Supplementary appendix

Supplement to: **Development and Validation of a Disease Specific Questionnaire to Assess Symptoms in Polycystic Liver Disease**

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Content of supplementary appendix:

Supplementary tables

Table S1. Characteristics of included patients and clinicians in the development phases of the PLD-Q

	Dutch patients (n=19)	US patients cognitive interviews (n=9)	US patients focus group (n=6)
Female, n (%)	18 (94)	9 (100)	6 (100)
Age (years) ± SD	53 ± 7	56 ± 6	47 ± 6
ADPLD/ADPKD, n (%)	11/8 (58/42)	3/9 (33/67)	0/6
Liver volume, mL (IQR)	3884 (2713-5967)	2055 (1478 - 3441)	2432 (1671 - 3659)
Kidney volume, mL (IQR) [a]	318 (274 - 393)	535 (374 - 820)	358 (242 - 805)

Data is presented as mean ± standard deviation for normally distributed variables and median (interquartile range) for non-normally distributed variables. Organ volumes are height corrected. [a]Kidney volumes are measured in ADPKD patients only. Abbreviations: ADPLD, isolated autosomal dominant polycystic liver disease; ADPKD, autosomal dominant polycystic kidney disease.

Table S2. Results of the Delphi Survey

	Round 1 respondents 11/15 (73%)						Round 2: respondents 10/11 (91%)					
Item	**1-3**	**4-6**	**7-9**	**Rating**	**Impact level**	**Consensus**	**1-3**	**4-6**	**7-9**	**Rating**	**Impact level**	**Consensus**
Feeling full	0	0	100	7	High	Unanimous[b]						
Bloating	0	0	100	8	High	Unanimous[b]						
Abdominal tightness	0	0	100	8	High	Unanimous[b]						
Lack of appetite	18,2	18,2	63,6	7	High	Weak			100	8	High	Unanimous[b]
Early satiety	0	0	100	8	High	Unanimous[b]						
Borborygmi	63,6	27,3	9,1	3	Low	Weak	100			1,5	Low	Unanimous[a]
Acid reflux	36,4	36,4	27,3	5	Moderate	None	40	30	30	4,5	Moderate	None[a]
Regurgitation	45,5	36,4	18,2	5	Moderate	None	60	30	10	3	Low	Weak[a]
Nausea	18,2	54,5	27,3	3	Low	None	10	60	30	6	Moderate	Weak[a]
Vomiting	63,6	27,3	9,1	3	Low	Weak	50	20	30	3,5	Moderate	None[a]
Obstipation	72,7	27,3	0	7	High	Moderate	90	10	0	1	Low	Strong[a]
Abdominal pain	0	27,3	72,7	6	Moderate	Moderate			100	8	High	Unanimous[b]
Backpain	18,2	54,4	27,3	8	High	None	0	44,4	55,6	6	Moderate	None[a]
Pain or pressure rib cage	9,1	18,2	72,7	7	High	Moderate	0	0	100	8	High	Unanimous[b]
Pain in side	9,1	27,3	63,6	5	Moderate	Weak	0	10	90	7,5	High	Strong[b]
Referred shoulder pain	45,5	36,4	18,2	3	Low	None	40	40	20	4,5	Moderate	None[a]
Pain in groin	72,7	27,3	0	3	Low	Moderate	90	10	0	1	Low	Strong[a]
Pain in legs	81,8	18,2	0	2	Low	Strong[a]						
Headache	81,8	18,2	0	1	Low	Strong[a]						
Pain during intercourse	45,5	45,5	9,1	4	Moderate	None	20	60	20	5	Moderate	Weak[a]
Discomfort during intercourse	27,3	27,3	45,5	6	Moderate	None	10	20	70	7	High	Moderate[b]
Easy bruisability	81,8	18,2	0	2	Low	Strong[a]						
Muscle cramps	63,6	36,4	0	1	Low	Weak	80	20	0	1	Low	Strong[a]
Limited mobility	9,1	45,5	45,5	6	Moderate	None	0	25	75	7	High	Moderate[b]

