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Core outcome domains for trials in autosomal dominant polycystic kidney disease: an international Delphi survey

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ABSTRACT

Rationale & Objective: Outcomes reported in trials involving patients with autosomal dominant polycystic kidney disease (ADPKD) are heterogeneous and rarely include patient-reported outcomes. We aimed to identify critically important consensus-based core outcome domains to be reported in trials in ADPKD.

Study Design: An international two-round online Delphi survey was conducted in English, French, Korean languages.

Setting & Participants: Patients/caregivers and health professionals completed a 9-point Likert scale (7-9 indicating critical importance) and a Best-Worst Scale.

Analytical Approach: The absolute and relative importance of outcomes were assessed. Comments were analyzed thematically.

Results: 1014 participants (603 [60%] patients/caregivers, 411 [40%] health professionals) from 56 countries completed Round 1, and 713 (70%) completed Round 2. The prioritized outcomes were kidney function (importance score 8.6), end-stage kidney disease (ESKD, 8.6), death (7.9), blood pressure (7.9), kidney cyst size/growth (7.8) and cerebral aneurysm (7.7). Kidney cyst-related pain was the highest rated patient-reported outcome by both stakeholder groups. Seven themes explained the prioritization of outcomes: protecting life and health, directly encountering life-threatening and debilitating consequences, specificity to ADPKD, optimizing and extending quality of life, hidden suffering, destroying self-confidence, and lost opportunities.

Limitations: Study design precluded involvement from those without access to internet or limited computer literacy.

Conclusions: Kidney function, ESKD, and death were the most important outcomes to patients, caregivers and health professionals. Kidney cyst-related pain was the

highest rated patient-reported outcome. Consistent reporting of these top prioritized outcomes may strengthen the value of trials in ADPKD for decision-making.

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic cause of chronic kidney disease. Up to 70% of patients with ADPKD progress to end-stage kidney disease (ESKD) by the age of 65 years[1,2]. Whilst kidney function often remains stable for many years after diagnosis, patients with ADPKD often suffer from debilitating symptoms, such as pain, which are related to kidney cyst growth and enlargement[3-6], and they are at risk of extra-renal complications, including stroke from ruptured intracranial aneurysm and severe polycystic liver disease[7].

Whilst there is some evidence to support lifestyle interventions (e.g. salt restriction[8]) and therapeutic agents (e.g. tolvaptan) in improving kidney function and total kidney volume (TKV)[9-13]; outcomes important to patients with ADPKD and their caregivers such as kidney pain and fatigue[14], anxiety/psychosocial distress[15], are infrequently reported in trials in ADPKD[7,16-18]. Trials in ADPKD most frequently report surrogate outcomes including kidney function, kidney/cyst volume, and blood pressure[19]. As part of the Standardized Outcomes in Nephrology – Polycystic Kidney Disease (SONG-PKD) initiative[20], the aim of this study was to generate consensus among patients, caregivers and health professionals on critically important outcomes to be reported in trials in ADPKD. This will inform the development of a core outcome set, defined as an "agreed minimum set of outcomes to be reported in all trials"[21,22], which can lead to improved consistency in reporting outcomes important to patients and clinicians across trials in ADPKD to better enable shared decision-making.

METHODS

Study design

The Delphi technique[23] is an internationally accepted approach used to establish consensus on core outcome sets for trials in nephrology and other disciplines[24-28]. The participants' anonymities are maintained, and they are able to complete the survey independently and allow for widespread international participation through online dissemination[29]. The survey was conducted online in three languages (English, French, Korean). The English survey was translated into French and Korean by a bilingual health professional and cross-checked by a second bilingual professional to ensure accuracy. The survey was pilot tested by members of the SONG-PKD Steering Group including three patients with ADPKD. There were two iterative rounds completed by a panel of participants with experience or expertise in ADPKD. Due to stability in results from Round 1 and 2, we did not proceed with an additional round. In the second round, participants could review their own score from Round 1, the distribution of scores (overall, patients/caregivers, health professionals) and comments provided by participants. The SONG-PKD Delphi process is shown in Figure S1.

