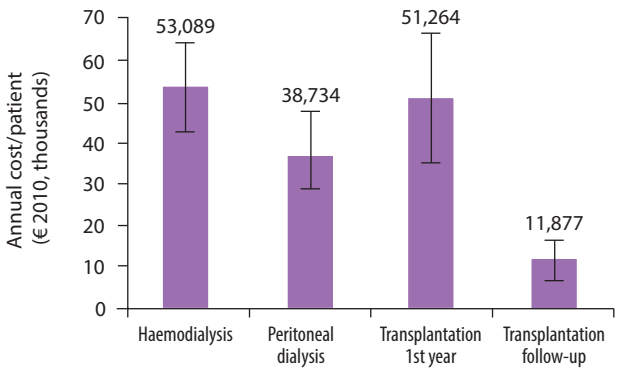
This total does not reflect the full cost of ADPKD, as it does not include the costs of care for patients who are not receiving dialysis or transplantation, the costs of complications (e.g. infections), or the 'indirect' costs of patients' lost productivity and earnings. Little is known about these indirect costs of ADPKD, although market research data suggest many patients need to take time off work due to ADPKD (Section 3.2).

Approximately 50,000 patients with ADPKD receive RRT in Europe at a cost of €1.5 billion.[10]

Across Europe, the average age at which patients with ADPKD start dialysis or transplantation across Europe is now 58 years. This is approximately 7 years younger than patients with other forms of chronic kidney disease.[13] Therefore, although patients with ADPKD are relatively few in number, they may account for a disproportionate quantity of total healthcare costs due to chronic kidney disease.

These data suggest that significant costs could be offset by early intervention with treatments that delay ADPKD progression and reduce the need for dialysis and transplantation. According to European experts,

Fig.7. Estimated annual costs of dialysis and transplantation per patient, averaged across countries (adapted from[10]). Error bars show 95% confidence intervals.



research on the prevention of ADPKD-related complications could offer a ***"tremendous return on investment"***.[14] Researchers in the USA have also concluded that, ***"Strategies that prevent loss of renal function below 30 ml/min have the potential to generate substantial reductions in medical charges"***.[12]

Research on the prevention of ADPKD-related complications could offer a "tremendous return on investment".[14]

Dialysis and transplant costs are expected to rise

The costs associated with dialysis and transplantation for ADPKD are expected to rise as the number of recipients increases and their life expectancy improves.

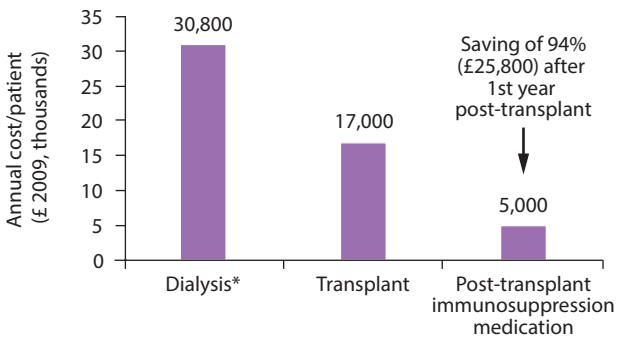
There is no good evidence that current approaches to protecting kidney function (Section 2) are effective. Indeed, there has been no reduction in the incidence of kidney failure among people with ADPKD over the last 15 years, either in Europe[12] or in the USA.[15]

Indeed, the number of patients receiving dialysis or transplantation for ADPKD in Europe increased by 60% between the periods of 1991–1995 and 2006–2010.[10] This is mainly because patients are living longer because of a reduction in deaths due to cardiovascular disease, due in turn to better treatment of high blood pressure and other risk factors.[10,16]

Transplantation saves costs vs dialysis

Transplantation is not only the treatment of choice for kidney failure due to ADPKD,[17–19] it is also cost-saving compared with dialysis. Across Europe, the estimated follow-up costs of transplantation (after the first year) among patients with ADPKD are approximately one-third of those of dialysis (Fig. 7).[10] However, at present, only 8% of patients undergo kidney transplantation as their first form of RRT. Instead, 92% of patients undergo dialysis as their first form of RRT, either by haemodialysis (70%) or peritoneal dialysis (22%).[13]

Fig. 8. Indicative average costs of dialysis and kidney transplantation in the UK (all indications), showing the potential cost saving associated with transplantation.[8]
*Average dialysis cost, including haemodialysis (£35,000) and peritoneal dialysis (£17,500).



4.3 Conclusions

ADPKD incurs substantial costs to health systems throughout the disease course. The annual cost of dialysis and transplantation alone for patients with ADPKD has recently been estimated at €1.5 billion across the EU.

Europeans with ADPKD are living longer than ever, mainly because of cardiovascular disease prevention. However, there is no approved treatment to delay the progression of ADPKD itself. As a result, the demands for costly dialysis and kidney transplants are increasing.

Transplantation is highly cost-effective compared with dialysis. Investments to increase transplantation rates and reduce waiting times are expected to be cost-saving.

UK case study: cost savings with transplantation

In 2009, the UK Department of Health estimated that kidney transplantation reduced the annual treatment costs of all patients with end-stage kidney disease by over 80% compared with dialysis (Fig. 8). The 23,000 functioning kidney transplants in 2009 saved the health service £512 million per year in dialysis costs. An additional 6,920 patients were awaiting a transplant and a further saving of £152 million/year could have been made if these patients received a transplant.[8] The shortage of donors meant that adults experienced a median waiting time of 1,110 days for a kidney transplant.[20]

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5. Unmet needs in ADPKD care

Key points

- **Patterns of clinical practice for ADPKD diagnosis, assessment, treatment and support vary within and between European countries. There is an unmet need for all patients with ADPKD to have access to a nephrologist knowledgeable about the disease, and greater coordination of care policies and services is required.**
- **The optimisation and standardisation of ADPKD care in Europe is hampered by the lack of evidence-based consensus guidelines and standardised care pathways.**
- **The total kidney volume is the most commonly used predictive factor to identify patients likely to progress rapidly, with the aim to allow care to be individualised, although there is no consensus yet on the optimal way to predict prognosis.**
- **There is an urgent need for new medicines that delay the decline in kidney function due to ADPKD, thereby maintaining quality of life (QoL) and improving life expectancy among patients and reducing the impact on European health systems.**
- **Further efforts to promote kidney transplantation for patients with kidney failure are necessary.**

5.1 Introduction

Individuals with ADPKD require complex, multidisciplinary care involving:

1) A careful and comprehensive assessment of the disease, its manifestations, complications and prognosis

2) Treatment to relieve symptoms, manage complications, preserve kidney function, lower the risk of cardiovascular disease, and maintain patients' quality of life (QoL)

3) The provision of information and support to help patients and their families deal with the condition.

This section identifies barriers to the optimal diagnosis, assessment and treatment of ADPKD as a basis for recommending policy-level strategies to help overcome these (Section 8).

5.2 Diagnosis

Clinical awareness of ADPKD

ADPKD is often found during investigations prompted by non-specific clinical findings, such as pain, bleeding in the urine, or high blood pressure. It is important that non-specialist physicians are aware of the potential diagnosis of ADPKD so that appropriate examinations are performed when necessary.

Also, the diagnosis of ADPKD may be missed in patients who do not experience symptoms, hence it is important to raise levels of awareness among primary care physicians and the public so that screening can be considered for individuals with a family history of ADPKD.