Leg edema	36,4	45,5	18,2	6	Moderate	None	40	50	10	4,5	Moderate	None[a]
Dyspnea	9,1	63,6	27,3	7	High	Weak	0	30	70	5	Moderate	Moderate[a]
Dyspnea after physical exertion	9,1	18,2	72,7	5	Moderate	Moderate	0	30	70	7	High	Moderate[b]
Frequent micturition	18,2	63,6	18,2	2	Low	Weak	30	60	10	4,5	Moderate	Weak[a]
Itch	72,7	18,2	9,1	5	Moderate	Moderate	70	30	0	1,5	Low	Moderate[a]
Sleep disorders	9,1	63,6	27,3	3	Low	Weak	10	50	40	6	Moderate	None[a]
Dizziness	54,5	45,5	0	6	Moderate	None	77,8	11,1	11,1	1,5	Low	Moderate[a]
Tiredness	18,2	36,4	45,5	3	Low	None	0	20	80	7	High	Strong[b]
Concentration problems	63,6	36,4	0	5	Moderate	Weak	60	40	0	2	Low	Weak[a]
Depression	36,4	27,3	36,4	5	Moderate	None	30	30	40	5	Moderate	None[a]
Anxiety about the future	18,2	27,3	54,5	7	High	None	10	20	70	7	High	Moderate[b]
Dissatisfaction size abdomen	9,1	36,4	54,5	7	High	None	0	20	80	7	High	Strong[b]

Rating is given as the median score. Items were selected if rated as relevant (rating score 7-9) and consensus was reached (80-100 % agreement). [a]Rejected items, [b]Selected items for the PLD-Q.

Table S3. Changes PLD-Q pilot version after cognitive debriefings and patient and clinicians focus groups

