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## Identifying patient-important outcomes in polycystic kidney disease: an international nominal group technique study

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## ABSTRACT

**Aim:** Patients with autosomal dominant polycystic kidney disease (ADPKD) are at increased risk of premature mortality, morbidities and complications, which severely impair quality of life.

However, patient-centred outcomes are not consistently reported in trials in ADPKD, which can limit shared decision-making. We aimed to identify outcomes important to patients and caregivers and the reasons for their priorities.

**Methods:** Nominal group technique was adopted involving patients with ADPKD and caregivers who were purposively selected from eight centres across Australia, France and the Republic of Korea. Participants identified, ranked and discussed outcomes for trials in ADPKD. We calculated an importance score (0-1) for each outcome and conducted thematic analyses.

**Results:** Across 17 groups, 154 participants (121 patients, 33 caregivers) aged 19 to 78 (mean 54.5 years) identified 55 outcomes. The 10 highest ranked outcomes were: kidney function (importance score 0.36), end stage kidney disease (0.32), survival (0.21), cyst size/growth (0.20), cyst pain/bleeding (0.18), blood pressure (0.17), ability to work (0.16), cerebral aneurysm/stroke (0.14), mobility/physical function (0.12), and fatigue (0.12). Three themes were identified: threatening semblance of normality, inability to control, and making sense of diverse risks.

**Conclusion:** For patients with ADPKD and their caregivers, kidney function, delayed progression to end stage kidney disease and survival were the highest priorities, and were focused on achieving normality, and maintaining control over health and lifestyle. Implementing these patient-important outcomes may improve the meaning and relevance of trials to inform clinical care in ADPKD.

**KEYWORDS**

Cyst, Kidney function, Outcomes, Patient, Polycystic kidney disease, Qualitative

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## INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited cystic kidney disease<sup>1-3</sup>. Up to 70% of patients progress to end-stage kidney disease (ESKD) requiring dialysis or kidney transplantation by the age of 65 years<sup>4</sup>. Patients with ADPKD are at an increased risk of premature mortality, co-morbidities and life-time complications including hepatic cysts, urinary tract infections, intracranial aneurysm and kidney pain, which severely impair quality of life. Whilst these outcomes would be expected to be critical for decision-making, they are infrequently and inconsistently reported across trials in ADPKD and often under-appreciated by treating physicians<sup>5</sup>.

Despite the emphasis on empowering patients to be active partners in care and to participate in decision-making and research<sup>5-8</sup>, patients are seldom involved in the selection of trial outcomes. This is problematic given the discordance in priorities for outcomes between health professionals and patients with kidney disease<sup>9</sup>. Studies in ADPKD<sup>10-13</sup> have predominantly focused on reporting rates of change in total kidney volume (TKV) and kidney function. Patient-reported outcomes, such as pain, fatigue, or anxiety<sup>14</sup>, have been largely omitted from trial reports. Patients involved in the development of guidelines on ADPKD identified psychosocial well-being, pain, work, and financial impact as important areas for support and decision-making<sup>9,15</sup>, which again are infrequently reported in research.

The aim of this study was to systematically identify patient and caregiver priorities for outcomes in trials in ADPKD, and to describe the reason for their decisions. This may inform the selection of

patient-important outcomes for research, and thereby improve the relevance of trials for decision-making in patients with ADPKD for improved care and outcomes.

## **METHODS**

A combination of focus group and nominal group techniques<sup>16,17</sup> was used to identify and rank outcomes considered important to ADPKD patients and their caregivers, and the reasons for their decisions. Nominal group technique has been used to prioritise outcomes across various health disciplines<sup>18-20</sup>. It encourages equal participation through minimising individual dominance and providing opportunity to systematically elicit the perspectives of participants<sup>18</sup>.

### *Participant selection*

Patients with ADPKD and their caregivers (i.e. family members or support person involved in the patient's care) aged over 18 years and able to give written informed consent were eligible. We recruited participants from eight centres across Australia (Brisbane, Melbourne, Sydney), France (Brest, La Roche-sur-Yon, Nantes, Tours), and the Republic of Korea (Seoul). We used purposive sampling to maximize diverse demographic (age, sex, socioeconomic status, ethnicity, and education) and clinical characteristics (stage of CKD: i.e. patients not on renal replacement therapy, CKD stage 1-5; patients on dialysis, 5D; and patients with a kidney transplant, 5T; time since diagnosis, comorbidities, and complications), as was feasible. Participants had to be able to speak the native language (English, French, Korean) in which the groups were conducted. Our target was 10 participants per group for manageability and optimal group dynamics. We reimbursed

participants (approximately \$50 USD-equivalent in local currency) for travel expenses. The Human Research Ethics Committee of the Western Sydney Local Health District (HREC2009/6/4.14), Monash Medical Centre (2010.031), Metro South Health District (17/QPAH/112), France (INSERM/2017) and Republic of Korea (1709-087-886) approved this study.