Imaging

Ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) can all be used to examine the kidneys for the presence of cysts in at-risk individuals with relevant clinical findings. Ultrasound is often used initially, owing to its convenience, wide availability, safety and low cost. Standardised diagnostic criteria for ADPKD (based on the number of cysts present relative to the patient's age) should be used in patients with a family history of the disease.[1,2]

Higher resolution imaging using CTI and MRI may be useful when the diagnosis is unclear or to provide additional prognostic information,[2,3] but specialist expertise is important. Costs and lack of appropriate expertise are potential barriers to CT and MRI use in some areas, reinforcing the need for specialist services to ensure that these methods are used as cost-effectively as possible (e.g. by avoiding unnecessary and duplicated scans).

Positron-emission tomography (PET) scanning is the best tool for the diagnosis of kidney and liver cyst infections if the 'gold standard' method of cyst aspiration is not available.[4]

Genetic testing

Genetic testing is a rapidly changing area of ADPKD diagnosis, owing to advances in the technology involved and in the models used to predict disease progression.

ADPKD can be caused by many different types of mutations in the ***PKD1*** and ***PKD2*** genes.[5] Genetic testing can identify the mutation in more than 90% of patients.[6] This is not usually necessary in adults when the disease can be diagnosed using imaging. However, it may be considered in some situations in adults, for example when the diagnosis is uncertain,[2,7] and it is vital for diagnosing ADPKD in children.[2] Genetic screening of family members of patients with ADPKD can be useful to determine if others are affected and there should be no barriers to this approach.

Importantly, there is no consensus on a diagnostic algorithm that integrates clinical findings with kidney imaging and genetic testing.[2]

There is no established diagnostic algorithm that integrates clinical signs and symptoms with kidney imaging and genetic testing.

Currently, genetic testing is laborious and costly. The recent development of faster and cheaper genetic tests that use 'next-generation sequencing' could herald a greater role for genetic testing in the diagnosis of ADPKD and in predicting the disease prognosis.[2,8,9] It should also aid important research on the genetic epidemiology of ADPKD.[8]

In the meantime, genetic testing for ADPKD is complex and should be performed by specialists in centres with appropriate experience and expertise.[2] Importantly, the results require careful interpretation and explanation to nephrologists, patients and parents. The KDIGO Conference Report on ADPKD recommended that standardised and informative reporting, as well as physician education, will be needed to optimise the use of new tests.[2]

Evidence from rare diseases shows that differences exist between member states in terms of access to and financing of cross-border genetic testing. Difficulties include reimbursement and payment, the cross-border sending of biological samples, high cost, and insufficient quality of laboratories. A European Commission Expert Committee has proposed that cross-border genetic testing could be improved through better information, facilitating access, homogenising consent requirements, reducing red tape and simplifying logistics.[10]

Diagnosis of extra-renal manifestations

ADPKD affects many parts of the body, in addition to the kidney (Section 2). Patients diagnosed with ADPKD should have access to a multidisciplinary assessment according to current best practice. For example, liver cysts are the most common non-kidney manifestation and hence liver imaging is recommended as part of the initial assessment of all patients diagnosed with ADPKD.[2]

However, comprehensive, integrated and accepted guidelines for the evaluation of extra-renal manifestations of ADPKD do not exist and patterns of practice are expected to vary across Europe.

5.3 Assessing prognosis and disease progress

The rate at which ADPKD progresses varies greatly between patients, even between family members who have inherited the same genetic mutation. Therefore, patients must be managed individually. The identification of patients whose disease is likely to progress more rapidly is important to help healthcare providers and patients select appropriate levels of treatment and monitoring. This will become increasingly important if new therapies are introduced, in order to target these to patients likely to benefit (Section 6).

In most forms of chronic kidney disease, kidney function is routinely monitored using the estimated glomerular filtration rate (GFR; Section 2). However, since estimated GFR does not measure the growth of cysts or alterations in renal tubule function, the GFR remains normal during the early stages of ADPKD and so is not useful in this setting. ADPKD-specific methods are therefore required.

Total kidney volume

The growth and proliferation of cysts causes kidneys volumes to increase exponentially throughout the life of patients with ADPKD (Section 2). Measuring the volume of the cysts themselves is at present impractical and so research has focused instead on measuring the total kidney volume (TKV). On average, TKV increases by about 5–6% each year in ADPKD, although this varies between patients.[11,12]

There is a consensus among ADPKD experts[2] that the TKV:

- *Accurately estimates the kidney cyst burden within the kidneys*
- *Increases at a rate related to the TKV measured, and the age of the patient, at the initial ('baseline') assessment*
- *Predicts the decline in kidney function*[11]
- *Correlates with many kidney manifestations of ADPKD in the kidney, including pain, bleeding, and high blood pressure.*[13]

Height-adjusted TKV is the most commonly used predictive factor in research to identify patients likely to progress rapidly, with the aim to allow care to be individualised. Research is ongoing to refine and validate predictive tools for use in clinical practice and clinical trials.[14–16]

TKV is the leading predictive factor to help identify patients likely to progress rapidly.

Repeated TKV monitoring is currently not recommended for routine care, as there is no approved treatment to delay disease progression.[2] However, new medicines are in development and TKV is expected to become increasingly important to allow these to be targeted to patients most likely to benefit, and to assess their efficacy (Section 6). Currently, the main barriers to routine TKV measurement are limitations on access to the MRI and CT scans and the necessary specialist expertise (see Panel).

Pre-implantation genetic diagnosis

Pre-implantation genetic diagnosis (PGD) is used in reproductive medicine to screen for DNA mutations that cause inherited diseases in embryos created by *in vitro* fertilisation. This allows unaffected embryos to be selected for implantation into the uterus. Using this method, couples affected by ADPKD can plan a pregnancy in the knowledge that the child will be free of the disease.[17,18]

ADPKD experts have recently recommended that PGD should be available to all patients.[2] However, PGD is a highly specialised technique requiring multidisciplinary collaboration. Access to PGD varies widely between European countries, in terms both of its availability and reimbursement.[2] Financial pressures may be an important barrier in some countries, even though in principle PGD may be cost-saving to society by preventing ADPKD in the offspring of affected patients. Other barriers may include low awareness of the method among patients and personal values among nephrologists and patients. When PGD is offered, genetic counselling and careful pre-conception assessment should be integral to the process.[18] Governments are encouraged to formulate national polices on PGD in ADPKD and other conditions, together with practice guidelines.

5.4 ADPKD management

There are three main unmet needs in ADPKD management in Europe:

Lack of disease-modifying therapy

There is no currently approved medicine available to slow the formation or growth of cysts and thereby preserve the kidney function in patients with ADPKD. Although various measures are widely used for this purpose (Section 2), there is no good evidence that they work.[2]

The incidence of kidney failure due to ADPKD has not fallen in Europe or the USA during the last decade.[19,20] Patients with ADPKD start dialysis on average at a younger age than patients with other types of chronic kidney disease, despite earlier referral and treatment by specialist renal services.[19,21] This average has not increased in recent years, except in elderly patients, further suggesting that existing approaches to delaying disease progression do not work.[19]

There is therefore an urgent need to invest in research to develop new therapies to delay ADPKD progression.

Lack of management guidelines and care pathways

Crucially, the optimisation and standardisation of ADPKD care in Europe is hampered by the lack of evidence-based consensus guidelines and standardised care pathways. Although guidelines have been developed in certain countries (e.g. Spain[7,20]) they are limited by the lack of good-quality data on many aspects of care. The KDIGO ADPKD Conference Report has recently recommended priority areas for further research.[2] This process is expected to inform the development of international guidelines in due course.

