
Dorothee Oberdhan, Jason C. Cole, Holly B. Krasa, Rebecca Cheng, Frank S. Czerwiec, Ron D. Hays, Arlene B. Chapman, and Ronald D. Perrone

Background: The impact of autosomal dominant polycystic kidney disease (ADPKD) on health-related quality of life (HRQoL) is not well understood due to a lack of instruments specific to the condition.

Study Design: Content for a new self-administered patient-reported outcome (PRO) questionnaire to assess ADPKD-related HRQoL was developed through clinical expert and patient focus group discussions. The new PRO instrument was administered to study patients with ADPKD to evaluate its reliability and validity.

Setting & Participants: 1,674 adult patients with ADPKD participated in this research: 285 patients in focus groups to generate questionnaire content, 15 patients in debriefing interviews to refine the PRO questionnaire, and 1,374 patients to assess the performance and measurement properties of the PRO questionnaire.

Outcome: A new PRO questionnaire.

Results: The ADPKD Impact Scale (ADPKD-IS), consisting of 14 items representing 3 conceptual domains (physical, emotional, and fatigue) plus 4 additional questions, was developed. The instrument’s reliability (regarding internal consistency and test-retest consistency) and validity (content and construct) were supported.

Limitations: Need for more responsiveness testing when more data from clinical use become available over time. Complex concepts such as ADPKD-related pain and impact on a patient’s HRQoL need further evaluation.

Conclusions: The ADPKD-IS is a new patient-centric tool that reliably and validly provides a standardized method for assessing HRQoL and overall disease burden in patients with ADPKD.

Methods

Overview

In developing the ADPKD-IS instrument, we followed standard guidelines for development of a new patient-reported outcome (PRO) instrument. Figure 1 provides an overview of the development process, which consisted of a series of individual studies. The New England Institutional Review Board (Needham, MA) served as the central review body for all studies included in this research.

Recruitment

Men and women 18 years or older with ADPKD were recruited through physician and family referrals, advocacy...
groups, and print advertising. Participating patients provided informed consent before any study-related activities.

**Development of a Conceptual Framework and Questionnaire**

A literature review that focused on disease-related unmet need and burden, PRO instruments, and key outcome gaps related to ADPKD was conducted. A list of categories (concepts) to be measured was compiled for further evaluation. Additional detail on the literature review is available in Item S1.

Twenty-six ADPKD clinical experts from North America (n = 16), Europe (n = 8), and Japan (n = 2) were interviewed regarding: (1) the relevance of identified PRO instruments from the literature review, (2) issues likely considered burdensome to patients with ADPKD, (3) aspects of patients’ lives likely to improve following successful ADPKD treatment, and (4) potential concepts and questions (items) for an ADPKD-specific PRO instrument. The expert feedback was reviewed to identify issues that, from the perspective of the clinician, affected the HRQoL of patients with ADPKD.

The burden of ADPKD on patients’ daily lives was explored in focus groups with 117 adult patients with ADPKD in chronic kidney disease (CKD) stages 1 to 5 from the United States, Turkey, Germany, United Kingdom, and Japan. Groups of up to 8 participants were single sex when possible due to urologic and body image topics. Patients discussed how ADPKD affected their general health, daily activities, physical or social activities, pain experience, urinary issues (urgency, frequency, and nocturia), and emotional well-being. Transcripts were coded, and concepts or themes mentioned by at least 2 participants in a group were considered relevant. Data saturation (the point at which additional sampling provides no new information) was achieved when no new concepts or themes were identified in subsequent groups.

Based on information from patients and clinical experts, an ADPKD-specific conceptual framework (a model representing concepts/themes to be measured and their relationships) and an initial questionnaire were created. Fifteen cognitive debriefing interviews with US-based patients assessed the level of comprehension, understanding, and interpretation of all instructions and questioned wording and response options by the target audience (content validity), and the instrument was refined (question wording, format, and structure) via an iterative process. Additional content validation focus groups with 168 patients in Australia, Argentina, Brazil, Canada, China, Czech Republic, Hungary, Japan, Poland, Romania, South Korea, Spain, and the United States were conducted to further explore ADPKD-related pain and ensure global applicability of the measured concepts. Finally, the ADPKD-IS was reviewed by clinical experts, including physicians and nurses, to ensure that the instrument was a good reflection of the concepts to be measured (face validity).