Participant selection and recruitment

Patients, caregivers and health professionals with an experience in ADPKD were eligible to participate. Patients/caregivers (aged 18 years or older) included patients with ADPKD across all stages of chronic kidney disease (CKD stages 1-5; dialysis [hemodialysis, peritoneal dialysis], transplantation) and family members and friends. Health professionals included physicians (nephrologists, hepatologists, surgeons, geneticists), nurses, allied health professionals, researchers, policy makers, industry and regulators.

To include a diverse range of participants, we used multiple recruitment strategies. Patients were recruited from hospitals, patient/consumer organizations, the SONG database and social media. Health professionals were recruited through the SONG database, investigator networks and professional organizations (Table S1). Participants received an email invitation including a link to the survey after registering their email on the SONG website (www.songinitiative.org). Ethics approval was provided by the University of Sydney (2015-228) and participating institutions (Table S1).

Data collection

Selection of outcome domains: The 41 outcome domains included in the survey were identified from a systematic review of ADPKD trials and a study of patient/caregiver priorities for outcomes in ADPKD[14]. The order in which outcome domains appeared in the survey was random and each outcome was accompanied by a plain language definition (Table S2). The SONG-PKD Steering Group and investigators reviewed the list of outcomes. The survey was administered online using Qualtrics (*Qualtrics software, Provo, UT, United States*) from June 2018 to February 2019.

Round 1: Participants scored the importance of each of the 41 outcome domains using a 9-point Likert scale. Scores 1-3 indicated "limited importance", 4-6 indicated "important but not critical" and 7-9 indicated "critical importance" (Figure S1), based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process[30]. For each outcome, there was an option to enter comments in free-text boxes. Participants also had an "unsure" option and could suggest new outcomes. New outcomes suggested by more than 10% of participants were considered for inclusion in the second round. Outcomes with a mean score of less

than 6 or a median score of less than 7 in both groups (patients/caregivers and health professionals) were excluded in Round 2. The comments from each outcome in Round 1 were separately evaluated to determine any overlap between outcome domains and the need to revise the outcome domains for Round 2.

Round 2: 17 outcomes were included in Round 2. Participants could review their own scores from Round 1 as well as the distribution of scores (overall and divided according to status of patients/caregivers and health professionals) displayed as percentage of participants in a column graph. De-identified comments from Round 1 were provided. After reviewing these results, participants were asked to re-rate the outcomes using the 9-point Likert scale following the same methods used for Round 1. On completion of rating all outcomes, participants were asked to complete a Best-Worst Scale (BWS) survey, to examine the relative importance of each outcome[24]. The BWS consists of choice tasks in which a participant is asked to indicate the best and the worst items/options, with the overall aim to obtain a ranking of items in the order of preference[31,32]. Five Best-Worst choice sets, each containing six of 17 outcomes selected using a balanced, incomplete block design were presented to each participant. For each Best-Worst choice set, participants had to select the most important and the least important outcome.

Data analysis

Quantitative analysis: For every outcome in each round, the mean score, median score and proportion of participants who rated the outcomes as critically important (from 7 to 9) were calculated. The scores were separately calculated for patients/caregivers and health professionals, and their mean differences in scores as well as changes between two survey rounds were analyzed using a t-test. Results from

the BWS survey were incorporated in a multinomial logistic regression model to determine the relative importance. Utility functions containing all outcomes and interaction terms for participant characteristics were constructed. Subsequently, the mean regression coefficients of these functions provided the relative importance scores for each outcome[32], where a scale of 1 represented the "least important" and 9 the "most important". Statistical analyses were performed using Stata (*version 14.0, StataCorp LP, College Station, TX, United States*), SPSS (*IBM SPS Statistics for Windows, Version 25.0. Armonk, NY*), Excel (*Microsoft Corporation, Product version 16.0*), and NLOGIT V6 (*Econometric Software Inc.*) for the BWS.

Definition of consensus for core outcomes: Due to unknown distribution of scores, the threshold for consensus for the core outcomes domains could not be pre-specified. The Delphi survey aimed to identify 3-5 outcome domains that were critically important to both stakeholder groups. "Consensus" for the critical outcome domains was defined based on both patient/caregiver and health professional groups yielding median scores of ≥7 and mean scores ≥7, as well as the proportions of both stakeholder groups rating the outcome as "critically important (defined as scores 7-9)" being greater than 75% in Round 2. These thresholds were discussed and approved by the SONG-PKD Steering Group. The scores obtained from the BWS were used to examine the relative differences in preference scores between patients/caregivers and health professionals.