### *Data Collection*

Each group was two hours in duration and held at a centrally located venue external to the hospital from June to November 2017. The focus groups were facilitated by trained moderators in native languages (English – A.T., T.G., Y.C.; French – B.S; Korean – Y.K.). The question guide (Supplementary Table 1) was adapted from those we have used to elicit patient-prioritised outcomes in kidney transplantation and hemodialysis<sup>24-21</sup>, and with input from the Standardised Outcomes in Nephrology – Polycystic Kidney Disease (SONG-PKD) Steering Group and investigators. The structure of the session included: i) general discussion on living with ADPKD, and the perceived benefits and harms of ADPKD-related treatment; ii) individual identification to generate a group list of outcomes believed to be important for research, which were augmented with outcomes identified from trials and previous nominal groups; and, iii) individual ranking of the printed list of outcomes (from 1=most important to xx=least important) and group discussion of the similarities and differences in rankings. Participants were asked to rank individual outcomes in the order of importance for research in all patients with ADPKD, independent of their stage of CKD (pre-dialysis, dialysis, transplant). We convened focus/nominal groups until data saturation, defined as when no new outcomes or reasons were being identified in subsequent groups. All discussions

during the session were audiotaped and transcribed verbatim, and a co-facilitator recorded the contextual details around the discussion.

### *Data Analysis*

#### Nominal Group Ranking

A measure of importance for each outcome, based on the ranking results from each focus/nominal group, was used to prioritise the outcomes. The steps involved in calculation of this measure were previously specified in the published protocol<sup>22</sup>. The importance scores represent a summary measure of importance of the outcome, which incorporates the consistency of being nominated and the rankings given by the participants. The importance score (IS) can be computed using the probabilities of each rank for each outcome ( $P(O_j \text{ in rank } i)$ , i.e., the probability of the outcome  $O_j$  being assigned the rank  $i$ ) and weighted sum of the inverted ranking ( $\frac{1}{i}$ ):

$$IS = \sum_{i=1}^{nr \text{ of outcomes}} P(O_j \text{ in rank } i) \times \frac{1}{i}$$

Higher values of the score identified outcomes that were considered more important by the participants. These scores were then calculated separately for a) patients and their caregivers, b) country, and c) stage of CKD (pre-dialysis CKD vs. CKD stage 5D vs. CKD stage 5T). The software packages Stata/SE version 14.0 (StataCorp. College Station, TX) and the R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria) were used to analyse the data.

## Qualitative Analysis

The transcripts were imported into HyperRESEARCH (ResearchWare Inc. [www.researchware.com](http://www.researchware.com), version 3.7.2) software to facilitate qualitative data analysis. The transcripts in the original language were coded line by line by the facilitators (Y.C., C.S., B.S.) to identify concepts. Similar concepts were grouped into themes that reflected the reasons for identifying and ranking the outcomes. Using investigator triangulation, the preliminary findings were discussed among the research team (A.T., T.G., B.S., C.G., C.L., Y.C.) to ensure that themes reflected the full breadth and depth of the data.

## **RESULTS**

### *Participant Characteristics*

Across the 17 groups, 154 participants (120 patients, 34 caregivers) attended (Table 1). The attendance rate was 87% and the reasons for non-attendance included work, inability to arrange transportation and illness. The participants were aged from 19 to 78 years (mean  $\pm$  standard deviation  $54.5 \pm 12.3$ ) and 67 (42%) were men. The majority of patients were pre-dialysis chronic kidney disease (CKD stages 1-5, n=76, 61%), followed by transplant recipients (n=31, 26%) and those on dialysis (n=19, 13%).

### *Identification and ranking of outcomes*

In total, 55 unique outcomes were identified across 17 groups (Australia (10), France (4), Republic of Korea (3)). The composition of the groups is provided in Supplementary Table 2. The mean number of outcomes identified by each group was 33 (range, 14 to 44). Across all participants, the ten highest ranked outcomes were kidney function (importance score = 0.36), end-stage kidney disease (ESKD, 0.32), survival (0.21), cyst size/growth (0.20), cyst pain/bleeding (0.18), blood pressure (0.17), ability to work (0.16), cerebral aneurysm/stroke (0.14), mobility/physical function (0.12), and fatigue (0.12) (Supplementary Table 3). Eight outcomes were common to all groups: cyst pain/bleeding, ESKD, cerebral aneurysm/stroke, survival, kidney function, cyst size/growth, blood pressure, and financial impact.

There were some differences by country, CKD stage, and patients/caregivers. Ability to work was ranked highest in France (0.31), whereas kidney function was ranked highest in Australia and Republic of Korea (0.40, 0.37; Figure 1). Some outcomes were prioritised within the top ten outcomes in one country only: in Australia, cardiovascular disease (0.17) and anxiety/stress (0.12), in France, fatigue (0.21), and impact on family (0.12), and in Republic of Korea, infection (0.25), financial impact (0.20) and muscle pain (0.10) (Table S3). By CKD stage, the top three outcomes were: in pre-dialysis CKD, kidney function (0.36), ESKD (0.31), and cyst size/growth (0.25); in dialysis patients, blood pressure (0.31), kidney function (0.30), and ESKD (0.24); and in transplant recipients, kidney function (0.36), ESKD (0.34) and ability to work (0.27; Supplementary Figure 1). For patients, the top three outcomes were ESKD (0.34), kidney function (0.34) and ability to work (0.28), whereas for caregivers, they were kidney function (0.43), ESKD (0.33), and cyst pain/bleed (0.21; Figure 2).

## Qualitative Analysis

We identified three themes that reflected the reasons for the identification and prioritisation of outcomes: threatening semblance of normality, inability to control, and making sense of diverse risks. The subthemes are described below and selected quotations illustrating each theme are provided in Table 2. A thematic schema to illustrate the relationship among themes and outcomes is provided in Figure 3.