**Quantitative Evaluation**

The ADPKD-IS was administered in an observational study (ClinicalTrial.gov study number NCT01430494) to obtain

---

**Figure 1.** Development of the Autosomal Dominant Polycystic Kidney Disease Impact Scale (ADPKD-IS). Abbreviations: CKD, chronic kidney disease; PRO, patient-reported outcome.
data for cross-sectional evaluation of its measurement properties (psychometrics) in 665 US-based patients with ADPKD and to evaluate clinical performance in 1,076 patients with ADPKD globally. The instrument’s stability at baseline and at 1 month was evaluated in a separate study with 298 US participants.

**Confirmatory Factor Analysis**
To evaluate construct validity (ie, how well a test measures what it claims to measure\(^{23}\)), data were subjected to confirmatory factor analysis to evaluate whether the hypothesized organization of questions in domains on the ADPKD-IS was empirically supported. Nonparametric and parametric tests were conducted to evaluate model fit (additional information on the specific tests can be found in Item S2). Iterative model refinements were performed using a randomly split data set (half used as a development sample and the other half used as a cross-validation sample).

**Item Response Theory**
After evaluating the assumption of local independence among items in each unidimensional APKD-IS construct, we estimated item response theory models to obtain item parameter estimates. Several 1- and 2-parameter models were compared to evaluate whether it was important to allow slopes to vary across items. Item category response curves and item/scale information functions were examined to evaluate the response categories for each item and detail the item and scale breadth of coverage for the latent state of ADPKD impact. Each domain was scored both as a simple sum-score and using item response theory parameters to apply differential weighting per item.

**Item-Level Psychometric Statistics**
Each item was examined to see whether it should be kept as part of its assigned domain in the conceptual framework. Within each domain, equality of item-total correlations was examined by testing the correlation difference between the mean of corrected item-total correlations (ie, correlation when the item is removed from the total score) and the most deviant corrected item correlation. Mean correlations for the scales were calculated using Fisher r transformation. Item-total correlations by item were calculated per domain, for the scales were calculated using Fisher z transformation. Mean correlations (both sum-score and item response theory–based score) and the BPI-SF\(^{16}\) Pain Interference Score. The BPI-SF Pain Interference Score, a measure of how much that pain interferes with 7 daily activities, was chosen for evaluation because the ADPKD-IS assesses disease impact. Correlations > 0.40 were considered to be strong and indicative of the domains and questions measuring the same construct.\(^ {51}\)

**Convergent Correlations Between ADPKD-IS and Other Instruments**
Convergent validity (how the instrument relates to other instruments that are supposed to measure the same or similar concept) was assessed by correlating domain scores (both sum-score and item response theory–based score) with the SF-12v2 Physical Component Summary (PCS) and Mental Component Summary (MCS) scale scores and the BPI-SF\(^ {16}\) Pain Interference Score. The BPI-SF Pain Interference Score, a measure of how much that pain interferes with 7 daily activities, was chosen for evaluation because the ADPKD-IS assesses disease impact. Correlations > 0.40 were considered to be strong and indicative of the domains and questions measuring the same construct.\(^ {31}\)

**Test-Retest Reliability, Responsiveness, and Meaningful Difference**
The stability of domain scores was assessed using intraclass correlation coefficients over a 1-month test-retest interval in which correlations should exceed a threshold of 0.70.\(^ {32}\) Correlations were examined between domain change scores and changes in SF-12v2 and BPI-SF scores.

In the study sample, meaningful change was estimated using anchor-based methods by evaluating associations between ADPKD-IS domains and the concept measured by anchors, including a pain-based global change scale,\(^ {33}\) SF-12v2 PCS and MCS, and BPI-SF Pain Severity domain (a measure of worst, least, average, and current pain severity).

**Clinical Evaluation**
The clinical performance of the ADPKD-IS in patients with ADPKD with CKD stages 1 to 5 was assessed in 1,076 participants by evaluating sensitivity in the overall population and by CKD stage at baseline and in 6-month intervals up to 3 years.