Qualitative analysis: The comments from the survey were imported into HyperRESEARCH (Version 3.7, Randolph, MA, United States) software for data analysis. Using thematic analysis, investigators coded the text (in English, Korean [YC], French [BS]) and inductively identified themes focusing on reasons for ratings,

differences between stakeholder groups and changes in scores across rounds. A third investigator (AT) read the qualitative data and reviewed the preliminary analysis to ensure that the themes captured all the data.

RESULTS

Participant characteristics

In Round 1, 1014 participants from 56 countries completed the survey, of whom 603 (60%) were patients/caregivers and 411 (40%) were health professionals. In Round 2, 713 participants (70% overall retention rate) from 47 countries completed the survey, which included 406 (57%) patients/caregivers and 307 (63%) health professionals (Tables 1, 2).

Of the 406 patients/caregivers who completed both rounds, 275 (74%) were patients not receiving kidney replacement therapy, 7 (2%) were on peritoneal dialysis, 22 (6%) were on hemodialysis, and 68 (18%) were kidney transplant recipients. Overall 65 caregivers/family members (total N>406 due to multiple roles, e.g. patients who were also caregivers to other family members affected by ADPKD) from 23 countries participated, including from the Republic of Korea (23%), United Kingdom (22%), United States (21%), Australia (14%) and Canada (7%). Of the 307 health professionals who also completed both rounds, 214 (70%) were nephrologists, 36 (12%) were researchers and 32 were nurses (10%). Dietitians, policy makers, surgeons, a geneticist, a hepatologist, industry representatives, and a psychologist also participated. Health professionals were from 41 countries, including Australia (18%), France (13%), United States (12%), United Kingdom (8%), Republic of Korea (8%) and Canada (8%).

Rating scores

Round 1: The mean and median scores and the proportions of participants scoring the outcomes from 7-9 separated by patients/caregivers and health professionals for each of the 41 outcome domains in Round 1 are provided in Table S3. The top five outcomes with the highest mean scores for patients/caregivers were kidney function (8.5), ESKD (8.4), cerebral aneurysm (8.0), kidney cyst size/growth (8.0) and blood pressure (7.9). For health professionals, the top five outcomes were kidney function (8.4), ESKD (8.4), death (7.8), cerebral aneurysm (7.5) and blood pressure (7.5). Twenty-four outcomes had mean scores less than 6.0 or median scores less than 7.0 across both groups and were excluded from Round 2. Although fatigue did not meet the criteria based on mean and median scores, it was included in Round 2 to ensure the inclusion of at least five patient-reported outcomes in Round 2. Kidney cyst infection and cyst related pain/bleeding were combined as kidney cyst pain/bleeding/infection due to overlap based on comments (i.e. prioritized due to pain caused by bleeding or infection) and similarity in scores. None of the new outcomes were suggested by more than 10% of the participants (Table S4) and were therefore not included in the next round.

Round 2: For each of the 17 outcome domains in Round 2, the mean and median scores and proportion of participants scoring the outcome as “critically important” are shown in Table S5. The top five prioritized outcomes from all participants were kidney function (8.6), ESKD (8.6), death (7.9), blood pressure (7.9) and kidney cyst size/growth (7.8). However, the top five outcomes list for patients/caregivers included cerebral aneurysm (7.8) instead of death. In general, top five outcomes according to language subtypes were comparable, except inclusion of cerebral aneurysm instead of kidney cyst size/growth and death in French and Korean, respectively (Table S6). The

mean scores of outcomes were generally higher for female patients/caregivers compared to male participants for all outcomes (Table S7).

Changes in scores from Round 1 to 2

The changes in mean scores from Rounds 1 to 2 are presented in Figures 1 (patients/caregivers) and 2 (health professionals). Between the two rounds, the mean scores for each outcome were generally stable with the top 10 outcomes consistent across both rounds (Tables S3, S5). Patient/caregiver mean scores increased between rounds for the following four outcomes: life participation (mean score difference, 0.27, p=0.006), ESKD (0.19, p=0.005), kidney function (0.14, p=0.02) and kidney cyst size/growth (0.15, p=0.049). For health professionals, mean scores increased for five outcomes from Round 1 to 2: death (0.33, p=0.002), cardiovascular disease (0.30, p=0.003), chronic pain (0.21, p=0.049), ESKD (0.20, p=0.002), and blood pressure (0.19, p=0.04). In Round 2, more health professionals rated blood pressure (Round 1 vs. 2: 82% vs. 89%, p=0.02), cardiovascular disease (81 vs. 88%, p=0.007), and fatigue (50% vs. 55%, p=0.04) as critically important compared to Round 1. Kidney function (95% vs. 98%, p=0.007) and life participation (73% vs. 79%, p=0.002) were the only outcomes with higher proportion of patients/caregivers who rated it to be critically important compared to Round 1 (Figure 4).