### Threatening semblance of normality

*Surviving, not thriving.* Outcomes that were perceived to impair their ability to “thrive in life” were ranked highly by participants. For example, “fatigue” impaired their ability to find gainful employment and to work. They were anxious about progression to “ESKD,” as they feared dialysis or transplant would interfere with being able to live an “ideal life”. Participants believed that this could lead to helplessness and ultimately “depression”. Patients in the Republic of Korea commented that “surviving” was not as important because “everyone dies eventually”.

*Restricted from activities of daily living.* Some participants reported that symptoms, such as cyst pain, were relentless, limited their ability to do simple daily tasks, such as “hanging washing” or “grocery shopping,” and prevented their leading a “normal life”. Some outcomes attributed to cyst growth, including “nausea”, “indigestion” and “vomiting”, were of higher importance for patients who had direct experience of these symptoms. These outcomes could lead to social isolation and dependency on their caregivers, which made patients feel vulnerable.

*Embarrassed by enlarged and distorted abdomen.* Some female patients suffered “embarrassment by appearing constantly pregnant” due to their protruding abdomen from enlarged kidneys with or without enlarged liver. However, they explained that it was not a life-threatening outcome and, as such, ranked this relatively lower than outcomes that were considered important for survival.

*Isolated and misunderstood.* Patients at early stages of CKD felt their disease was “invisible” and perceived that others, including their family, could not comprehend the impact of their symptoms, such as “fatigue” and “depression.” One stated, “in some ways, it is better to have a broken arm. People can at least see the cast, they can talk about it, and they care about you. But there is nothing to see about our disease.” Symptoms, such as “fatigue”, “pain” and “cognitive impairment”, which were not apparent to others, led to termination of employment as patients could not meet their employers’ expectations, and were forced to depend on disability support pensions leading to financial insecurity.

#### Inability to control

*Impossible to cure symptoms.* Patients believed they had no choice but to endure symptoms, such as “fatigue” and “cyst pain,” and complications from “cyst growth” from kidneys and/or liver, such as “nausea or vomiting,” for the duration of their life. They could not envisage ever being symptom-free, and thus ranked the importance of these outcomes highly. Even after transplant, some patients still suffered from persistent cyst pain, which supported their higher ranking.

*Rendered powerless by prognostic uncertainties.* The inevitable progression to ESKD made patients feel “powerless” and left them wanting to “delay it as long as possible.” They had “anxiety” and concerns about the wellbeing of their future generations. Participants stated that life-changing or physically disabling complications, such as “cerebral aneurysm,” took “precedence over anything else”, as there were no treatments available to prevent the outcome.

*Visible suffering in affected family members.* Some participants had seen the suffering of other family members with ADPKD and were anxious that they may endure the same consequences. This underpinned outcomes that they ranked highly: “I’ve got many members of the family with PKD and only one person in the family hasn’t got it. But we haven’t had any positive outcomes. All my family have died of cardiovascular disease.” Some patients were conscious that ADPKD imposed a “burden” on their family.

#### Making sense of diverse risks

*Unpredictable and severe consequences.* Patients felt planning for the future was impossible as they felt that they were in a “waiting game” where they did not know how quickly their kidney function would decline and whether they would require dialysis or a kidney transplant. Patients felt ambivalent about their ability to directly “influence” rate of decline in kidney function through lifestyle modification or medical therapy. Ongoing costs associated with continuous investigations to monitor status to avoid complications from ADPKD placed financial burden on participants in the Republic of Korea.

*False sense of security in imperceptible sickness.* Some patients felt that ADPKD did not impact on their “current” life situation: “I’ve never been sick from it all. So, I’ve never felt unwell.” Thus, outcomes, such as diverticulitis, breathlessness, kidney stones and hernia, were ranked lower.

*Living with perpetual guilt.* Patients felt responsible for passing on ADPKD to their younger generations: “to our pain is added that of seeing our children in the face of all that we have lived, who have seen all that we have suffered. And knowing that they take the same path, it destroys even more.” Parental caregivers believed prevention of progression to ESKD would ensure a better future for their affected children. Diagnosis of ADPKD in children, especially sons, brought on challenges for parents in the Republic of Korea, as they were worried for jeopardizing future job opportunities due to military service exemption because of ADPKD.

*Fear of discrimination.* Patients worried about losing their jobs and insurability: “I was diagnosed with it at 25 and I kept it very quiet for the longest that I possibly could and not just for employment purposes, but also insurances.” Patients in Republic of Korea were fearful of discrimination at work because the “restricted diet, abstinence from alcohol and cigarette smoking” prevented them from fulfilling expectations of them to participate in work and social activities.

## **DISCUSSION**

For patients with ADPKD and their caregivers, clinical outcomes such as kidney function, ESKD, blood pressure, cerebral aneurysm/stroke, and cyst size/growth, and patient-reported outcomes including cyst pain/bleed, fatigue, ability to work, anxiety/stress, were of critical importance.

Kidney function was interpreted by patients to be a key determinant of their prognosis, specifically progression to ESKD. Progression to ESKD necessitating renal replacement therapy was perceived to severely limit the ability to live a “normal” life as there was concern that dialysis would interfere with their ability to work and participate in life activities as they desired. Uncertainty about their prognosis provoked anxiety and stress in patients, which were further exacerbated by the unremitting physical symptom burden, causing patients to feel powerless. These also impaired their capacity to work, ability to do usual activities, financial stability, and overall lifestyle. Some patients suffered guilt stemming from the genetic nature of ADPKD, and also had anxieties about their children being diagnosed with ADPKD and their prognosis.