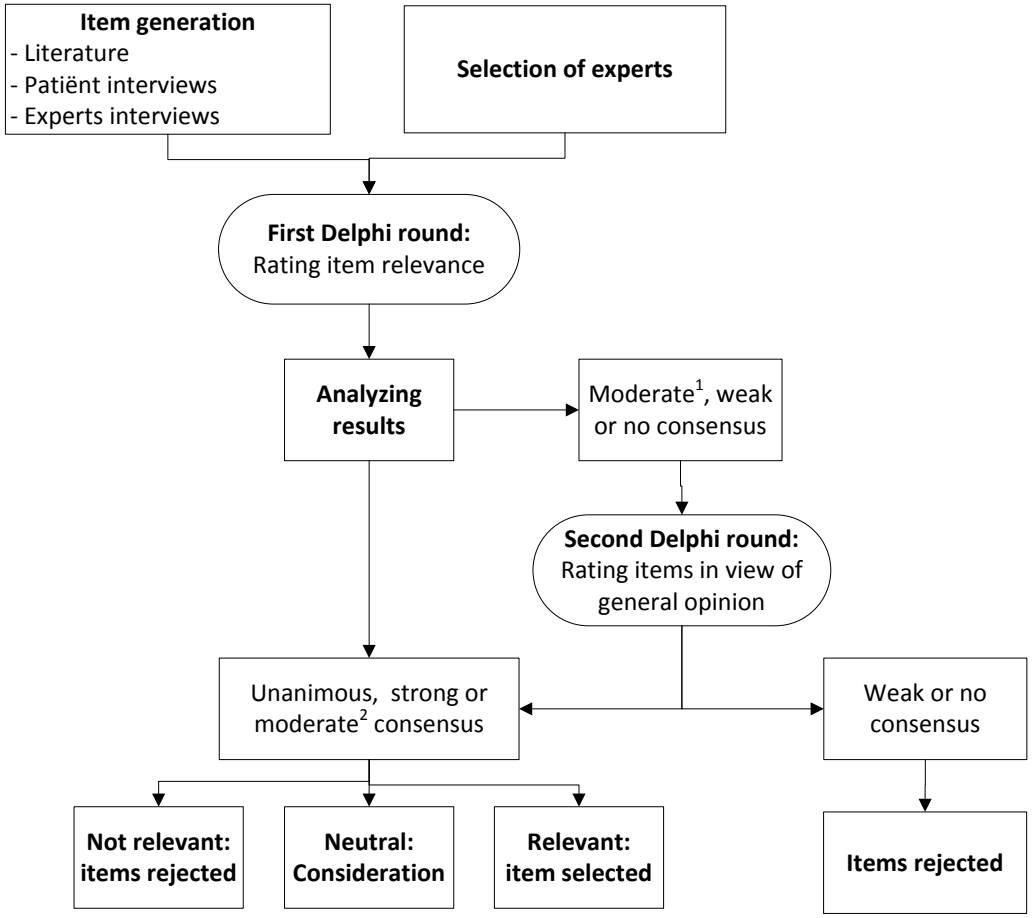
Item	Pilot version PLD-Q	Improved PLD-Q	Comment
Fullness	How often did you feel full?	How often did you experience fullness in your abdomen related to your polycystic liver?	Added 'related to your polycystic liver' to distinguish between fullness after a meal and fullness because of a polycystic liver
Early satiety	How often were you quickly satiated, or did you eat a smaller portion as a result of being quickly satiated?	How often have you felt full up too quickly after beginning to eat?	Not all patients understood the word satiated.
Acid reflux	-	How often did you have acid reflux?	Patients and clinicians agreed item was missing
Abdominal pain	How often did you have stomach pain?	How often did you have abdominal pain?	Stomach pain was considered as only the region of the stomach by patients and clinicians, not the whole abdomen.
Back pain	-	How often did you have back pain?	Patients and clinicians agreed item was missing
Shortness of breath	How often were you short of breath after physical exertion?	How often were you short of breath after physical exertion (for example climbing the stairs)?	Added example to improve understanding
Concern of liver growth	-	How often were you concerned that your abdomen is getting larger?	Patients and clinicians agreed item was missing
Discomfort intercourse	'No sexual intercourse' option	-	Removed 'no sexual intercourse' option as it leads to confusion and problems with data analysis
Discomfort intercourse	How often did you have a problem with intercourse?	How often did your polycystic liver disease cause you to have a problem with intercourse?	In old question patients were unable to address their problem. Some patients did not have intercourse because of their polycystic liver.

Table S4. Result factor analysis

Item	Dutch cohort			US cohort	
	Factor 1	**Factor 2**	**Factor 3**	**Factor 1**	**Factor 2**
Q1. Feeling full	0.793	0.331	0.140	0.803	0.172
Q2. Lack of appetite	0.755	0.425	-0.034	0.775	-0.264
Q3. Early satiety	0.763	0.330	0.049	0.796	0.065
Q4. Acid Reflux	N/A	N/A	N/A	0.530	-0.054
Q5. Nausea	0.432	0.581	-0.026	0.762	-0.269
Q6. Pressure or pain rib cage	0.755	0.030	-0.099	0.763	-0.249
Q7. Pain in side	0.665	-0.028	-0.456	0.741	-0.373
Q8. Abdominal pain	0.651	0.298	0.274	0.771	-0.373
Q9. Back pain	N/A	N/A	N/A	0.618	-0.024
Q10. Shortness of breath	0.675	-0.305	-0.319	0.725	0.040
Q11. Limited mobility	0.820	-0.350	-0.151	0.771	0.016
Q12. Tiredness	0.665	-0.226	-0.369	0.782	0.011
Q13. Anxiety about the future	0.532	-0.371	0.438	0.651	0.316
Q14. Concern abdomen getting larger	N/A	N/A	N/A	0.769	0.433
Q15. Dissatisfaction size abdomen	0.702	-0.230	0.429	0.759	0.479
Q16. Intercourse discomfort	0.636	-0.443	0.217	0.635	0.104
Eigenvalues	6.154	1.480	1.000	8.572	1.048
% of variance	47	11	8	54	7