Differences between stakeholder groups

Differences in mean scores between patients/caregivers and health professionals for Rounds 1 and 2 are shown in Figure 3. Of the 17 outcomes in Round 2, patients/caregivers rated 14 outcomes higher than health professionals on the Likert scale, with the greatest difference in scores for liver cyst (absolute mean difference, 0.81, p<0.001), fatigue (0.74, p<0.001) and kidney cyst size/growth (0.68, p<0.001).

Death was the only outcome which was rated higher on the Likert scale by the health professionals (0.37, p=0.001). The differences in mean scores were comparable between the two participant groups for hospitalization (0.05, p=0.65) and ESKD (0.07, p=0.26). Similar differences were observed when results were analyzed by comparing proportions of "critically important" outcomes between patients/caregivers and health professionals (Figure 4).

Best-Worst Scale

In the BWS survey, both stakeholder groups identified ESKD as the most important outcome, but there were notable differences in the subsequent order of outcomes (Figure 5, Figures S2-4). Patients and caregivers prioritized ESKD, kidney function, cerebral aneurysm, cardiovascular disease and blood pressure in descending order, whereas health professionals considered death to be the second most important outcome, followed by kidney function and cardiovascular disease. Patients and caregivers identified chronic pain, kidney cyst size/growth, and kidney cyst pain/bleeding/infection to be as important as death. Results from the BWS survey were comparable for all participants when outcomes were analyzed according to language, except that kidney cyst size/growth was given higher priority by participants who completed the survey in Korean language. Patients and caregivers also highly rated chronic pain, which was the most important outcome among participants who completed the survey in French language.

Thematic analysis

Seven themes reflecting the reasons, changes and differences in the rating of outcomes were identified: protecting life and health, directly encountering life-threatening and debilitating consequences, specificity to ADPKD, optimizing and

extending quality of life, hidden suffering, destroying self-confidence, and lost opportunities. The themes reflected the perspectives of all stakeholder groups unless otherwise specified. Illustrative quotations supporting each theme are provided in Table 3.

Protecting life and health: Outcomes, such as blood pressure, kidney function and kidney cyst size/growth, were rated highly as they were considered important "biomarkers" to "keep healthy" and "to prevent damage", to delay progression to ESKD or development of cardiovascular disease. Cerebral aneurysm was noted to be uncommon and not relevant to all patients with ADPKD but was rated highly due to its "life threatening" consequences.

Directly encountering life-threatening and debilitating consequences: Some patients witnessed life-threatening consequences, such as premature death or severe disability involving their family members caused by cardiovascular disease and aneurysm/stroke, and these were thus rated critically important – "heart problems is what killed my father, who had PKD. His transplanted kidney was still working but his heart failed". Other outcomes, such as ability to do usual activities (i.e. life participation), were prioritized based on having direct experience with outcomes that caused fear and frustration, "near end-stage, lots of activities are impossible. Very frustrating".

Specificity to ADPKD: Outcomes, such as cardiovascular disease, were considered, "important but not specific to ADPKD" and similar views were held for blood pressure which was, "not any more important in PKD than in any other kidney disease", by some health professionals.

Optimizing and extending quality of life: Living with ADPKD was "long lasting" and patients were "more concerned with quality of life than survival" with lower scores for death among patients/caregivers compared to results from health professionals. Outcomes directly related to day-to-day symptom burden, such as kidney cyst size/growth, kidney cyst-related pain/bleeding/infection and chronic pain, were rated highly because they caused a "huge amount of morbidity", which "has a big impact on day to day life".