Overall, kidney function and progression to ESKD were consistently prioritised as the most important outcomes in patients with ADPKD and their caregivers. Stability in kidney function provided reassurance to patients, whereas a decline in function provoked anxiety because their prognosis was perceived to be beyond their control. Whilst the importance of progressing to ESKD is undisputed<sup>5,15</sup>, trials in ADPKD have largely focused on measuring kidney function, often reported as change in estimated glomerular filtration rate (eGFR) and TKV, and have not explicitly examined progression to ESKD<sup>10,11,23</sup>. This may relate to the long natural history of the disease, with a lack of a reliable biomarker to assess progression to ESKD in early stage CKD patients with ADPKD who are typically eligible to be enrolled in clinical trials<sup>10,11,23,24</sup>. Further, interventions in far advanced CKD when kidneys are large and presumably fibrotic, where ESKD is more likely, are thought to be less likely to be successful.

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Patient-reported outcomes, such as pain and fatigue, ranked high in importance because they relentless and constantly reminded patients of their condition. These often unrelenting symptoms impaired their lifestyle, usual activities, and vocational potential, and threatened their financial security. Subsequently, this had a detrimental impact on their mental well-being, and they felt guilty in having to remain dependent on their family. Some patients reported being depressed from social isolation and experienced a loss of self-confidence from incapacity to work with deterioration in financial status. The lack of such patient-reported outcomes in trials was recently identified as a major gap in ADPKD trials at the Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference<sup>15</sup>. Recently, a new health-related quality of life instrument for patients with ADPKD (ADPKD-IS) was developed, which consists of 14 items that measure three conceptual domains: physical, emotional and fatigue, and four additional questions on guilt, sleep, size/shape of abdomen, and urinary frequency/urgency<sup>25</sup>. This measure includes outcomes identified in our study, including ability to work, life participation, fatigue, physical function, pain, anxiety, depression, gastrointestinal symptoms (early satiety), sleep, appearance and urine output<sup>25</sup>. However, impact on family, financial impact, and cognition are not included in the ADPKD-IS.

In our study, there were notable differences in the ranking of outcomes across countries, stages of CKD, and patients versus caregivers. Ability to work was ranked highest in France, whereas financial impact was ranked in the top ten only in the Republic of Korea. Although the proportion of participants in fulltime/part time employment in France (40%) was lower than Republic of Korea (69%), it was comparable to Australia (40%). In France, ability to work was often considered synonymous to health, supported by findings of a national survey, which showed that the majority of French loved their work (76%) and/or were proud of it (56%)<sup>26</sup>. For patients/caregivers in the

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Republic of Korea, the ongoing health care costs incurred a substantive financial burden owing to perceived insufficient government funded support and some investigations including genetic test for ADPKD are not covered by the National Health Insurance scheme. Of note, progression to ESKD was ranked lower in the Republic of Korea (0.18) compared to other countries (Australia: 0.38, France: 0.27), which could be because the majority were pre-dialysis CKD patients (83%). Regional differences in how patient-reported outcomes were prioritized across focus groups conducted in United States, Europe and Japan were also observed by ADPKD-IS investigators, reinforcing the importance of capturing diverse population<sup>25</sup>. These results are not surprising given the heterogeneous nature of ADPKD with variable symptom burden, and the potential variability in values attached to outcomes by country and cultures. Patients also prioritised outcomes based on direct relevance to their current stage of CKD. For example, patients on dialysis ranked pruritus and blood pressure more importantly. Patients gave higher priority to outcomes related to physical function (mobility/physical strength, fatigue) and psychosocial impact (ability to work, impact on family) that hindered ability to participate in life, whereas caregivers were concerned about patients suffering from symptom burden (cyst pain/bleed; cyst size/growth) and life threatening outcomes (cardiovascular disease).

We recruited patients with ADPKD and their caregivers from three countries to capture diverse cultural backgrounds and healthcare systems. A combined quantitative and qualitative methodology based on nominal group technique provided comprehensive data about their priorities, attitudes and beliefs with regards to ADPKD outcomes. However, there are some potential limitations. Most patients were in the pre-dialysis stage of CKD (61%) with the highest proportion of pre-dialysis CKD patients amongst Korean participants (83%). All focus groups took place in

high-income countries, and the majority of participants were older than 40 years of age. Therefore, transferability of the findings beyond these populations is uncertain.

International guidelines on ADPKD emphasize the need to deliver patient-centred care, which involves shared decision-making<sup>9,15</sup>. This may be facilitated by consistent reporting of outcomes that are meaningful and relevant to patients across trials in ADPKD. The findings from the current study will directly inform the development of a core outcome set for trials in ADPKD incorporating priorities of all stakeholders including patients, based on the Standardized Outcomes in Nephrology (SONG) initiative, to enable consistent measurement and reporting of relevant and important outcomes in trials<sup>22</sup>.