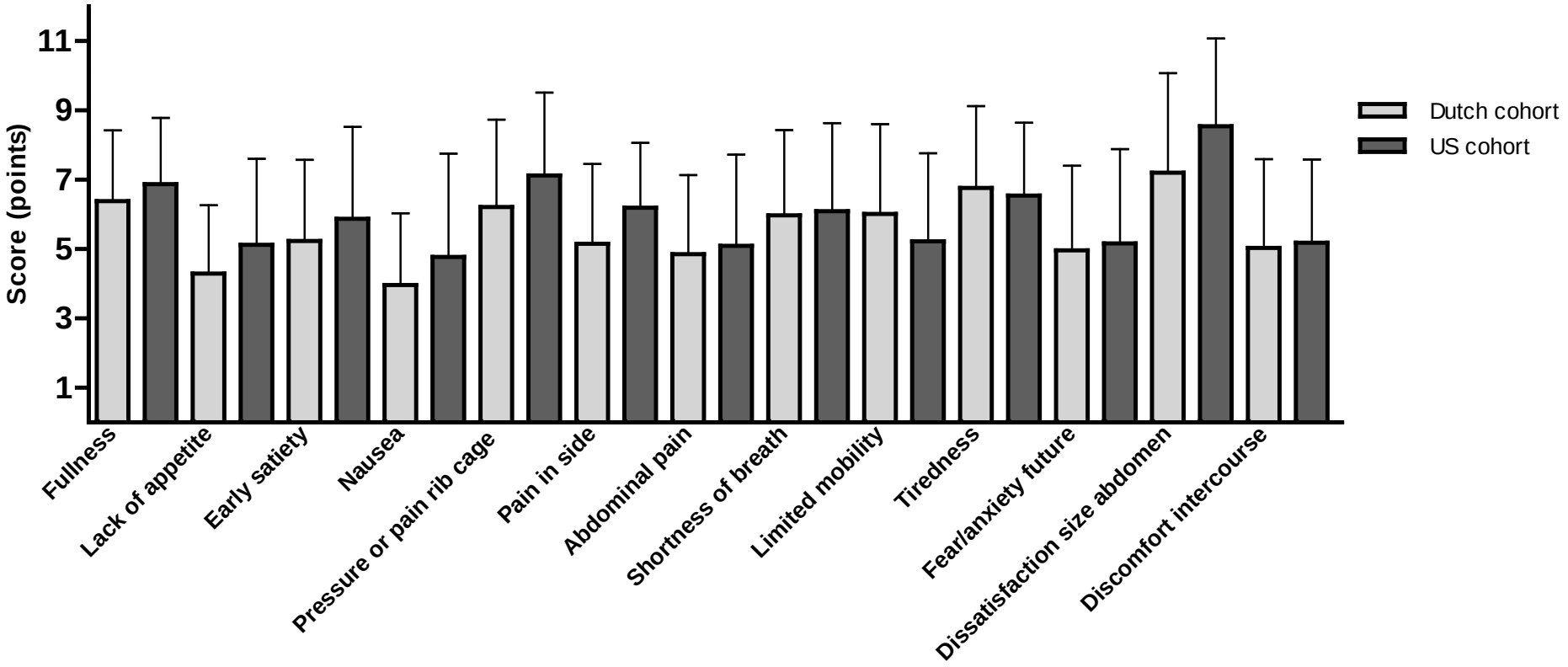
To determine a factor, the eigenvalue has to exceed 1. The factor analysis shows that the variability is largely explained by the first factor, suggesting unidimensionality of the questionnaire. N/A; not applicable.