Hidden suffering: Outcomes, including chronic pain, kidney cyst-related pain/bleeding/infection and mood, were rated highly by patients/caregivers because they were often "overlooked", "minimized" and "misunderstood" by others. Moreover, these outcomes often led to "debilitating" symptom burden, which could be present "despite not being on dialysis (or anywhere near it)."

Destroying self-confidence: For some patients, change in appearance or weight from ADPKD was critically important. It led to shattering "self-confidence - as the cysts/kidneys grew, it brought up issues other than just physical health. It's harder to find well-fitting clothes and …. Can contribute to an existing feeling of sadness, anger, and despair" as well as "embarrassment and fear of social stigma." Often patients felt they had "no control" over these outcomes.

Lost opportunities: Financial impact was rated highly by some participants, who lost employment opportunities due to illnesses caused by ADPKD. Even if it was not directly experienced, participants recognized this to be an important concern – "many

PKD patients lose their jobs or face employment disciplinary procedures because of illness and hospitalizations".

DISCUSSION

Kidney function, ESKD, death, blood pressure and kidney cyst size/growth were the highest prioritized outcomes in ADPKD among patients/caregivers and health professionals. Kidney cyst size/growth was in the top five outcomes for patients/caregivers only, whilst death was in the top five for health professionals only. Kidney cyst-related pain/bleeding/infection was the highest rated patient-reported outcome by both stakeholder groups, whereas other patient-reported outcomes, such as anxiety, muscle pain, itch/skin and sexual function, were deemed less important. Kidney pain due to cyst size/growth and infection/bleeding were highly prioritized due to their relentless symptom burden limiting life participation and as an indicator of disease progression towards ESKD. Similarly, other outcomes affecting quality of life, including liver cysts, financial impact and fatigue, were rated higher by patients/caregivers because these outcomes disrupted daily living and restricted their ability to fulfil their social roles and goals. In contrast, health professionals placed greater emphasis on death.

Both patients/caregivers and health professionals consistently prioritized kidney function and ESKD as the most important outcomes in ADPKD. ESKD requiring kidney replacement therapy was a feared consequence to be avoided as it threatened quality of life, and kidney function was used to monitor progression to ESKD via its trajectory. The paramount importance attributed to kidney function and ESKD is in line with prior work on identifying outcomes important to patients with ADPKD and their caregivers[14]. Other outcomes with life-threatening or life changing

consequences, such as cerebral aneurysm and cardiovascular disease, and those believed to promote their occurrence, such as blood pressure, were also highly prioritized by both groups. Blood pressure may also have been perceived as critically important by patients and clinicians because hypertension is reported to affect up to 70% of patients and often diagnosed around 30 years of age, usually prior to any apparent kidney dysfunction[33-35]. In contrast, surrogate outcomes perceived not to impose a similar risk of harm, such as anemia, proteinuria or lipids, were considered less important, even though these are frequently reported in ADPKD trials[19].

In general, health professionals gave lower priority to most outcomes compared to patients/caregivers except for three clinical outcomes, ESKD, death and hospitalization. Having direct experience of ADPKD, patients placed greater emphasis on life participation, indicating that they were limited by day-to-day symptom burden (e.g. cyst-related pain, fatigue) and its impact on practical aspects of life (e.g. financial impact). They rated these similarly to death in terms of relative importance. This finding also reinforces the profound impacts of ADPKD on lifestyle and wellbeing, which have been identified in previous studies[14,15,36]. Often these impacts have been perceived by patients to be underestimated by their physicians, and their symptom burden can result in dissatisfaction with care and treatment[36]. The high priority given to lifestyle-related outcomes has also been repeatedly shown in studies conducted in hemodialysis, peritoneal dialysis and kidney transplant populations[27,28,37,38].

Outcome domains related to cysts were prioritized highly by both stakeholder groups for different reasons. Health professionals, particularly from the Republic of Korea, rated kidney cyst size/growth highly due to its importance as a biomarker of disease

progression[39]. In contrast, patients/caregivers who completed the survey in French placed highest importance on chronic pain, due to its detrimental impact on quality of life. Patients from the Republic of Korea were also concerned about changes in physical appearance from enlarged cysts, which led to embarrassment and social stigma limiting their employment opportunities. Cyst-related outcomes were perceived to be underrecognized and inadequately managed, which in part explained the higher prioritization of these outcomes. Other studies have also shown that cyst-related symptom burden is associated with worse quality of life and is a barrier to achieving long-term life goals[17,18]. An increase in economic burden from healthcare utilization due to cyst complications in ADPKD prior to clinically evident kidney dysfunction is now widely acknowledged[15,40,41], and tools are being developed to better capture the cyst-related symptom burden of ADPKD (e.g. ADPKD-Impact Scale, GPRI-PKD)[15,42].