Patients with ADPKD and their caregivers gave highest priority to clinical outcomes (such as kidney function, ESKD, and cyst size/growth), as well as symptoms, psychosocial and lifestyle impacts (cyst pain, fatigue, ability to work, and anxiety/stress). These outcomes were highly prioritised because they were perceived to substantively diminish their sense of control and normality, and ability to achieve the life goals they valued. Yet, many of these outcomes are not universally reported in trials in ADPKD<sup>10,11,23,24</sup>. Consistent reporting of outcomes that are most relevant and meaningful to patients with ADPKD is needed to empower patients and clinicians for shared decision-making.

## **Authors' Contributions**

Research idea and study design: YC, BS, TG, CG, AT; data acquisition: YC, BS, YK, CG, TG, AT; data analysis/interpretation: YC, BS, TG, CG, CL, AT, ATP; statistical analysis: ATP; supervision and mentorship: AT, GR, JC. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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**Table 1. Participant Demographic Characteristics.**

<b>Characteristic</b>	<b>Australia n=85 (%)</b>	<b>France n=40 (%)</b>	<b>Republic of Korea n=29 (%)</b>	<b>All participants n=154 (%)</b>
<b>Participant Status</b>				
Patient	61 (72)	36 (90)	24 (83)	121 (79)
Caregiver	24 (28)	4 (10)	5 (17)	33 (21)
<b>Male</b>	35 (41)	17 (43)	12 (41)	64 (42)
<b>Age (years)</b>				
18-39	16 (19)	2 (5)	3 (10)	21 (13)
40-59	34 (40)	18 (45)	20 (69)	72 (47)
60-79	35 (41)	20 (50)	6 (21)	61 (40)
<b>Highest level of education<sup>^</sup></b>				
Primary school: grade 6	4 (5)	2 (5)	1 (4)	7 (5)
Secondary school: grade 10	18 (22)	8 (20)	2 (7)	28 (18)
Secondary school: grade 12	7 (8)	14 (35)	5 (17)	26 (17)
Tertiary: certificate/diploma	25 (30)	4 (10)	0 (0)	29 (19)
Tertiary: university degree	29 (35)	12 (30)	21 (72)	62 (41)
<b>Employment status</b>				
Full-time	21 (25)	12 (30)	17 (59)	50 (32)
Part-time or casual	17 (20)	4 (10)	3 (10)	24 (16)
Not employed	11 (13)	0 (0)	4 (14)	15 (10)
Retired	28 (33)	19 (47)	2 (7)	49 (32)
Other (e.g. income protection insurance)	8 (9)	5 (13)	3 (10)	16 (10)
<b>Ethnicity</b>				
White	72 (85)	40 (100)	0 (0)	112 (73)
Asian	7 (8)	0 (0)	29 (100)	36 (23)
Other	6 (7)	0 (0)	0 (0)	6 (4)
<b>CKD Stage<sup>**</sup></b>				
Pre-dialysis	34 (56)	20 (55)	20 (83)	74 (61)
Dialysis	11 (18)	2 (6)	3 (13)	16 (13)
Transplantation	16 (26)	14 (39)	1 (4)	31 (26)
<b>Age at Diagnosis<sup>^**</sup></b>				
0-20 y	10 (17)	6 (17)	3 (13)	19 (16)
21-40 y	35 (57)	21 (58)	14 (58)	70 (58)

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41-60 y	13 (21)	7 (19)	6 (25)	26 (21)
>60 y	3 (5)	2 (6)	1 (4)	6 (5)

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^missing data from 2 participants; \*\* patient-only (n=61; n=31; n=24).Abbreviations: ADPKD,

autosomal dominant polycystic kidney disease; CKD, chronic kidney disease.

**Table 2. Select participant quotations for each theme reflecting the reasons for the ranking of outcomes.**

Subthemes	Quotations
<b>Surviving, not thriving</b>	<p style="text-align: center;"><b><u>Threatening semblance of normality</u></b></p> <p><i>“Just have a normal life. See when you have polycystic kidneys, you don’t have a normal life. What you eat, what you drink, how you sleep, no exercise, constant pain, the effect on your family. Because when you start out it’s ok, but as the years go on, you become more debilitating, and all you’re doing is surviving, not living.” (FG7, patient)</i></p> <p><i>“Depression he battled because he can’t – he was a workaholic all his life and now he can’t do anything. So he gets really depressed about it.” (FG1, caregiver)</i></p> <p><i>“I’ve actually ended up having to leave work at age 44 and I had intended to work until 60, so having to manage on a small pension was very hard.” (FG5, patient)</i></p> <p><i>“Everyone dies eventually, so I don’t think death is very important.” (FG15, patient)</i></p>
<b>Restricted from activities of daily living</b>	<p><i>“If you can’t push a trolley or you can’t access the world in the way that you want to access it that has implications for your mental health and your just general wellbeing.” (FG5, patient)</i></p> <p><i>“I can’t go out for meals at night, as the cysts in my liver and kidney are getting bigger and bigger there’s no room and it’s pushing up my stomach. So if I go out with friends at night I usually end up vomiting.” (FG5, patient)</i></p> <p><i>“There are days when I will sit and have a sook to myself... why is this happening? Why? I just want a normal day.. pain-free day... it all comes back to PKD.” (FG6, patient)</i></p>
<b>Embarrassed by enlarged and distorted abdomen</b>	<p><i>“I’m not going to worry about going to hospital because I know that’s going to happen but if you’re going to come up with solutions it’s solutions around reducing the size of the growth or the size of the kidneys, it affects everyone, the clothes you wear, the way people perceive you, other people’s perception.” (FG2, patient)</i></p> <p><i>“I’m embarrassed by perceptions of others who must think I am too old to be pregnant.” (FG16, patient)</i></p> <p><i>“I can’t find clothes that fit me properly because I am thin except around the abdomen. I have to wear pants with elastic band, but really you can’t wear such clothes to work..... also, when I get on the train, people ask me to take their seat because they think I’m pregnant. I don’t know how to respond, I don’t want to</i></p>