Mean scores and change from baseline were compared for the ADPKD-IS, SF-12v2, and EQ-5D (3-level version; EuroQol). Cohen d effect size was evaluated relative to patients with CKD stage 1.\(^ {31}\)

**Results**

**Qualitative Development**
Literature review (4,801 articles, 27 relevant) identified several concepts relevant to HRQoL. The PRO instruments of potential interest due to ADPKD-relevant concepts (eg, kidney disease, pain, anxiety, depression, and urologic issues) or prior use in ADPKD studies were identified. However, there were no instruments specifically designed for or their validity evaluated in an ADPKD population. Identified concepts, including physical impact, emotional
impact, and urinary concerns, and PRO instruments were discussed with 26 clinical experts from North America, Japan, and Europe. Clinical experts noted that patients with ADPKD typically are not affected in early disease stages, but with disease progression, concerns increase (eg, shortness of breath from pressure of the kidneys, difficulty eating, depression, and physical and emotional burden). Pain and discomfort were reported as a potential issue and recommended for probing with patients.

Focus groups with 117 patients (United States = 42, Turkey = 15, Germany = 29, United Kingdom = 20, and Japan = 11) reflected the concepts generated from discussions with clinical experts and literature review. More than half the concepts were observed in the first focus group, and saturation was achieved by the fifth of the initial 20 concept-generating focus groups. Overall, 20 concepts were identified related to physical impact, emotional impact, urinary concerns, and other issues (Table 1). Examples of patient quotations are provided in Box 1 and Item S3. Contrary to clinical expert feedback, participants in all disease stages reported disease burden.

**Table 1. ADPKD Focus Group Concepts**

<table>
<thead>
<tr>
<th>Concept</th>
<th>Focus Groups Region United States (n = 42)</th>
<th>Europe (n = 64)</th>
<th>Japan (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical impact</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impact on work/housework</td>
<td>10 (23.8%)</td>
<td>10 (15.6%)</td>
<td>11 (100%)</td>
</tr>
<tr>
<td>Limited functioning</td>
<td>22 (52.4%)</td>
<td>26 (40.6%)</td>
<td>9 (81.8%)</td>
</tr>
<tr>
<td>Self-care</td>
<td>6 (14.3%)</td>
<td>3 (4.7%)</td>
<td>4 (36.4%)</td>
</tr>
<tr>
<td>Effect on relationships (intimacy/sex)</td>
<td>4 (9.5%)</td>
<td>2 (3.1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pain/discomfort</td>
<td>34 (81.0%)</td>
<td>28 (43.8%)</td>
<td>11 (100%)</td>
</tr>
<tr>
<td>Pain affecting work/housework</td>
<td>5 (11.9%)</td>
<td>2 (3.1%)</td>
<td>4 (36.4%)</td>
</tr>
<tr>
<td>Pain with physical activity</td>
<td>3 (7.1%)</td>
<td>12 (18.8%)</td>
<td>5 (45.5%)</td>
</tr>
<tr>
<td>Lifestyle modification</td>
<td>15 (35.7%)</td>
<td>18 (28.1%)</td>
<td>3 (27.3%)</td>
</tr>
<tr>
<td>Emotional impact</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>36 (85.7%)</td>
<td>29 (45.3%)</td>
<td>3 (27.3%)</td>
</tr>
<tr>
<td>Depression</td>
<td>27 (64.3%)</td>
<td>15 (23.4%)</td>
<td>2 (18.2%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>31 (73.8%)</td>
<td>30 (46.9%)</td>
<td>2 (18.2%)</td>
</tr>
<tr>
<td>Guilt</td>
<td>15 (35.7%)</td>
<td>12 (18.8%)</td>
<td>6 (54.5%)</td>
</tr>
<tr>
<td>Acceptance</td>
<td>5 (11.9%)</td>
<td>32 (50.0%)</td>
<td>5 (45.5%)</td>
</tr>
<tr>
<td>Urinary concerns</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary urgency</td>
<td>17 (40.5%)</td>
<td>20 (31.3%)</td>
<td>4 (36.4%)</td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>17 (40.5%)</td>
<td>27 (42.2%)</td>
<td>3 (27.3%)</td>
</tr>
<tr>
<td>Nocturia</td>
<td>18 (42.9%)</td>
<td>24 (37.5%)</td>
<td>2 (18.2%)</td>
</tr>
<tr>
<td>Other impacts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect on diet</td>
<td>5 (11.9%)</td>
<td>32 (50.0%)</td>
<td>7 (63.6%)</td>
</tr>
<tr>
<td>Concern about body image</td>
<td>22 (52.4%)</td>
<td>25 (39.1%)</td>
<td>10 (90.9%)</td>
</tr>
<tr>
<td>Feeling thirsty</td>
<td>10 (23.8%)</td>
<td>19 (29.7%)</td>
<td>4 (36.4%)</td>
</tr>
<tr>
<td>Disruption of social/leisure activities</td>
<td>26 (61.9%)</td>
<td>24 (37.5%)</td>
<td>11 (100%)</td>
</tr>
</tbody>
</table>