We have shown that kidney cyst-related pain/bleeding/infection was the most important patient-reported outcome. This is in contrast to other patient CKD populations (those receiving hemodialysis[43] and transplant[44]) where fatigue and life participation were identified as core patient-reported outcomes, respectively. This highlights the need for a core outcome set that is specific to ADPKD.

This Delphi survey involved a large and diverse range of participants from 56 countries with a high retention rate of 70% from Round 1 to 2. The survey was available in multiple languages to enable wider engagement. The qualitative data elucidated reasons that explain the prioritization of outcomes. However, there are some potential limitations. The survey did not measure details including ethnicity or stage of CKD to allow subgroup analysis. The number of surveys completed in

French (n=47) was relatively low compared to Korean (n=96) and English (n=461). Furthermore, the online mode of administration used to ensure wider participation precluded involvement from those without access to internet or limited computer literacy. However, the top prioritized outcomes in this study were similar to those identified in prior studies of patients with ADPKD elicited through other methods, such as focus groups and workshops[14,17,18].

In conclusion, the most important outcomes to patients/caregivers and health professionals were ESKD, kidney function, cerebral aneurysm and blood pressure. Kidney cyst pain and life participation were the most highly prioritized patient-reported outcomes by patients/caregivers. Prior to finalizing the core set of outcome domains, public consultation will be sought through a Consensus Workshop involving patients, caregivers and health professionals, and any members of the public will be able to access the proposed core outcomes over a two-week time-frame and provide feedback through the SONG website. All input will be reviewed and considered by the SONG-PKD Steering Group to establish a core outcome set. Once a core outcome set has been identified, outcomes measures will be developed through a systematic process (systematic review and workshop) prior to its implementation in trials. Establishing and implementing a core outcome set will help to improve the relevance and consistency of evidence to better inform shared decision-making for patients with ADPKD.

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Authors' Contributions

Research idea and study design: YC, GR, TG, CL, BS, JC, JC; data acquisition: YC, BS, CL, HR, TG, AT, ACNF, RAM, HH, MC, AKV; data analysis/interpretation: CL, YC, BS, HR, TG, AT, KM, AJ; statistical analysis: YC, ATP, BS, MH, KM, AT; supervision or mentorship: GR, RP, TH, JC, AO, AC, CA, HC, JK, RG, VT, YP, DJ, AT. Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for the author's own contributions, and agrees to ensure 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. Characteristics of patients/caregivers.

Characteristic	Round 1, n (%) 603 participants	Round 2, n (%) 406 participants
Participant type[a]		
Patient	536 (89)	372 (92)
Caregiver/family members	107 (18)	65 (16)
Sex[b]		
Female	388 (65)	252 (62)
Male	212 (35)	154 (38)
Age group (years)		
18-30	49 (8)	27 (7)
31-40	117 (19)	72 (18)
41-50	139 (23)	84 (21)
51-60	175 (29)	125 (31)
61-70	102 (17)	82 (20)
71-80	21 (3)	16 (4)
Marital status		
Married/de facto	476 (79)	336 (83)
Partner	18 (3)	14 (3)
Single	71 (12)	34 (8)
Divorced/separated/widowed	38 (6)	22 (5)
Employment status		
Employed full-time	299 (50)	200 (49)
Employed part-time/casual	86 (14)	62 (15)
Unemployed	39 (6)	21 (5)
Retired	97 (16)	81 (20)
Student or other	82 (14)	42 (10)
Education		
Did not complete high school	39 (6)	27 (7)
High school graduate	83 (14)	45 (11)
Professional certificate	97 (16)	65 (16)
Undergraduate degree	242 (40)	159 (39)
Postgraduate degree	142 (24)	110 (27)
Current type of treatment (patients only)		
No kidney replacement therapy	401 (67)	275 (74)
Peritoneal dialysis	9 (1)	7 (2)
Hemodialysis	37 (6)	22 (6)
Kidney transplant	89 (15)	68 (18)
Age group at diagnosis of ADPKD (patients only)[c]		
<10	11 (3)	8 (3)
11-20	51 (14)	32 (13)
21-30	101 (28)	75 (30)
31-40	117 (32)	70 (28)
41-50	51 (14)	38 (15)
51-60	24 (7)	19 (8)
>60	6 (2)	6 (2)
Family history of ADPKD (patients only)		
Yes	393 (73)	276 (74)
No	96 (18)	68 (18)
Unsure	47 (9)	28 (8)
Country		
Republic of Korea	182 (30)	94 (23)
United States	134 (22)	86 (21)
United Kingdom	104 (17)	90 (22)
Australia	75 (12)	58 (14)
Canada	30 (5)	28 (7)
Italy	20 (3)	9 (2)
Other*	58 (10)	41 (10)