In the meantime, the EAF recommends the development of tiered care approaches to ensure that patients have appropriate access to specialist, multidisciplinary management (Section 8).

Variations in dialysis and transplantation provision

The prevalence of dialysis or transplantation use for ADPKD varies between European countries.[22] This variation is expected to be due to international differences in policies governing access to, and reimbursement of, dialysis and transplantation, which are linked in turn to social and economic factors.[22–27] For example, the Living Organ Donation in Europe (EULOD)

How is total kidney volume measured?

Total kidney volume (TKV) is calculated from measurements of the kidney (length, width and depth) obtained using ultrasound, magnetic resonance imaging (MRI) or computed tomography (CT). Ultrasound is inexpensive and useful in clinical practice, although it is not precise enough for use in clinical trials of new ADPKD treatments. MRI and CT are more accurate, but are more expensive and labour-intensive, with limited availability of the necessary expertise. CT also carries the risks associated with exposure to radiation. Research is ongoing to facilitate TKV estimation and to optimise models that combine TKV and other variables to predict kidney function decline in patients with ADPKD.

"Six weeks ago, I had a kidney transplant. The operation took about 4 hours and apparently the minute they connected the kidney to the blood vessels, it started to work. The symptoms that I'd had with the kidney failure, some of them are still there. But I was elated, I couldn't stop smiling, I suppose I didn't feel any younger but I just couldn't stop smiling. I had colour in my cheeks for the first time in a long time. I feel I've had a very positive attitude – yes I've got the disease, but it's not going to beat me."
Fiona, UK

survey, conducted in 2011, documented disparities between European Union member states in the rates of living donor kidney transplantation and in policies such as reimbursement of donors' expenses.[26]

Kidney transplantation is the treatment of choice for kidney failure due to ADPKD.[2,7,28] As the kidney function declines in a relatively predictable manner in patients with ADPKD, the use of pre-emptive transplantation from a living donor should be encouraged where possible. The principal barriers to wider use of kidney transplantation are financial pressures, a shortage of donated organs and limitations in medical, surgical and nursing expertise.[27] However, as discussed in Section 4, kidney transplantation is far more cost-effective than dialysis and brings savings for public health budgets, as the European Commission acknowledged in its 2014 mid-term review of the Action Plan on Organ Donation and Transplantation.[29]

The proportion of patients with ADPKD who undergo kidney transplantation as their first form of renal replacement therapy has doubled since the early 1990s and is higher than that among patients with other forms of chronic kidney disease.[19] This is thought to be because patients with ADPKD typically engage with specialist kidney services earlier, are younger, and have fewer co-existing illnesses.[21] A further increase in transplantation over dialysis for patients with ADPKD would be expected to be cost saving.

Kidney transplantation should be further promoted in line with ongoing efforts to enhance organ transplantation services across Europe.[29] The proportion of patients with ADPKD who have access to and have been treated by kidney transplantation critically depends on national policies on transplantation.

5.5 Conclusions

There is an unmet need for all patients with ADPKD to have access to nephrologists knowledgeable about the disease.[2] Patterns of clinical practice for ADPKD diagnosis, assessment, treatment and support vary within and between European countries, with little coordination of care policies and services. The lack of therapeutic options to slow the progression of ADPKD, thereby to delay the need for invasive and costly dialysis and kidney transplantation, reflects various barriers discussed further in Section 6.

In Section 8, we propose a suite of strategic solutions to help address these needs.

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6. Therapeutic innovation in ADPKD

Key points

- **Although our understanding of ADPKD has improved, challenges remain in translating these advances into new disease-modifying medicines available to patients.**
- **Collaborative multi-centre efforts are required to provide patient populations large enough for research.**
- **ADPKD research is also complicated by the chronic, progressive disease course affecting many parts of the body. Research is ongoing to refine and validate methods to predict disease prognosis for research and clinical purposes.**
- **At present there is no well-accepted patient-reported outcome of the impact of ADPKD.**

6.1 Introduction

Nephrology ranked last among other internal medicine specialties in the number of randomised clinical trials published between 1966 and 2010.[1] The lack of innovation and incentive for the development of new therapies in chronic kidney disease is due in part to barriers faced by companies and researchers in the discovery phase of development, in developing new therapeutics, and in establishing the evidence base for clinical practice. These include the lack of infrastructure, uncertain regulatory landscape, lack of universally accepted clinical trial endpoints, and payer/reimbursement issues.[2]

As Section 5 explains, new medicines to slow ADPKD progression are urgently needed to maintain patients' quality of life (QoL) and delay the need for dialysis and transplantation. This section explores the challenges to translational research and therapeutic innovation in this setting.

Among patients with ADPKD, the most common hopes for the future are a cure (23%) followed by better treatment options (20%).[3]

6.2 Challenges to innovation in ADPKD

Advances in animal and other experimental models that mimic ADPKD have allowed researchers to identify targets for new medicines that may modify disease progression (see Panel).

Despite these breakthroughs, clinical research in patients with ADPKD is difficult because it requires the formation of registries to allow information to be collected on sufficiently large numbers of patients. This is complicated by the fact that ADPKD is a chronic disease that has highly variable effects on different parts of the body over the whole lifetime of the patient. Currently available data are fragmented across Europe and there are no national or European disease or patient registries specific to ADPKD.

The following sections look further at difficulties in assessing the benefit of treatments for ADPKD.

Chronic progressive disease course

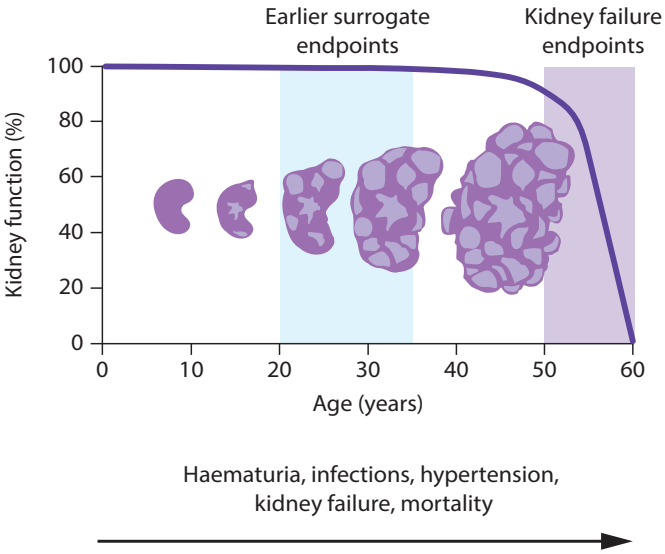
Treatments to delay ADPKD progression should ideally start early in the disease course when the kidney function is relatively well preserved and a treatment that slows cyst growth could delay the progression to kidney failure (Fig. 9). Starting treatment late in the disease course, after kidney function has started to decline, offers a shorter period of potential benefit.

Drug development landscape in ADPKD

Research into how cysts develop in ADPKD has identified targets for new medicines that may delay disease progression.[4,5] Clinical trials have been completed with three types of medicines, known as vasopressin V2 receptor antagonists, somatostatin analogues and mTOR inhibitors. Further research is underway with these and other investigational treatments. However, these are subject to various challenges discussed in this section.