<p><b>Isolated and misunderstood</b></p>	<p><i>explain every time that I am not pregnant but then don't want to say I am pregnant.</i>” (FG16, patient)</p> <p><i>“I left my job in a way because I wasn't thinking right anymore. .... My ability, I really felt, went down and I started getting embarrassed in class.... I lost it.”</i> (FG4, patient)</p> <p><i>“Probably depression and pain is probably the worst for me, because I had a, just thought I was, you know, making it all up basically.”</i> (FG8, patient)</p> <p><i>“Sometimes from the family.. who doesn't understand. Because our sickness is invisible. In some way, it is better to have a broken arm. People can at least see the cast, they can talk about it. They care about you. But there is nothing to see about our disease.”</i> (FG13, patient)</p>
<p><b>Impossible to cure symptoms</b></p> <p><b>Rendered powerless by prognostic uncertainties</b></p>	<p style="text-align: center;"><b><u>Inability to control</u></b></p> <p><i>“You can't handle anything if you're tired. You just don't cope.”</i> (FG1, patient)</p> <p><i>“It impacts so much on your general comfort in life and that's huge. If you're not comfortable, if you're in pain or discomfort or just feeling full it really impacts on your life every moment of the day and night.”</i> (FG5, patient)</p> <p><i>“I've had a transplant, but PKD still affected me because my liver is full of cysts. I've got a transplanted kidney and there's no issues, it gets bigger issues because your liver, you still get the pain and whatever is related to the cysts. It still stays with you, doesn't go away.”</i> (FG7, patient)</p> <p><i>“Well, just a fact of life, I think. What can you do about it? I guess, it just hopes delay it [decline in kidney function] as long as possible. You've really got no power over it.”</i> (FG5, patient)</p> <p><i>“she's [daughter] got a cerebral aneurysm.... And that's quite hard to live with, because it takes precedence over anything else, even the kidneys... there's really not much that anyone can do.”</i> (FG5, patient)</p> <p><i>“I just think having children, my own sons, obviously that's the first thing that comes to my mind, you know. Are they, how, are they going to have a normal life and live to become grandparents themselves, that's my worry. The first thing that comes to mind is, you know, how long will they survive for”</i> (FG10, caregiver)</p>
<p><b>Visible suffering in affected family members</b></p>	<p><i>“I've got many members of the family with PKD and only one person in the family hasn't got it. But we haven't had any positive outcomes. All my family have died of cardiovascular disease.”</i> (FG5, patient)</p> <p><i>“My grandfather and my father both died young. So, I pretty much assumed I wasn't going to live too long either.”</i> (FG1, patient)</p> <p><i>“It's been fear for me, seeing what my mother went through and the age that her</i></p>

	<p><i>kidneys failed, and reaching, or just before reaching that same age, yeah, just the fear factor of, yeah, everything she went through.” (FG3, patient)</i></p>
	<p><b><u>Making sense of diverse risks</u></b></p>
<p><b>Unpredictable and severe consequences</b></p>	<p><i>“I guess, from diagnosis it’s a waiting game. Now knowing when, how fast or when your kidneys are going to deteriorate.” (FG5, patient)</i></p> <p><i>“It’s also very difficult living your life from blood test to blood test. The closer you get to needing some sort of kidney replacement therapy, you know, is it going to be this time, you know, every time you have the test. And that’s quite stressful just wondering is it going to be this time.” (FG5, patient)</i></p> <p><i>“A sword of Damocles all the time. I’m scared all the time of what’s going to happen... and for me, it’s really a sword that will hit, we do not know when, we do not know where, but we know it will hit. It will hit us, it will hit for others.” (FG14, patient)</i></p>
<p><b>False sense of security in imperceptible sickness</b></p>	<p><i>“I’ve never been sick from it all. So, I’ve never felt unwell.” (FG1, patient)</i></p> <p><i>“I’d never felt ill or anything, and so everything came back pretty normal except my kidney functions.” (FG4, patient)</i></p> <p><i>“I never felt sick. Yes I’d be going to hospital when I had a cyst burst or I’d bleed and got pain, but the rest of the time I was working full time and commuting to and from work, going to the gym, exercising and everything, I mean, it wasn’t making me sick.” (FG7, patient)</i></p>
<p><b>Living with perpetual guilt</b></p>	<p><i>“The first thing that comes to me is guilt. When I look at my three children and then look at my grandchildren and think which one of you. And, yeah, that’s pretty rotten to know that you’re responsible for... not that it’s any fault of yours, but handing it down the line.” (FG5, patient)</i></p> <p><i>“I was thinking of point of view of knowing two of my children have got it so younger generation I would like anything like this to happen that would minimize the develop of end stage kidney failure...” (FG6, patient)</i></p> <p><i>“It threatens our children. And that’s the hardest thing. To be sick, I am used to. But to know that.. it’s going to happen to my son... that’s unbearable. Because we are responsible.” (FG14, patient)</i></p>
<p><b>Fear of discrimination</b></p>	<p><i>“I was diagnosed with it at 25 and I kept it very quiet for the longest that I possibly could and not just for employment purposes but also insurances, things like that, life insurance they won’t touch you.” (FG2, patient)</i></p> <p><i>“For men, when you work, you become fearful of attending company workshops or dinners. Because when you go, you are expected to drink alcohol, smoke cigarette, eat meat.... And these fears [of adverse health impact] negatively affect your ability to work freely.” (FG15, patient)</i></p>