[a]Some have multiple roles; [b]N ≠ 603 for rounds 1 due to missing data; *Other includes 22 countries (in descending order of number of participants): Norway, France, Singapore, Span, Netherlands, New Zealand, South Africa, China, Germany, Pakistan, Poland, Switzerland, Belarus, Denmark, Hong Kong, India, Ireland, Japan, Malaysia, Nepal, Nigeria, Turkey; [c]N = 361, 248 for round 1 and 2, respectively, due to missing data.

Table 2. Characteristics of health professionals.

Characteristic	Round 1, n (%) 411 participants	Round 2, n (%) 307 participants
Participant role[a]		
Nephrologist	272 (66)	214 (70)
Researcher	72 (18)	36 (12)
Nurse	62 (15)	32 (10)
Industry	11 (3)	6 (2)
Dietician	6 (1)	5 (2)
Policy maker	6 (1)	5 (2)
Surgeon	5 (1)	4 (1)
Social worker	3 (1)	2 (<1)
Other	28 (7)	26 (8)
Sex[b]		
Female	217 (53)	166 (54)
Male	185 (46)	140 (46)
Age group (years)		
18-30	22 (5)	15 (5)
31-40	121 (29)	84 (27)
41-50	106 (26)	76 (25)
51-60	108 (26)	85 (28)
61-70	49 (12)	42 (14)
71-80	5 (1)	5 (2)
Experience in PKD (years)		
≤10	141 (34)	100 (33)
11-20	110 (27)	82 (27)
21-30	82 (20)	68 (22)
>30	56 (14)	47 (15)
not applicable	22 (5)	10 (3)
No. of PKD trials as investigators		
0	229 (56)	163 (53)
1-5	111 (27)	97 (32)
6-10	16 (4)	10 (3)
11-15	2 (<1)	2 (<1)
>15	4 (1)	4 (1)
not applicable	49 (12)	31 (10)
Country		
Australia	64 (16)	55 (18)
France	49 (12)	39 (13)
Republic of Korea	49 (12)	25 (8)
United States	45 (11)	36 (12)
Canada	31 (8)	24 (8)
United Kingdom	28 (7)	26 (8)
Singapore	17 (4)	1 (<1)
Hong Kong	14 (3)	9 (3)
Other*	114 (27)	92 (30)

[a]Some have multiple roles; [b]N ≠ 411 for round 1, due to missing data *Other includes 42 countries (in descending order): Italy, New Zealand, Japan, Spain, China, India, Portugal, Belgium, Argentina, Netherlands, Egypt, Germany, Greece, Lithuania, Malaysia, Pakistan, Poland, Thailand, Brazil, Finland, Nigeria, Philippines, Vietnam, Albania, Algeria, Austria, Belarus, Bosnia and Herzegovina, Bulgaria, Croatia, Denmark, Ecuador, El Salvador, Libya, Montenegro, Romania, Russia Federation, Slovakia, Sweden, Syrian Arab Republic, Ukraine, United Arab Emirates