*Note: Values are given as number (percentage). Abbreviation: ADPKD, autosomal dominant polycystic kidney disease.*

**Box 1. Patient Quotations**

**Impact on Daily Activities and Physical Limitations**
- “General housework, really, is quite difficult. I get tired and I have to keep sitting down. When my son was younger, I had trouble picking him up, because of the pain in the kidneys.”
- “I have difficulties breathing sometimes, because my abdominal region is located fairly high up in my body and pushes up. It makes me pant sometimes.”
- “I try to find shoes that don’t need to be tied up. I get ones where I can use a shoehorn only.”
- “I used to do Aqua Fitness, too, but they give you these swim rings and I couldn’t wear them anymore, because of the pressure on my midriff.”
- “It’s not an actual pain, but it’s a constant presence of something that’s not right. It’s led to my not doing things that I used to do every day, like cycling, which I loved doing.”

**Work and Financial Impact**
- “The pain only allows me to perform 50%. I always try to do my best, 100%. But when the pain comes, I can’t.”
- “If it is a really bad pain day, you don’t want to go to work. You don’t want to go out and do anything. You just want to take a bunch of Tylenol and stay in bed.”
- “Even at work, walking across the office and back, I would always have shortness of breath and I always attributed that to PKD.”

**Emotional Impact**
- “It’s not just the intensity of pain. It can be relatively low-level, but it’s dragged out over a long period of time it wears you down and psychologically somebody can develop like a feeling of doom.”
- “I think the psychological aspect is the most difficult one to bear and to come to terms with. The complications, the difficulties, the course and further course of the disease and all of that. The fear.”
- “I know that there’s something in my body that’s not functioning or that may not one day function 100%. You’d like to think that you are invincible, so yeah, it’s a little bit scary. I think, oh well, my mom had an aneurysm. What if I’m going to have one too. It’s just the unknown, I guess.”

*Abbreviation: PKD, polycystic kidney disease.*

but many accepted this as a normal state worsening with disease progression.

Cognitive debriefing interviews with 15 US-based patients resulted in an instrument with 18 items grouped into 2 general domains: physical impact and social/emotional impact of ADPKD. In additional focus groups with 168 patients (North America = 31, South Korea = 16, Australia = 8, South America = 18, China = 15, Taiwan = 16, Japan = 12, Romania = 7, Spain = 16, Czech Republic = 15, Hungary = 6, and Poland = 8), initial concepts were confirmed as globally consistent. Patient focus groups showed general agreement in concepts between sexes and regions. Pain was described as complex, with 3 distinct types of pain (sharp acute, dull chronic, and fullness/discomfort) being relevant to patients with ADPKD.
Nine model iterations were performed for confirmatory factor analysis. The hypothesized questionnaire organization was inconsistent with the empirically tested latent structure of the initial model. The best fit to the data was found using a bifactor model with 3 domains (Physical Debility, Fatigue, and Emotional Distress). The final model (Fig 2) showed no substantive differences between the parametric and nonparametric models, and fit statistics were similar between the developmental and cross-validation samples (Table 2). Analyses resulted in the removal of 4 items (coping, sleep, size/shape of abdomen, and frequent and/or urgent urination) from the domains. These domain-independent items were retained in the final questionnaire (Fig 2) due to strong endorsement by patients and relationship to some of the main disease features (eg, abdomen shape and urinary concerns).

We also compared concepts measured by the SF-12v2 and ADPKD-IS (Fig 3) demonstrating a low level of overlap between the general instrument and the patient-centered measures of the ADPKD-IS.

### Measurement Properties

Patients of all CKD stages were included in the cross-sectional study of 665 participants at baseline. Although earlier stages were more represented than later stages, a similar distribution of participants across disease stages was seen in the longitudinal study (Tables S1 and S2).