However, demonstrating a benefit of early treatment in ADPKD on the preservation of kidney function is difficult because of the long time lag between the growth and proliferation of cysts and the eventual decline in kidney function that usually occurs late in the disease course (Section 2). This means that tests usually used to monitor kidney function in patients with chronic kidney disease (CKD) (e.g. glomerular filtration rate [GFR]) are not useful in early stage ADPKD. Demonstrating that early treatment ultimately delays the onset of kidney failure would require clinical trials of unfeasible length, perhaps lasting decades.

Fig. 9. Time course of ADPKD progression with respect to endpoints for assessing treatment efficacy. Early to mid-term endpoints are required to assess early therapy. Such endpoints would represent 'surrogate' endpoints predicting kidney failure later in life.



The acceptance by regulatory authorities of 'surrogate' assessments of drug efficacy is a priority so that ADPKD treatments can be tested earlier in the disease course via clinical trials of feasible duration and cost. A surrogate endpoint would be one that can be reliably measured over a suitable time-frame and which correlates with kidney failure, the principal long-term outcome of interest.

The height-adjusted total kidney volume (TKV) is the most commonly used predictor of kidney function decline in patients with ADPKD (Section 5). TKV has been employed as the primary endpoint in clinical trials for new ADPKD medicines and this remains subject to review by regulatory authorities. Further research is underway to optimise its use within predictive models for selecting patients at risk of rapid disease progression, both for future clinical trials and for assessing patients during routine care.[7,8] Additional shorter-term surrogate markers are now required to help 'translational' research, i.e. to allow relatively small and short early phase trials in patients to bridge the current gap between animal studies and large-scale clinical trials using TKV and other endpoints.

The Polycystic Kidney Disease Outcomes Consortium Project (PKDOC) epitomises the collaborative effort required to establish regulatory endpoints to measure early disease progression. The PKDOC involves the PKD Foundation, Critical Path Institute, members of the pharmaceutical industry, researchers and clinicians, and the US Food and Drug Administration (FDA).[9]

More broadly, there are calls for fundamental changes to the drug development process to reduce costs. It is suggested that clinical trials could be redesigned to establish efficacy and basic safety among fewer patients, while safety is further evaluated through mandatory post-marketing surveillance via high-quality and transparent registries using electronic health records and modern data analysis tools.[10–12] The so-called 'adaptive licensing' approach is under development in Europe. It is considered by the European Medicines Agency (EMA) to be particularly relevant for medicines with the potential to treat serious conditions where there is an unmet medical need[13] – a definition fulfilled by ADPKD. An adaptive licensing approach requires cooperation between a wide range of stakeholders, including medicines regulators, the pharmaceutical industry, health technology assessment (HTA) bodies, organisations issuing clinical treatment guidelines, patient and consumer organisations, healthcare professionals, researchers and academics.[13]

Clinical diversity of ADPKD: how to measure the impact on patients?

ADPKD can affect many parts of the body and the manifestations and complications can vary considerably between patients, even within the same family (Sections 2 and 3). This diversity makes it difficult to assess the impact of the disease on patients, and hence the benefit of new treatments.

Until recently, no 'patient-reported outcome' had specifically been developed to capture the impact of ADPKD symptoms on patients.[14] Studies employing the widely used SF-36 QoL questionnaire have had mixed results. In one study in the USA, pre-dialysis patients with ADPKD had SF-36 scores similar to the general population.[15] More recently, in Japan, a group that included both pre- and post-dialysis patients with ADPKD had lower SF-36 scores than those of the general population.[16] The SF-36 is a generic instrument and researchers have concluded that it is not sufficiently sensitive to measure the impact of the diverse and slowly progressive effects of ADPKD. A reliable and validated

ADPKD-specific measure of physical and psychological well-being in patients with ADPKD is urgently needed.[6]

There is no specific, validated and recognised measure of the impact of ADPKD on patients.

Progress has been made in the USA with the ongoing development of ADPKD-specific scales assessing the impact of pain and other symptoms.[17,18] Further research is required to evaluate and implement such measures.

6.3 Current ADPKD research structures

Collaborative, multi-centre, international efforts are required to provide patient populations large enough to establish the natural history and epidemiology of ADPKD, along with translational and clinical research to find new treatments. Important progress in this regard has taken place in recent years. Examples of this progress include:

National ADPKD registries

Local or national ADPKD cohorts in some countries have provided useful regional or national information.[19–26] However, the fragmentation of cohorts has been an obstacle to a better understanding of the disease.[27]

ERA-EDTA European registry

The European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Registry is a collaborative project that collects data from 24 national and regional registries in 12 European countries: Austria, Belgium, Denmark, Finland, France, Greece, Italy, Netherlands, Romania, Spain, Sweden and the United Kingdom. It has recently been used to profile the epidemiology, outcomes and costs of dialysis and transplantation among patients with ADPKD across Europe using the largest dataset yet published (Section 4).[28,29]

However, it does not contain information on the actual use of treatments used to help protect the kidneys, not all European Union countries participate, and the available data on patient follow-up vary between the participating registries.

EuroCYST initiative

EuroCYST is an international project funded by the ERA-EDTA.[27] The objectives of the EuroCYST initiative are to:

- *Build a network of ADPKD reference centres across Europe to provide a translational research platform for the study of the pathogenesis, progression factors, morbidity, comorbidity and health economic issues in patients with ADPKD*
- *Harmonise and develop common standards for ADPKD-related research and a common ADPKD biobank*
- *Create a scaffold to facilitate the integration of current and upcoming technologies into ADPKD practice*
- *Develop evidence-based best practice and needs assessments*
- *Serve as an impetus to expand ADPKD training programmes*
- *Improve awareness of the relevance of ADPKD including disease-specific complications and socioeconomic consequences of the disease among healthcare professionals and payers.*

EuroCYST has established a network of 14 ADPKD centres in Belgium, Czech Republic, France, Germany, Italy, Netherlands, Spain, Switzerland, Turkey and the United Kingdom. These aim to build a total population of 1100 adult patients by 2015. The patients will be followed for at least 3 years in an observational cohort study. In future, participation of additional centres will be possible, subject to appropriate funding.[27]

News from the USA

In the USA, the National Institutes of Health intends to commit $4.4 million in 2015 to support basic and clinical research into polycystic kidney disease via PKD Research and Translation Core Centres.[30] The goal of these centres is to provide resources for communication and collaboration between researchers. The NIH spent $165 million on research into polycystic kidney disease between 2010 and 2013, and is expected to spend a further $82 million across 2014 and 2015.[31] The EAF Faculty is not aware of any direct funding for polycystic kidney disease from the European Commission.

6.4 Conclusions

Novel treatments to delay the need for costly renal replacement therapy (RRT) have the potential to decrease the costs of ADPKD to healthcare systems. Therapeutic innovation in this area is subject to particular challenges and in Section 8 we propose strategic, policy-focused solutions to help address these.