Supplementary figures



Supplementary Figure S1: Flowchart Delphi survey for item selection

Consensus rated as percentage of experts which rated in one of the three ranges (1-3, 4-6 or 7-9*) of the questionnaire; Unanimous: 100%, Strong consensus: <100% and ≥80%, Moderate ≤80 and ≥70, Weak consensus ≤ 70 and ≥60, No consensus <60%. Range 1-3 is considered as not relevant, 4-6 as neutral and 7-9 as relevant. Moderate[1]; after first Delphi round, moderate[2]; after second Delphi round



Supplementary Figure S2. Score distributions of the Dutch PLD-Q and the pilot version of the English PLD-Q.

Supplementary Files

Supplementary File 1. Methods and results Delphi survey for item selection of the PLD-Q

1a) Conducting the Delphi survey for item selection

The Delphi survey consisted of a two-round survey in a panel of 15 clinicians using a web-based questionnaire. The questionnaire was designed to assess which of the generated items were considered as relevant for a PLD-specific questionnaire sensitive to detect changes in the occurrence of PLD associated symptoms. Each item was scored on an end-anchored rating scale of 1-9, were 1=not relevant and 9= highly relevant. Experts completed the questionnaires anonymously to prevent them from influencing each other's answers. The facilitator provides summarized answers after each round and the experts are asked to reconsider their answer in view of the general opinion. The second round contained only items were no consensus was reached in the first round. See Supplementary file 2 for a systematic overview of the Delphi Survey.

1b) Item selection

After the first round we calculated the median ratings of each item and we considered ratings of 1-3 as no or very low relevance, 4-6 as medium relevance, and 7-9 as high relevance for the questionnaire. Five levels of consensus were established: unanimous (100% of the clinicians have ratings in one of the three ranges 1-3, 4-6 or 7-9), strong (80- 99%); moderate (70-79%); weak consensus (60 – 69%) and no consensus (<60%). After the second round, we considered 80-100 % agreement as consensus. We selected items for the questionnaire if they were rated as relevant (mean score 7-9) and consensus was reached. Supplementary Figure 1 shows an overview of the item selection process.

Supplementary File 2. Results of the pilot version of the English PLD-Q in a US cohort

We identified 216 US patients that fitted our inclusion criteria. Of them, 54 patients were selected based on matching age and gender of the Dutch cohort. In total, 34 patients (91% female, 35% ADPLD) with a mean age of 57 years returned their questionnaire (response rate 63%)**.** Mean score in the US cohort was 45 ± 20 points (range 9-91). No total score could be calculated in 2 patients due to missing results. Missing results of the individual questionnaires ranged between 0 and 2.9%. There were no floor (0%) or ceiling effects (0%). The PLD-Q total score showed a positive correlation to the symptom scale of the EORTC QLQ-C30 of r=0.835, *P* =0.002 and a negative correlation to the global health status of the EQ-5D of 0.544, *P* =0.002. Score distributions were similar across the Dutch and US population, see Supplementary Figure 2.

Supplementary File 3. Final version of the PLD-Q

Polycystic Liver Disease Questionnaire

Instructions:

- This questionnaire consists of 16 paired questions investigating symptoms that you possible may have.
- The questions relate to the past month
- Please try to answer all the questions
- For each question mark one box, see the example below:

Never	Seldom	Sometimes	Regularly	Often	Always
☐	☐	☒	☐	☐	☐

1a) How often did you experience fullness in your abdomen related to your polycystic liver?

Never	Seldom	Sometimes	Regularly	Often	Always
☐	☐	☐	☐	☐	☐

1b) How much did this bother you?

Not at all	A little	Somewhat	Quite a bit	A lot
☐	☐	☐	☐	☐

2a) How often did you experience lack of appetite?

Never	Seldom	Sometimes	Regularly	Often	Always
☐	☐	☐	☐	☐	☐

2b) How much did this bother you?

Not at all	A little	Somewhat	Quite a bit	A lot
☐	☐	☐	☐	☐

3a) How often have you felt full quickly after beginning to eat?