### Item Discrimination

Using a 2-parameter logistic graded-response model, item discriminations (an item’s ability to distinguish among persons who have different levels of the trait being measured; ≥0.80 is recommended) were found to range from 1.19 to 2.82 across scales (Table S3).

The physical domain provided the greatest range of measurement of the target concept, while the fatigue domain provided the most restricted range of measurement. Compared to the SF-12v2, low levels of physical impact were less common in the study population, whereas low levels of emotional impact were more common.

### Table 2. ADPKD-IS Model Fit Statistics

<table>
<thead>
<tr>
<th>Sample</th>
<th>$\chi^2$</th>
<th>df</th>
<th>CFI</th>
<th>NNFI</th>
<th>RMSEA</th>
<th>RMSEA 90% CI</th>
<th>SRMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parametric development split sample</td>
<td>104.51</td>
<td>59</td>
<td>0.968</td>
<td>0.950</td>
<td>0.048</td>
<td>0.033-0.063</td>
<td>0.032</td>
</tr>
<tr>
<td>Parametric validation split sample</td>
<td>109.67</td>
<td>59</td>
<td>0.970</td>
<td>0.954</td>
<td>0.051</td>
<td>0.036-0.066</td>
<td>0.028</td>
</tr>
</tbody>
</table>

Abbreviations: ADPKD-IS, Autosomal Dominant Polycystic Kidney Disease Impact Scale; CFI, comparative fit index; CI, confidence interval; NNFI, non-normed fit index; RMSEA, root mean square error of approximation; SRMR, standardized root mean square residual; $\chi^2$, Chi square.
Correlations between individual item scores and overall domain scores ranged from 0.75 to 0.85 for physical, 0.86 to 0.90 for fatigue, and 0.51 to 0.81 for emotional, which are considered substantial and satisfactory to the hypothesized scale (Table S4). The lowest correlation was 0.70 for Item 13 (“feeling full before appetite was satisfied”). Hartley Fmax test (equality of variances for each item per scale) was 2.62 for physical, 1.24 for fatigue, and 1.53 for emotional.

The percentage of patients reporting the lowest score (floor effects) on the 18 items ranged from 42% to 77%, whereas the percentage of patients reporting the highest score (ceiling effects) ranged from 1% to 6% per item (Table S5). Item-level skewness and kurtosis parameters likewise indicated a substantial departure from normality, with greater numbers of patients reporting lower scores on each item than higher scores.

**Domain-Level Psychometric Statistics**

Internal consistency of the domains was measured by coefficient alpha and average interitem correlation. Coefficient alphas exceeded the 0.70 reliability threshold for group comparisons for each domain: 0.94 for physical, 0.94 for fatigue, and 0.85 for emotional. The domains achieved appropriate average interitem correlations: 0.71 for physical, 0.84 for fatigue, and 0.58 for emotional. Minimal ceiling effects were observed per domain (0.5% physical, 2% fatigue, and 0.3% emotional). Observed floor effects were 44%, 41%, and 30% for physical, fatigue, and emotional, respectively (Table 3).

<table>
<thead>
<tr>
<th>Table 3. ADPKD-IS Reliability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean ± SD</strong></td>
</tr>
<tr>
<td>Overall score</td>
</tr>
<tr>
<td>Physical</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Emotional</td>
</tr>
</tbody>
</table>

Abbreviations: ADPKD-IS, Autosomal Dominant Polycystic Kidney Disease Impact Scale; SD, standard deviation.
Convergent Correlations With Other Instruments

Correlations of domains with the SF-12v2 summary scores were all large: −0.68 for physical with the PCS, −0.58 for fatigue with the PCS, and −0.54 for emotional with the MCS, indicating that the domains measured related concepts (Table 4).

Test-Retest Reliability, Responsiveness, and Meaningful Difference

Test-retest reliability coefficients (traditional correlations) for the 3 domains were high (0.89 for physical, 0.92 for fatigue, and 0.86 for emotional). Intraclass correlations between 3 and 4 weeks were consistent with this finding. Within-participant change scores observed for items and domain assessments indicated little change over the test-retest period, consistent with the slow gradual disease progression of ADPKD (Table 5).