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7. Empowering patients with ADPKD

Key points

- **Patients and families affected by ADPKD need specific, comprehensive, accessible information about their disease in order to fully participate in decision-making.**
- **Patients have important roles in driving improvements in ADPKD diagnosis and care in partnership with healthcare professionals, researchers, healthcare system managers and health ministries.**
- **All stakeholders, including the European Commission, national governments and healthcare providers, should support efforts to better inform individual patients and families affected by ADPKD, and to include patient organisations within strategic and tactical aspects of healthcare planning and delivery, including the design of care services and research.**
- **Authorities responsible for assessing the effectiveness and value of ADPKD treatments and services should engage patients in their processes and use patient evidence to inform their decision-making.**

7.1 Introduction

Empowerment is a process through which people gain greater control over decisions and actions affecting their health and which increases the capacity of people to act on issues that they themselves define as important.[1,2] Individual empowerment refers primarily to the individuals' ability to make decisions and have control over their personal life. Community empowerment involves individuals acting collectively to gain greater influence and control over the determinants of health and the QoL in their community.[1]

Patients with chronic conditions have critical roles both in the management of their own condition and in the design and implementation of new healthcare policies, systems and services. These roles have increased in recent years with the rising predominance of chronic diseases as healthcare priorities, and with developments in information access (e.g. via the internet and social media), self-management, legal requirements for patient involvement, reorganization of healthcare systems and new technologies. Indeed, patients often become experts in their condition and hence it is important for the healthcare provider to acknowledge the active role of the patient as an informed, involved and interactive partner in the treatment process.[3] The WHO has proposed policy options to help foster health literacy, shared decision-making and self-management, arguing that *"Strategies for informing and empowering patients and for improving the responsiveness of health care delivery systems should be high on the policy agenda in all countries. This is important not only because it is the right thing to do, but also because it may be the best way to enhance people's health and ensure the future sustainability of health systems"*.[4]

Empowering patients with uncommon or rare diseases is particularly vital, as there may be limited clinical expertise among healthcare professionals. Not only can the patient's experience inform their own care, but also the community of patients' experiences can improve health service design and delivery.

Patient empowerment is integral to various ongoing European health policy initiatives, including those relating to chronic diseases,[5,6] rare diseases,[7–11] health improvement and equity in access to healthcare,[12] research[13] and therapeutic innovation.[14,15] EU-level activities underway include the EMPATHiE project, which aims to identify and evaluate best practices for patient empowerment and to develop approaches to validate their transferability and future EU collaboration.[2]

Despite this progress, patients with ADPKD face important challenges in their relations with healthcare services with regard to their own care (e.g. with regard to obtaining information, negotiating access, and obtaining support) and that of the wider community of patients with ADPKD. This section delineates the role of patient empowerment in improving ADPKD care.

7.2 Inform to empower

Patients' own preferences and decisions should be central to individualised care in ADPKD. Accordingly, patients need to be appropriately informed in order that they can fully participate in decision-making, and to be their own advocates for care.[16]

Specific information products for patients and their families have been developed in some countries, including France, Italy, Turkey and North America (Section 9). However, considering that ADPKD is the most common inherited kidney disease, information for patients is generally limited and fragmented.

Initial information around diagnosis

There has been little research into the levels of knowledge and awareness among patients with ADPKD, or into the implementation and effectiveness of educational programmes or tools.[16] Market research results suggest that information given to patients at the time of diagnosis is mostly provided verbally.[17]

There is a pressing need to improve the modes of communication and content of information provided to newly diagnosed patients. All patients and their families should be systematically provided with simple, user-friendly information on ADPKD (see Panel). Information should be country specific and preferably provided in a printed form so that it can be read later.

Some people with ADPKD find it difficult or frustrating to explain their condition and its effects to their employer, in part because there is little awareness of ADPKD among the public. As well as information about ADPKD, it is also important that patients are given advice and support in matters relating to their employment and other issues, such as health insurance.

ADPKD patient organisations have a crucial role in driving disease education and awareness locally and nationally, including in the development of information resources. Individuals diagnosed with ADPKD should be referred to patient organisations for further information and support. There is a need for the establishment of patient organisations or further support for existing patient organisations in some countries.

Access to counselling services or mental health services can also be important to ameliorate the psychological effects of inheriting and living with ADPKD (Section 2).

Information later in disease course

Patients with ADPKD may be more aware of their kidney function later in life, when the decline becomes evident.[17] However, research suggests that important deficiencies exist in the information provided when patients with chronic kidney disease progress to dialysis or transplantation, a time of particular stress and concern.

A large multinational survey of patients undergoing dialysis for all forms of chronic kidney disease in Hungary, Italy, Poland, Portugal and Argentina found that fewer than half (46.5%) rated their overall dialysis care as excellent. Aspects of care least frequently ranked as excellent included information provided when patients chose a dialysis modality (23%), amount of information from dialysis staff (34%), accuracy of information from nephrologist (for example, about prognosis or likelihood of a kidney transplant) (37%), and accuracy of nephrologist's instructions (39%). The authors concluded that meeting patients' expectations for information is likely to improve patient satisfaction of dialysis care.[18]

Information for patients and carers

Information provided to patients with ADPKD, and carers, should ideally include:

At initial diagnosis

- Explanation of the disease and its potential course
- ADPKD management approaches
- Measures to reduce cardiovascular risk
- Potential impact of the disease on work and lifestyle
- Family planning, including genetic counselling and pre-implantation genetic diagnosis
- Discussing ADPKD with employers
- Issues regarding health insurance and mortgage applications
- Registry entry and associated issues – all patients should be offered the opportunity to join an ADPKD Registry
- Details of ADPKD patient organisations

Later in disease course

- Prognostic information
- Dialysis and transplantation options: procedures, benefits, risks, etc

Patients in the later stages of ADPKD therefore need specific, tailored information (see Panel).

"Patient support is really poor"
(Patient with Stage 4 ADPKD, France).

In the USA, a survey of patients with all forms of kidney failure also found a variety of knowledge-related barriers to kidney transplantation – the treatment of choice for patients with ADPKD. These barriers included fears, a perception that dialysis is 'not that bad', a lack of information on how to proceed, and a poor understanding of the transplantation process and benefits.[19]

Reproductive counselling and other specific needs
Reproductive counselling is also important to explain the risks of passing the disease to the children, certain risks of pregnancy, and the use of contraception. Referral to a geneticist is important for reproductive counselling as well as other issues such as genetic screening and testing. Referral to an obstetrician specialising in the management of high-risk pregnancies may be appropriate and is certainly recommended for a pregnant woman with uncontrolled hypertension or kidney damage. Prenatal screening for ADPKD is not currently recommended.[16]

7.3 Patients' roles in driving improvement in ADPKD care

Patients have important roles in driving improvements in ADPKD diagnosis and care in partnership with healthcare professionals, researchers, healthcare system managers and health ministries.

ADPKD patient organisations should be consulted to inform decisions regarding relevant European and national level health policies concerning the provision, organisation and resourcing of care, and the development and introduction of future treatments (i.e. research, regulation, reimbursement, health technology assessment).

Design of care services
ADPKD patient organisations should contribute to the design and delivery of care services at the national and European levels (Section 8).

Research
Patient organisations have important contributions to make within research networks in kidney health generally. They have an important role in informing patients about ongoing trials. However, as well as being involved as the subjects of research, patients and their representative organisations should be involved as full partners in initiating, informing, advising, commissioning, reviewing and conducting research.[20–22] Importantly, these organisations can also help disseminate the results of research to patients and the public.

For example, more needs to be done to ensure that patients genuinely influence clinical study design, in order that outcomes of importance to patients are studied and that the study process is acceptable to patients and will be adhered to. As the Chief Medical Officer for England, Dame Sally Davies, has acknowledged: ***"No matter how complicated the research, or how brilliant the researcher, patients and the public always offer unique, invaluable insights. Their advice when designing, implementing and evaluating research invariably makes studies more effective, more credible and often more cost effective"***.[23]

Industry, academia and health system researchers should therefore involve ADPKD patient organisations in various aspects of research, including the:

- *Development of patient-relevant outcomes for clinical trials (Section 6)*
- *Design of clinic visit schedules that will suit patients' capabilities*
- *Approval of patient study consent forms*
- *Promotion of patients' participation in clinical trials*
- *Dissemination of results in clear, understandable language*
- *Design, conduct and monitoring of patient registries. For example, a patient (Tess Harris, President of PKD International) currently chairs the UK Renal Registry ADPKD Study Group.*

Where do ADPKD patient organisations exist?