Never	Seldom	Sometimes	Regularly	Often	Always
☐	☐	☐	☐	☐	☐

3b) How much did this bother you?

Not at all	A little	Somewhat	Quite a bit	A lot
☐	☐	☐	☐	☐

4a) How often did you have acid reflux?

Never	Seldom	Sometimes	Regularly	Often	Always
☐	☐	☐	☐	☐	☐

4b) How much did this bother you?

Not at all	A little	Somewhat	Quite a bit	A lot
☐	☐	☐	☐	☐

5a) How often did you experience nausea?

Never	Seldom	Sometimes	Regularly	Often	Always
☐	☐	☐	☐	☐	☐

5b) How much did this bother you?

Not at all	A little	Somewhat	Quite a bit	A lot
☐	☐	☐	☐	☐

6a) How often did you feel pain or pressure in your rib cage?

Never	Seldom	Sometimes	Regularly	Often	Always
☐	☐	☐	☐	☐	☐

6b) How much did this bother you?

Not at all	A little	Somewhat	Quite a bit	A lot
☐	☐	☐	☐	☐

7a) How often did you have pain in your side?

Never	Seldom	Sometimes	Regularly	Often	Always
☐	☐	☐	☐	☐	☐

7b) How much did this bother you?

Not at all	A little	Somewhat	Quite a bit	A lot
☐	☐	☐	☐	☐

8a) How often did you have abdominal pain?

Never	Seldom	Sometimes	Regularly	Often	Always
☐	☐	☐	☐	☐	☐

8b) How much did this bother you?

Not at all	A little	Somewhat	Quite a bit	A lot
☐	☐	☐	☐	☐

9a) How often did you have back pain?

Never	Seldom	Sometimes	Regularly	Often	Always
☐	☐	☐	☐	☐	☐

9b) How much did this bother you?

Not at all	A little	Somewhat	Quite a bit	A lot
☐	☐	☐	☐	☐

10a) How often were you short of breath after physical exertion (for example climbing the stairs)?

Never	Seldom	Sometimes	Regularly	Often	Always
☐	☐	☐	☐	☐	☐

10b) How much did this bother you?

Not at all	A little	Somewhat	Quite a bit	A lot
☐	☐	☐	☐	☐

11a) How often were you limited in your mobility?

Never	Seldom	Sometimes	Regularly	Often	Always
☐	☐	☐	☐	☐	☐

11b) How much did this bother you?

Not at all	A little	Somewhat	Quite a bit	A lot
☐	☐	☐	☐	☐

12a) How often were you tired?

Never	Seldom	Sometimes	Regularly	Often	Always
☐	☐	☐	☐	☐	☐

12b) How much did this bother you?

Not at all	A little	Somewhat	Quite a bit	A lot
☐	☐	☐	☐	☐

13a) How often were you fearful or anxious when you thought about the future?

Never	Seldom	Sometimes	Regularly	Often	Always
☐	☐	☐	☐	☐	☐

13b) How much did this bother you?

Not at all	A little	Somewhat	Quite a bit	A lot
☐	☐	☐	☐	☐

14a) How often were you concerned that the size of your abdomen is getting larger?

Never	Seldom	Sometimes	Regularly	Often	Always
☐	☐	☐	☐	☐	☐

14b) How much did this bother you?

Not at all	A little	Somewhat	Quite a bit	A lot
☐	☐	☐	☐	☐

15a) How often were you dissatisfied by the size of your abdomen?

Never	Seldom	Sometimes	Regularly	Often	Always
☐	☐	☐	☐	☐	☐

15b) How much did this bother you?

Not at all	A little	Somewhat	Quite a bit	A lot
☐	☐	☐	☐	☐

16a) How often did your polycystic liver disease cause you to have a problem with intercourse?

Never	Seldom	Sometimes	Regularly	Often	Always
☐	☐	☐	☐	☐	☐

16b) How much did this bother you?

Not at all	A little	Somewhat	Quite a bit	A lot
☐	☐	☐	☐	☐