Responder groups defined by pain showed significant differences on the ADPKD-IS physical domain (P = 0.003), with marginal differences on the Fatigue scale (P = 0.06). The impact of perceived change among 23% (n = 25) of the sample reporting any change was related to physical function, but not fatigue or emotional distress. Similarly, the BPI-SF Pain Severity scale demonstrated change related to physical function (P = 0.001), but not fatigue or emotional distress. More marked changes in pain severity on the BPI-SF appear to be associated with urinary symptoms on the ADPKD-IS. None of the domain assessments responded to change groups defined by criteria on the SF-12v2 PCS or SF-12v2 MCS (Table 5).

Scoring

For all items, each response option is assigned a value between 1 and 5. A score of 1 indicates “not difficult at all” or “not bothered at all.” A score of 5 indicates “extremely difficult” or “extremely bothered.” Each domain is scored by summing the 1 to 5 scores for the items in that domain (Fig 2) and dividing by the number of items completed.

Clinical Evaluation

Scores on the physical, emotional, and fatigue domains of the ADPKD-IS differed significantly between patients in CKD stage 3b versus CKD stage 1 at baseline. On the SF-12 PCS and EQ-5D index, differentiation from CKD stage 1 was observed as early as CKD stage 3a. The SF-12 MCS did not show differentiation. The SF-12 PCS and MCS scores were consistently above normal scores for a CKD population throughout all disease stages. SF-12 PCS score was above or at the level for the US general population through

### Table 4. ADPKD-IS Convergent Validity

<table>
<thead>
<tr>
<th></th>
<th>Physical</th>
<th>Fatigue</th>
<th>Emotional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
<td>—</td>
<td>0.8092</td>
<td>0.7166</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.8092</td>
<td>—</td>
<td>0.6776</td>
</tr>
<tr>
<td>Emotional</td>
<td>0.7166</td>
<td>0.6776</td>
<td>—</td>
</tr>
</tbody>
</table>

### Table 5. ADPKD-IS Responsiveness

<table>
<thead>
<tr>
<th>Global rating of change in pain</th>
<th>Physical</th>
<th>Fatigue</th>
<th>Emotional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved +1 (n = 15)</td>
<td>0.003</td>
<td>0.06</td>
<td>0.3</td>
</tr>
<tr>
<td>No change (n = 83)</td>
<td>−0.362 ± 0.81</td>
<td>−0.444 ± 0.79</td>
<td>−0.233 ± 0.50</td>
</tr>
<tr>
<td>Worsened −1 (n = 10)</td>
<td>0.443 ± 1.02</td>
<td>0.100 ± 0.74</td>
<td>0.125 ± 0.63</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BPI-SF Pain Severity</th>
<th>Physical</th>
<th>Fatigue</th>
<th>Emotional</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2.0 points improved (n = 10)</td>
<td>0.001</td>
<td>0.23</td>
<td>0.3</td>
</tr>
<tr>
<td>−2 to +2 points; no change (n = 89)</td>
<td>−0.082 ± 0.43</td>
<td>−0.172 ± 0.49</td>
<td>−0.124 ± 0.57</td>
</tr>
<tr>
<td>≤2 points worsened (n = 9)</td>
<td>0.651 ± 0.93</td>
<td>0.185 ± 0.62</td>
<td>0.139 ± 0.68</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SF-12v2 PCS</th>
<th>Physical</th>
<th>Fatigue</th>
<th>Emotional</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3.0 points improved (n = 36)</td>
<td>−0.036 ± 0.75</td>
<td>0.001 ± 0.68</td>
<td>0.021 ± 0.57</td>
</tr>
<tr>
<td>≤3 points worsened (n = 25)</td>
<td>−0.023 ± 0.48</td>
<td>−0.240 ± 0.56</td>
<td>−0.280 ± 0.80</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SF-12v2 MCS</th>
<th>Physical</th>
<th>Fatigue</th>
<th>Emotional</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2.0 points improved (n = 28)</td>
<td>0.066 ± 0.38</td>
<td>−0.036 ± 0.68</td>
<td>−0.045 ± 0.64</td>
</tr>
<tr>
<td>≤2 points worsened (n = 42)</td>
<td>−0.116 ± 0.81</td>
<td>−0.175 ± 0.65</td>
<td>−0.089 ± 0.60</td>
</tr>
</tbody>
</table>