Countries with patient organisations dedicated to polycystic kidney disease include France, Germany, Italy, Switzerland and the UK (see Section 10). In addition, several national kidney disease organisations have sub-groups dedicated to polycystic kidney disease, e.g. in Spain, Netherlands and Finland.

Medicines regulation

Before a medicine can be considered for use in any health system it must receive a marketing authorisation/ licence that approves it use on the basis of evidence about its quality, safety and efficacy, with an overall assessment of the benefit-risk ratio of using the medicine.

ADPKD patient organisations should be actively engaged by regulatory agencies at the European and national levels so that patients' values with regard to benefit-risk assessment of new treatments directly informs decision-making. One good example of this comes from the UK, where the Genetics Alliance UK organisation collaborated with the Welsh Institute for Health and Social Care to conduct research among patients on weighing the risks and benefits of new medicines for serious conditions.[24,25] Using the Citizens' Jury model of participatory research, this project found that:

- *Regulators should include psychosocial factors in their decision-making, to avoid overreliance on biomedical endpoints without consideration of the impact on a patient's day-to-day life. Increased communication, openness and transparency in the regulatory process would help to make it clear to patients when such factors are indeed taken into account.*
- *Patients affected by rare, serious conditions would like regulators to be more permissive when making their decisions on the balance between benefit and risk for new treatments.*
- *Patients should be more involved in all stages of the licensing process, from setting the research agenda, to post-market authorisation (licensing) decisions.*
- *If patients are to be more involved in licensing decisions, or if they will need to decide whether or not to take a medicine based on the balance of risk and benefit, they will need additional support.*[25]

The EMA acknowledges the added value that patients contribute within its Scientific Committees, one of which is evaluating TKV as a clinical trial endpoint in ADPKD. As members of Scientific Committees, patients provide a ***"unique and critical input based on their real-life experience of being affected by a disease and its current therapeutic environment" and this contribution "enriches the quality of the opinion given by the scientific committees"***.[15]

Health technology assessment

Health technology assessment (HTA) involves the systematic evaluation of the clinical effectiveness and/ or cost-effectiveness and/or the social and ethical impact of a health technology on the lives of patients and the healthcare system.[26] It is now often used to inform medicine reimbursement decisions and increasingly seems to focus on value for money.

Some authorities recognise that patients and their representatives have important roles to play at all stages of HTA, particularly in defining the scope of the assessment, submitting patient evidence to inform decision-making, and commenting on draft reports. However, patient involvement in HTA is at an early stage and there is major variation in the way in which HTA organisations actually engage patients. Some processes endeavour to be transparent, accountable and engaging of patients, whilst others are conducted behind closed doors with no opportunities for input or influence. The HTA International society has overviewed the patient involvement approaches used by HTA organisations.[27] Patient organisations need to strive to understand how treatments are reimbursed in their own healthcare system and find ways to influence that decision-making.

One of the most important ways of influencing the process is by the submission of patients' evidence. Only a few countries, such as the UK, Canada and Australia, currently allow such submissions, but a generic patient group submission form has been created by HTA International and could be used in other countries.[28] Patient organisations can use such a form to gather a wide range of perspectives from patients about living with ADPKD, its physical and emotional impact and the challenges of current treatments, together with their priorities and preferences regarding novel treatments. The form helps patient groups present this important knowledge in a structured manner so that it has the best chance of contributing to the highly complex deliberations that take place during an HTA to illuminate the wider social and ethical impacts of the disease and the unmet needs that a new treatment might fulfil.

Other guidance and resources to support patients to participate in HTA is available online, for example at HTA International (http://www.htai.org/index.php?id=545).

It has been recognised internationally that patient involvement in HTA leads to relevance, fairness, equity, legitimacy and capacity building. However, to achieve this, structured processes of involvement are needed in the form of 10 published quality standards.[29] These should be promoted by all stakeholders.

7.4 Conclusions

The practical enhancement of patients' roles in decision-making, both in their own care and more widely in the organisation of care for all patients, is central to efforts to drive improvements in ADPKD care. This will require all parties, including governments and healthcare providers, to recognise the value of patients' input and to support efforts to better inform patients, and to include patient representatives fully and in a timely manner within strategic and tactical aspects of healthcare planning, research and delivery.

Importantly, national ADPKD patient organisations currently differ in their capabilities to contribute to such consultations, for example in terms of their level of development, personnel and resources and standards of service provision. A supportive framework is therefore necessary to build capacity and foster effective advocacy.

Patient empowerment is central to the strategic approaches proposed in the following section (Section 8) to help improve ADPKD care across Europe.

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8. EAF policy recommendations

Key point summary

- **The EAF hereby provides a short series of policy-focused recommendations to help address the unmet needs identified in this Report and to promote access to high-quality care for all patients with ADPKD in Europe.**
- ***Recommendation 1:*** **Governments should support the development of a nationally coordinated, tiered approach to ADPKD care in collaboration with experts, patient organisations and other stakeholders.**
- ***Recommendation 2:*** **An expanded European network of ADPKD reference centres would facilitate further research and the establishment of harmonised, integrated, patient-centred care pathways.**
- ***Recommendation 3:*** **The European Commission and national governments should support research to develop disease-modifying treatments for ADPKD with the potential to maintain quality of life, delay renal decline and improve life expectancy among patients, and to reduce the economic impact on healthcare systems.**
- ***Recommendation 4:*** **Governments and healthcare providers should support the implementation of methods to routinely assess prognosis in patients with ADPKD to inform clinical decision-making, research and innovation.**
- ***Recommendation 5:*** **All stakeholders, including the European Commission, national governments and healthcare providers, should support efforts to better inform individual patients and families affected by ADPKD, and to involve patient organisations in policy making regarding healthcare planning and delivery related to ADPKD.**
- ***Recommendation 6:*** **Health technology assessment (HTA) organisations should seek to engage patients and patient organisations in their assessments to provide patients' unique knowledge about the impact of living with ADPKD, and their aspirations for new treatments, according to the HTA International Quality Standards for Patient Involvement in HTA.**

8.1 Introduction

ADPKD offers a unique combination of challenges warranting a specific response from healthcare policymakers and providers. It is a complex, chronic, progressive and incurable genetic disease with a diverse and often profound physical and psychological impact on affected patients and families. It confers high healthcare costs due in particular to dialysis and transplantation (Sections 2–4). The impact of ADPKD is often underestimated by healthcare professionals and other stakeholders.