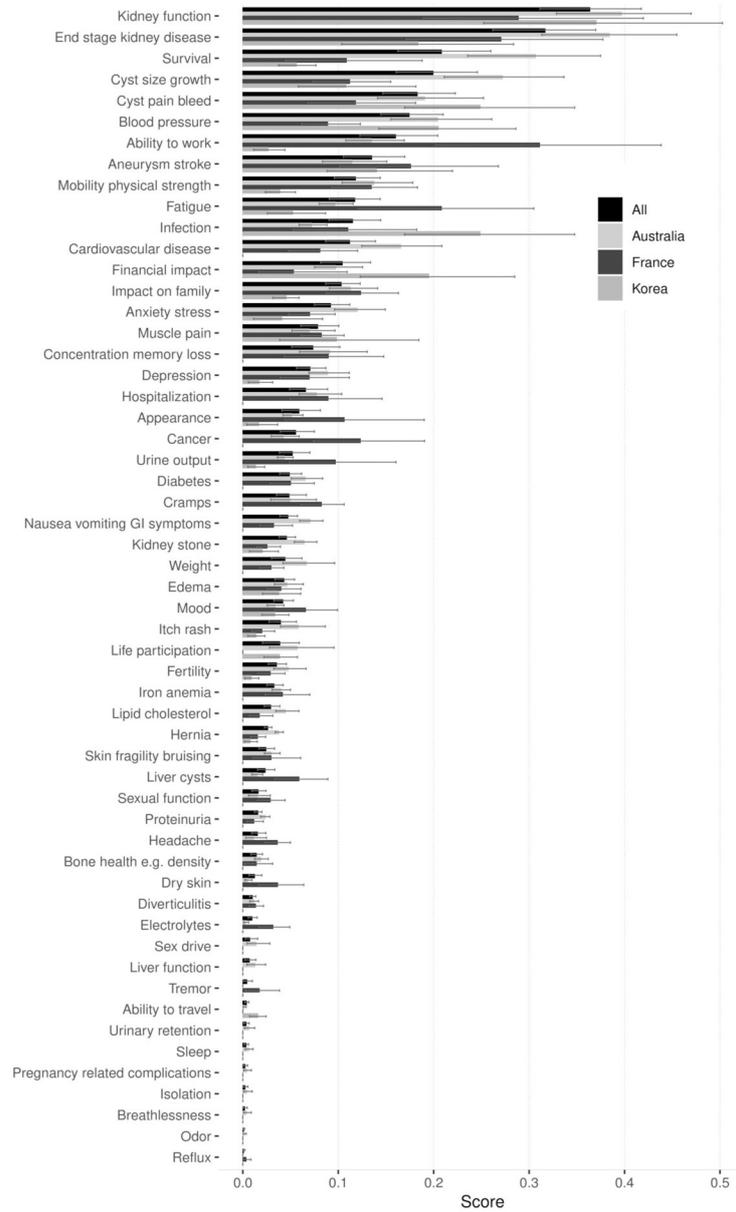
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**Figure Legends**

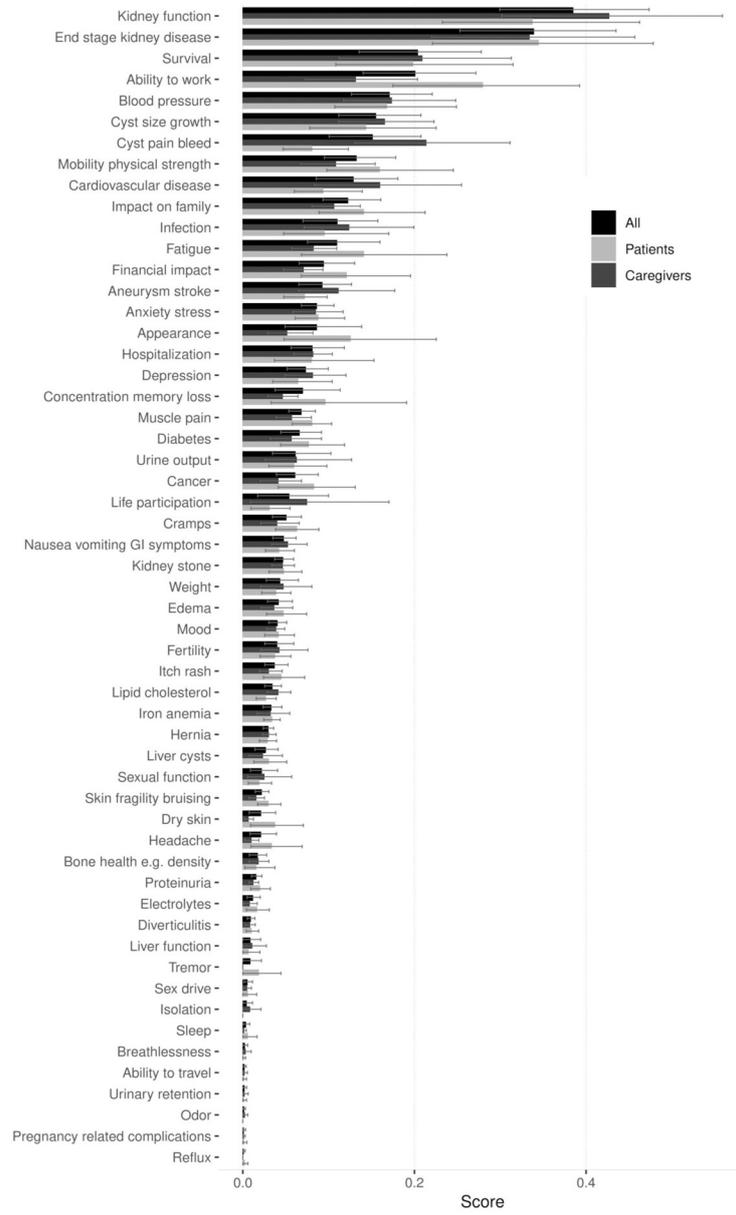
**Figure 1.** Importance score for outcomes identified according to country status