Table 3. Selected illustrative quotations

Theme	Illustrative Quotations
Protecting life and health	I like to know how my kidney is going so I am able to keep healthy (kidney function; Patient) Not common, but very life threatening (aneurysm/stroke; HP) BP to be controlled to prevent damage (BP; Patient) Cyst growth is associated with decline in kidney function and is an important surrogate outcome measure (cyst size/growth; HP) Reducing blood pressure can be beneficial for extending the loss of function of the kidney (BP; Patient) Kidney size is the most feared aspect of the disease for me. Very debilitating and absolutely ruins the way you look as well (cyst size/growth; Patient) This is very important to me when my kidneys will start to fail (ESKD; Patient)
Directly encountering life-threatening and debilitating consequences	Heart problems is actually what killed my father, who had PKD; his transplanted kidney was still working but his heart failed (CVD; PCG) My father died at 52 and had heart attack which caused transplant to fail and required bilateral amputee (CVD; PCG) My dad died of a heart attack, probably from uncontrolled BP (BP; PCG) When I was diagnosed (more than 40 years ago), I read in a medical dictionary that average age of death with PKD was 57. My dad died at 57. My sister died at 60. Death is critical outcome for me (death; PCG). I am in a wheelchair due to a brain bleed after going into cardiac arrest after having an aneurysm coiled (ability to do usual activities; Patient) Near end stage, lots of activities are impossible. Very frustrating (life participation; Patient) Father had aneurysm at age 46 and he lived but was disabled. This impacted our family of 8 tremendously (aneurysm/stroke; PCG)
Fundamental importance	CVD is important but not specific to ADPKD so although should be reported in all trials in CKD not a specific outcome for ADPKD (CVD; HP)
Optimising and extending quality of life	PKD is usually long lasting. More concerned with quality of life than survival (death; Patient) Increased size can lead to decreased function and pain (cyst size/growth; Patient) Ability to function with enlarged kidneys (cyst size/growth; Patient) I suffer from constant chronic pain and it impacts on my quality of life so much (chronic pain; Patient) It has a big impact on day to day life (chronic pain; Patient)
Hidden suffering	Hidden symptom, feeling of being heavily pregnant, even though I'm slim (chronic pain; Patient) Despite not being on dialysis (or anywhere near it just yet), I still get kidney pain which fluctuates (chronic pain; Patient) I have been disability status based on my pain (chronic pain; Patient) Full abdomen feeling makes me think I'm full all the time (weight change; Patient) Mental and emotional health are so very important in getting through life with PKD (depression; Patient) I've had a couple of very serious cyst infections which caused agonising pain (cyst related pain/bleeding; Patient) In my experience this complication was overlooked and became quite painful and made me very sick (cyst infection; Patient) These are debilitating, painful and sometimes make people (patients and carers) feel hopeless (cyst infection; Patient). I think pain in PKD patients is hugely misunderstood by doctors and often overlooked (chronic pain; Patient) When mentioning pain physician tends to minimize this complaint (chronic pain; Patient) A lot of people do not understand how PKD can affect someone long term (impact on family/friends; Patient) Dealing with a disease for which there is no cure can really get to a person especially if you're not getting support from family and friends. It's hard to explain how you feel to someone who doesn't have this disease and it gets frustrating (mood; Patient).
Destroying self-confidence	For a patient, the importance of appearance is much underestimated. It's all about self confidence, as the cysts/kidneys grow it brings up issues other than just physical health. It's harder to find well fitting clothes and lack of confidence can contribute to an existing feeling of sadness, anger, despair (weight change; Patient) Huge belly is incredibly depressing and debilitating (appearance; Patient) I feel like I have no control over how people see me (appearance; Patient)
Lost opportunities	Lost my job, was too unwell to return (financial impact; Patient) Many PKDers lose their jobs or face employment disciplinary procedures because of illness and hospitals. People don't get promoted I'm sure, or have to cut short their careers because of physical limitations (financial impact; Patient)

HP, Health professionals; PCG, Patient/Caregiver

Figure legends

Figure 1. Mean scores of patients/caregivers in rounds 1 and 2. ESKD, end stage kidney disease

Figure 2. Mean scores of health professionals in rounds 1 and 2. ESKD, end stage kidney disease

Figure 3. Difference in mean scores between patients/caregivers and health professionals for rounds 1 and 2. Error bars refer to 95% confidence interval.

Figure 4. Proportion of outcomes rated critically important (scores 7-9 using a 9-point Likert scale), important (scores 4-6) and limited importance (scores 1-3) for patients/caregivers and health professionals in rounds 1 and 2. ESKD, end stage kidney disease.

Figure 5. Mean relative importance scores of patients/caregivers and health professionals based on the Best-Worst Scale. Ordered by the mean importance scores of patients/caregivers (bars with 95% confidence interval).

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