According to the 2013 report of the European Commission's Reflection Process on Chronic Diseases:

"There is a need for a strong emphasis on prevention as well as on sustainable disease management, and for a reorientation of budgets towards innovative approaches with an impact on the quality of life of people affected or at risk of chronic diseases. Prevention and strategies to delay the onset of chronic diseases along the life cycle need to be strengthened, making use of innovative concepts to avoid or reduce the need for health care interventions. This requires adaptations and changes in the systems, infrastructures, policies and legislation as well as incentives to support inclusive approaches and (behavioural) changes of people at risk."[1]

Patients with ADPKD need specialist diagnostic, therapeutic and preventative healthcare from various healthcare professionals throughout their lives. The preceding sections have drawn attention to the principal unmet needs in ADPKD care in Europe (Sections 5–7). Of particular importance:

- *There is an unmet need for all ADPKD patients to have access to a nephrologist knowledgeable about the disease.*

- *Patterns of clinical practice for ADPKD diagnosis, assessment, treatment and support vary within and between European countries, with little coordination of care policies and services.*
- *Variations in clinical care result in part from of a lack of accepted guidelines, due in turn largely to limitations in the current evidence base.*
- *There is a lack of approved treatments to slow disease progression and thereby avoid complications, maintain patients' quality of life (QoL) and delay the need for disruptive, invasive and costly dialysis and kidney transplantation.*

The Brussels Declaration on ADPKD hereby comprises a short series of policy focused recommendations to help address these unmet needs and promote access to high-quality care for all patients with ADPKD in Europe.

8.2 National tiered care model

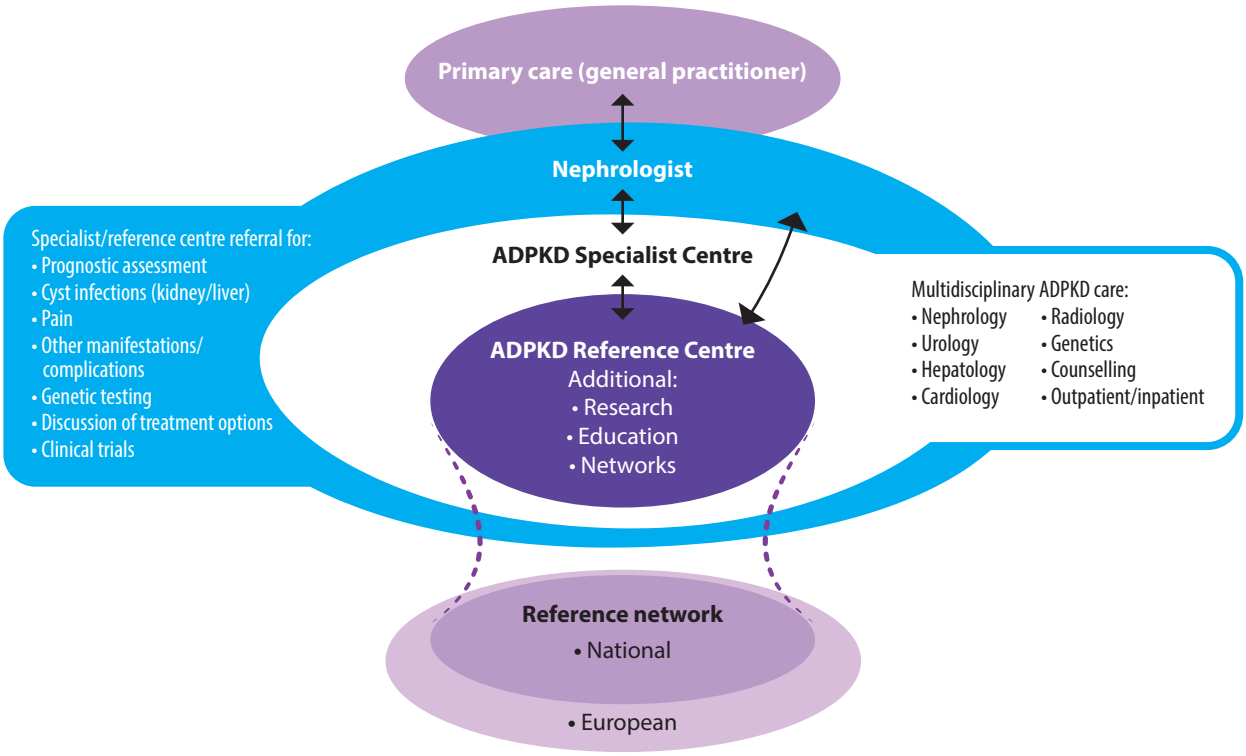
Recommendation 1: ***Governments should support the development of a nationally coordinated, tiered approach to ADPKD care in collaboration with experts, patient organisations and other stakeholders.***

ADPKD is a complex genetic disease that can affect many parts of the body. Patients with ADPKD therefore require access to care from a range of medical specialists with expertise in ADPKD, according to the evolving evidence on best practice.[2] The delivery of such care will depend on the local, regional or national organisation of healthcare services. Here we propose an example of a simple, adaptable model, showing the levels of care to which all patients with ADPKD should have access (Fig. 10).

According to this type of model, all patients should have access to referral to an ADPKD specialist nephrology centre, where multidisciplinary, patient-centred care can be provided on an inpatient or outpatient basis, according to clinical need. Referral to specialist centres would be encouraged for such aspects as early prognostic assessment (according to evolving predictive models), genetic testing (where clinically appropriate) and the investigation and management of the diverse manifestations and complications associated with ADPKD. The expertise of specialists in hepatology, urology, cardiology and radiology should be available according to need, together with associated counselling services.

The model envisages that some ADPKD specialist centres would be designated as Reference Centres. Additional roles of Reference Centres may include basic, translational and clinical research and the provision of medical education regarding ADPKD. Such centres would be central to the development and

Fig. 10. Schematic illustration showing an example of an adaptable model for national or regional use, showing the levels of non-specialist and ADPKD specialist care to which patients with ADPKD should have access. Arrows illustrate the referral of patients and/or the transfer of information, according to need.



implementation of future clinical guidelines and standards of best practice, according to the emerging evidence base.[2] Potentially, networks of such centres at the national and European levels could offer important benefits (see Declaration 2).

Data on the cost-effectiveness of ADPKD care are lacking. Nevertheless, a model that encourages coordinated specialist care is likely to improve the efficiency of healthcare provision by:

- *Reducing the unnecessary duplication of tests and scans*
- *Facilitating the targeting of novel diagnostic and therapeutic interventions according to clinical need and expected benefit*
- *Reducing the impact of ADPKD-related complications and the number of unplanned hospital admissions through better care*
- *Targeting the use of future disease-modifying therapies, and thereby contributing to a delay in the need for dialysis and transplantation among patients with ADPKD.*

By promoting the access of all patients to a standardised model of high-quality, cost-effective care, such a model would also be in line with the European Commission policy priority to address health inequalities.[3]

We urge responsible national and regional authorities to collaborate with representatives of all healthcare professionals responsible for managing patients with ADPKD, including nephrologists, other medical specialties (including hepatologists and geneticists), nurses and patient organisations, to design and implement a suitable model to improve ADPKD care.

8.3 European reference network

Recommendation 2: ***An expanded European network of ADPKD reference centres would facilitate further research and the establishment of harmonised, integrated, patient-centred care pathways.***

The 2014 Kidney Disease: Improving Global Outcomes (KDIGO) ADPKD Report has defined the priority areas for research to address outstanding evidence gaps, and hence to inform future clinical guidelines and care pathways for ADPKD.[2] Governments and the European Commission should support collaborative expert-led research to resolve key controversies.

Building on the achievement of the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA)-funded EuroCYST initiative (Section 6), we support a continued dialogue between all stakeholders towards the further development of a network of European ADPKD reference networks to facilitate coordinated research and the development and implementation of best practice in ADPKD.