**Figure 2.** Importance score for outcomes identified according to patient status.

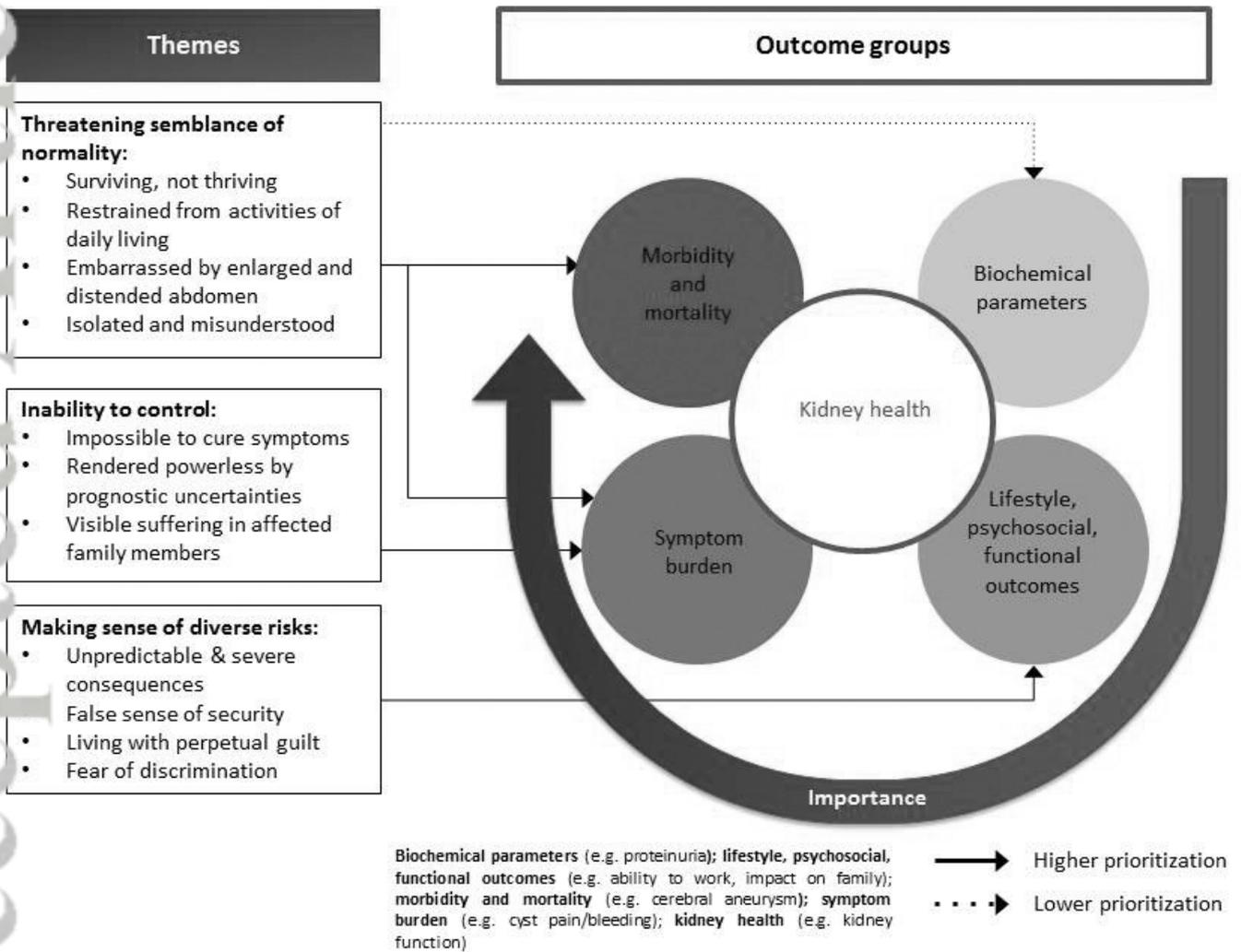
**Figure 3.** Thematic Schema.



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NEP\_13566\_Figure 2\_Role\_se\_rev\_001.jpg



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