*Note: Table shows product-moment correlations of ADPKD-IS domains with the SF-12v2 (convergent validity). Abbreviations: ADPKD-IS, Autosomal Dominant Polycystic Kidney Disease Impact Scale; MCS, Mental Component Summary; PCS, Physical Component Summary; SF-12v2, 12-Item Short Form Health Survey version 2.*
CKD stage 3a, whereas SF-12 MCS score was above or at the level for the US general population through CKD stage 4 (Fig 4). Percent change between CKD stages was more pronounced for the ADPKD-IS domains compared with other instruments (Fig 5). Using Cohen $d$ effect size relative to CKD stage 1, the burden of disease could be distinguished as early as CKD stage 3 across all 3 domains of the ADPKD-IS, the SF-12 vs PCS, and the EQ-5D, with the largest effect seen for CKD stage 5 across all scales (Fig 6).35

Discussion
At the outset of our research, we were faced with discrepant reports of disease burden in ADPKD and its onset based on literature and physician reports versus anecdotal reports through patient foundations and patients. This discrepancy was also observed in the feedback from clinical experts, who may not be aware of patients’ early concerns due to the very intermittent visit schedules in the earlier disease stages, and patients, who may not bring concerns to physicians because they have adjusted to the disease impact on their lives and experiences with trivialization of these concerns by physicians.9 Lack of patient-centric tools to assess ADPKD-related disease burden has led to a knowledge gap for disease stages, giving the impression that the burden of patients with ADPKD is no different from that of the general population (Fig 4).9,12,19 New initiatives for further understanding of priorities for different stakeholders, including patients, caregivers, physicians, and researchers (such as Standardized Outcomes in Nephrology [SONG]), have been initiated since we started our research, but to date, they focus on other areas in nephrology, and ADPKD-specific outcome measures have yet to emerge.

The ADPKD-IS is a new tool with support for its reliability (internal consistency and test-retest) and validity (content and construct). The ADPKD-IS is useful for assessing ADPKD-related disease burden across all CKD stages (Fig 6).35

Figure 4. Autosomal Dominant Polycystic Kidney Disease Impact Scale (ADPKD-IS), EQ-5D, and 12-Item Short Form Health Survey (SF-12) mean at baseline by chronic kidney disease (CKD) stage. Abbreviations: MCS, Mental Component Summary; PCS, Physical Component Summary.

Figure 5. Percent difference compared to patients with chronic kidney disease stage 1 (CKD 1) at baseline. Abbreviations: ADPKD-IS, Autosomal Dominant Polycystic Kidney Disease Impact Scale; MCS, Mental Component Summary; PCS, Physical Component Summary; SF-12, 12-Item Short Form Health Survey.
stages in a cross-sectional cohort, but also tracking disease burden long term.

The physical domain includes 5 items measuring impact on the ability to perform various activities and 2 items measuring impact of disease-associated pain on daily activities. Identification of 3 distinct types of pain led to retention of the existing pain questions as descriptive of the overall pain concept. However, we also proceeded to develop an additional questionnaire specific to ADPKD-related pain.36,37 The fatigue domain assesses 3 specific features of ADPKD-associated fatigue: general fatigue, tiredness while driving, and fatigue after a good night’s sleep. Items within this domain exhibited higher intra-domain correlations than interdomain correlations (Table S3). Therefore, fatigue among patients with ADPKD appears likely to encompass aspects of both emotional and physical burden. The emotional domain assesses the emotional impact of ADPKD via 3 concepts common to many instruments (acceptance, anxiety, and sadness) and a fourth disease-specific item (feeling full before appetite is satisfied).

The ADPKD-IS covers the entire range of health burdens associated with ADPKD across CKD stages in a single instrument, which is not the case for any other PRO instruments. All items were non-normally distributed, and most patients reported at the lower (less affected) end of the range, consistent with the natural history progression of the disease, for which hyperfiltration can compensate for the early loss of kidney tissue, leading to little change in kidney function until decades after birth.1,2 Individual items also showed limited ceiling effects, indicating the ability of the ADPKD-IS to differentiate between health burdens as patients progress to later stages of the disease, in which HRQoL is more dramatically affected. Consistent with its predicted ability to assess HRQoL across the entire disease spectrum, the ADPKD-IS can show differentiation between disease stages with more sensitivity than general instruments.