In principle, this would align with the European Commission's call for Member States to connect appropriate healthcare providers and centres of expertise so they can work toward the development of European reference networks for patients with rare or low-prevalence complex diseases requiring a particular concentration of expertise in medical domains where expertise is rare.[4,5]

8.4 Therapeutic innovation

Recommendation 3: ***The European Commission and national governments should support research to develop disease-modifying treatments for ADPKD with the potential to maintain quality of life, delay renal decline and improve life expectancy among patients, and to reduce the economic impact on healthcare systems.***

Recommendation 4: ***Governments and healthcare providers should support the implementation of methods to routinely assess prognosis in patients with ADPKD to inform clinical decision-making, research and innovation.***

This report outlines the need for new therapeutic agents and the barriers facing this process. The acceptance by the European Medicines Agency and other regulatory authorities of 'surrogate' assessments of drug efficacy is a priority so that ADPKD treatments can be evaluated at early stages of disease course when patients are expected to benefit. Total kidney volume (TKV) has already been used as the principal endpoint of clinical trials for this purpose. Efforts should continue to evaluate and establish the use of TKV within models to predict disease progression and to identify patients most likely to benefit from novel disease-modifying therapies, both for the purposes of future clinical trials and for decision-making in clinical practice. Furthermore, all stakeholders should support further research to validate shorter-term surrogate endpoints to facilitate early phase translational research as a bridge to longer-term clinical studies using TKV and other endpoints.

In addition, future clinical trials of new agents should also assess their effect on the burden of ADPKD among patients. Instruments for the measurement of patient-reported outcomes in patients with ADPKD (including the physical and psychosocial impact) need to be developed, validated and incorporated into clinical trials and practice.[2,6]

8.5 Empowering patients

Recommendation 5: *All stakeholders, including the European Commission, national governments and healthcare providers, should support efforts to better inform individual patients and families affected by ADPKD, and to involve patient organisations in policy-making regarding healthcare planning and delivery related to ADPKD.*

Recommendation 6: *Health technology assessment (HTA) organisations should seek to engage patients and patient organisations in assessments to provide patients' unique knowledge about the impact of living with ADPKD, and their aspirations for new treatments, according to the HTA International Quality Standards for Patient Involvement in HTA.*

National health ministries should support the establishment (where necessary) and work of ADPKD patient organisations. All stakeholders should collaborate to provide affected patients and families with specific, comprehensive and reliable written information about ADPKD and to establish pathways whereby diagnosed patients are routinely referred to patient organisations for further information and support. Patient organisations should also be involved in relevant educational initiatives directed to healthcare professionals, patients, parents and carers, and the public.

More fundamentally, patient organisations should be involved in the development of policies relating to strategic and tactical aspects of healthcare planning and delivery in ADPKD, including the design of care services, research, and health technology assessment (according to published quality standards[7]).

8.6 Conclusion

This Report has delineated the often-unrecognised burden of ADPKD on patients and health systems in Europe and identified key unmet needs in, and barriers to, the provision of care. In this section we have offered a series of strategic recommendations to improve access to high-quality, cost-effective care across Europe, in context with various ongoing healthy policy initiatives.

The process of designing and implementing the strategies proposed will require national and international collaboration between all stakeholders in ADPKD care, including:

- *Patients and their representative organisations*
- *Nephrologists and other specialist physicians involved in ADPKD care*
- *Geneticists*
- *Healthcare system managers*
- *National government health ministries*
- *Bodies responsible for medicines regulation and HTA.*

The EAF intends to facilitate dialogue and collaboration between these groups and looks forward to working with all bodies to improve and lengthen the lives of patients with ADPKD.

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9. European ADPKD Forum members

The following table lists the members of the EAF faculty.

Co-Chairs	
Dr Richard Sandford	University of Cambridge/Addenbrookes Hospital, Cambridge, UK
Tess Harris	PKD International, London, UK

All participants by specialty	
Nephrology	
Prof. Olivier Devuyst	University of Zurich, Zurich, Switzerland
Prof. Tevfik Ecder	Istanbul Bilim University, Istanbul, Turkey
Dr Ron T. Gansevoort	University Medical Center Groningen, Groningen, Netherlands
Dr José Luis Górriz	Hospital Universitario Dr. Peset Valencia, Valencia, Spain
Prof. Albert Ong	University of Sheffield, Sheffield, UK
Prof. Yves Pirson	Université catholique de Louvain, Brussels, Belgium
Prof. Vicente Torres	Mayo Clinic, Rochester, MN, USA
Prof. Gerd Walz	University Hospital Freiburg, Freiburg, Germany
Hepatology	
Prof. Joost Drenth	Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands
Genetics	
Dr Richard Sandford	Cambridge University/Addenbrookes Hospital Cambridge, Cambridge, UK
Patient advocacy	
Brenda de Coninck	Dutch Kidney Patient Association (NVN), Bussum, Netherlands
Tess Harris	PKD International, London, UK
Alastair Kent	Patients Network for Medical Research and Health (EGAN), London, UK

The authors thank Dr Karen Facey, University of Glasgow, Glasgow, UK, for her review and contribution to Section 7.

10. Polycystic kidney disease organisations

Country	Organisation	Website
Europe		
Belgium	Association pour l'Information et la Recherche sur les maladies Rénales Génétiques (AIRG) Belgique	www.airg-belgique.org
Finland	Munuais- ja maksaliitto (The Finnish Kidney and Liver Organization)	www.musili.fi
France	Association Polykystose France (APKF)	www.polykystose.org
	Association pour l'Information et la Recherche sur les maladies Rénales Génétiques (AIRG) France	www.airg-france.fr
Germany	PKD Familiäre Zystennieren e.V.	www.pkdcure.de
Italy	Associazione Italiana Rene Policistico (AIRP)	www.renepolicistico.it
Netherlands	Nierpatienten Vereniging Nederland (NVN)	www.nvn.nl/
Spain	Asociación para la Información y la Investigación de las Enfermedades Renales Genéticas	www. airg-e.onmedic.org www. airg-e.org/
Switzerland	SwissPKD	www.swisspkd.ch/de/home
	Association pour l'Information et la Recherche sur les maladies Rénales Génétiques (AIRG) Suisse	www.airg-suisse.org
Turkey	Turkish Society of Nephrology Cystic Kidney Diseases Working Group	www.tsn.org.tr/icerik.php?gid=39
UK	PKD Charity	www.pkdcharity.org.uk
North America		
Canada	PKD Foundation of Canada	www.endpkd.ca
USA	PKD Foundation	www.pkdcure.org
Asia		
Japan	PKD Foundation	www.pkdfcj.org
Australasia		
Australia	PKD Foundation Australia	www.pkdaustralia.org
International		
	Federation of European associations of patients affected by Renal Genetic diseases (FEDERG)	www.federg2012.wordpress.com
	PKD International	www.pkdinternational.org

11. Glossary of acronyms

ACE inhibitor	Angiotensin converting enzyme inhibitor
ADPKD	Autosomal dominant polycystic kidney disease
ARB	Angiotensin receptor blocker
CKD	Chronic kidney disease
CT	Computed tomography
EAF	European ADPKD Forum
EKHA	European Kidney Health Alliance
EMA	European Medicines Agency
ERA-EDTA	European Renal Association-European Dialysis and Transplant Association
EULOD	Living Organ Donation in Europe
GFR	Glomerular filtration rate
HTA	Health technology assessment
KDIGO	Kidney Disease Improving Global Outcomes
MRI	Magnetic Resonance Imaging
PET	Positron-emission tomography
PGD	Pre-implantation genetic diagnosis
PKD	Polycystic kidney disease
PKDOC	Polycystic Kidney Disease Outcomes Consortium Project
QoL	Quality of life
RRT	Renal replacement therapy
TKV	Total kidney volume
WHO	World Health Organization


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