Use of properly developed PRO instruments is a key element of drug development programs using patient-focused end points and for characterization of disease-specific burden with increasing importance given the 21st Century Cures Act requirements. We also see the ADPKD-IS as a tool for researchers and health care providers to better understand ADPKD-specific patient burden with potential use as a patient management tool in clinical practice. Access to the full US-English ADPKD-IS questionnaire, its user manual, and other language versions are available via Mapi Research Trust at https://eprovide.mapi-trust.org/.

One consideration to note is that there are a variety of techniques to evaluate responsiveness. As the instrument gains use, additional responsiveness evaluations should be performed.

Supplementary Material

**Item S1:** Literature search.
**Item S2:** Confirmatory factor analysis.
**Item S3:** Additional patient quotations from focus groups.
**Table S1:** Initial quantitative sample demographics.
**Table S2:** Quantitative study demographics.

---

Figure 6. Autosomal Dominant Polycystic Kidney Disease Impact Scale (ADPKD-IS), EQ-5D, and 12-Item Short Form Health Survey (SF-12) Cohen $d$ effect size at baseline by chronic kidney disease (CKD) stage. Abbreviations: MCS, Mental Component Summary; PCS, Physical Component Summary.
Table S3: Results of a two-parameter logistic graded-response model by item.
Table S4: Item-level psychometrics.
Table S5: ADPKD-IS item-level descriptive statistics.

Article Information

Authors’ Full Names and Academic Degrees: Dorothee Oberdhan, MS, Jason C. Cole, PhD, Holly B. Krasa, MS, Rebecca Cheng, PhD, Frank S. Czerwiec, MD, PhD, Ron D. Hays, PhD, Arlene B. Chapman, MD, and Ronald D. Perrone, MD.

Authors’ Affiliations: Otsuka Pharmaceutical Development and Commercialization, Rockville, MD (DO, HBK, FSC); Covance Market Access Services, San Diego (JCC, RC); Department of Medicine, University of California, Los Angeles, CA (RDH); Section of Nephrology, University of Chicago, Chicago, IL (ABC); and Division of Nephrology, Tufts Medical Center, Boston, MA (RDP).

Address for Correspondence: Dorothee Oberdhan, MS, Otsuka Pharmaceutical Development and Commercialization, Inc, 2440 Research Blvd, Rockville, MD 20850. E-mail: dorothee.oberdhan@otsuka-us.com.

Authors’ Contributions: Research idea and design: HBK, DO, JCC; data acquisition: JCC; data analysis and psychometric analysis: JCC, RC; data interpretation: RDP, ABC, FSC, RC, JCC, DO, RDH, HBK. 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.

Support: Development of the ADPKD-IS and the manuscript was funded by Otsuka Pharmaceutical Development & Commercialization Inc, which was involved in the initiation, design, and interpretation of the data and the decision to submit the research for publication. The authors thank David Norris, PhD, of Ecosse Medical Communications LLC for editorial assistance, which was funded by Otsuka. The final decision on the content of the manuscript, including study outcomes and relevant data to be presented, was made by DO as the lead author. The final decision of the main points including conclusions to be communicated in the manuscript was made by DO as the lead author. All decisions about content of the manuscript were reviewed with the co-authors and their approval was obtained before submission.

Financial Disclosure: Dr Czerwiec, Ms Krasa, and Ms Oberdhan are employees of Otsuka. Drs Cole and Cheng were employed by Covance Market Access at the time of the research. Dr Hays is a member of the steering committee of Otsuka’s ADPKD clinical trial program and is employed by Tufts Medical Center in Boston, MA. Dr Chapman is a member of the steering committee of Otsuka’s ADPKD clinical trial program and was employed by Emory University at the time of the research.

Other Disclosures: The ADPKD-IS (registered US Copyright #TXu 1-889-583) is the result of work sponsored by Otsuka, which owns intellectual property over the ADPKD-IS including but not limited to all and any translations and other derivatives (eg, electronic versions). Otsuka has assigned Mapi Research Trust for the management of the instrument licenses and permission to use; further information is available at https://eprovide.mapi-trust.org/.

Acknowledgements: The authors thank the patients and clinical experts who participated in the development of the ADPKD-IS and the US PKD Foundation and Tess Harris from the UK PKD Charity for support.

Peer Review: Received December 19, 2016. Evaluated by 2 external peer reviewers and an external methods reviewer, with editorial input from an Associate Editor and the Editor-in-Chief. Accepted in revised form August 20, 2017.

References