PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	"A sword of Damocles": Patient and caregiver beliefs, attitudes and perspectives on presymptomatic testing for autosomal dominant polycystic kidney disease – a focus group study
AUTHORS	Logeman, Charlotte; Cho, Yeoungjee; Sautenet, Benedicte; Rangan, Gopala; Gutman, Talia; Craig, Jonathan; Ong, Albert; Chapman, Arlene; Ahn, Curie; Coolican, Helen; Tze-Wah Kao, Juliana; Gansevoort, Ron T.; Perrone, R; Harris, Tess; Torres, Vincent; Fowler, Kevin; Pei, York; Kerr, Peter; Ryan, Jessica; Johnson, David; Viecelli, Andrea; Geneste, Clair; Kim, Hyunsuk; Kim, Yaerim; Howell, Martin; Ju, Angela; Manera, Karine; Teixeira-Pinto, Armando; Parasivam, Gayathri; Tong, Allison

VERSION 1 – REVIEW

REVIEWER	Stéphanie De Rechter University Hospitals Leuven, Belgium
REVIEW RETURNED	21-Apr-2020

GENERAL COMMENTS	The study by Logeman et al. gives an important overview of the challenges both ADPKD patients as caregivers are currently facing, including qualitative data. Their work stresses the importance of genetic counseling in ADPKD, and uniformely inform patients to enable them make their own decissions. The paper is clearly written. All major themes are discussed in detail. Despite this, in some parts, the paper lacks nuance. Comments: - The used selection process inevitably leads to selection bias. In this paper, testing for disease presence is discussed only in patients diagnosed with the disorder and of whom up to 40% has ESKD. The opinion of those refusing to be tested would of course be very meaningful, but including those at-risk persons is (ethically) impossible. Nevertheless, this should be clearly mentioned as a major limitation. To have a better view on the included patients: please add the following: what was the reason for diagnosis (all asymptomatic at diagnosis?, testing at the request of the patient?); what was the used method for diagnosis? Do you have data on genetics? (PKD1 vs 2: perhaps PKD1 patients are less reluctant towards testing given they in general more severely affected) - Could you give more details about the caregivers? Are they all nephrologists? Are there pediatricians involved? Other disciplines? It would be very interesting to have multiple disciplines involved here, however given the small number of caregivers it would be hard to draw conclusions. - Please make subdivisions on testing of adults (their own decision) and testing of minors (parents' decision). Now this is discussed as

	entirety in contrast to the bio-ethical/legal implications. Moreover, in the current consensus statements (KDIGO, EAF) testing in adults is overall accepted and encouraged in constrast to testing in minors. In this light, please rephrase l39 introduction. - As discussed in the introduction part, l46, testing includes all possible methods: genetics, radiology, etc. However, in some parts testing only includes genetic testing (cfr. Sup Table 1; in discussion about testing in Korea and its funding. This created the impression the authors only discuss genetic testing of asymptomatic patients and not other methods. Please clarify into detail and in case multiple testing methods, please subdivide. Moreover, do patients or caregivers have different opinion on the different possible ways to test for disease presence? Is their attitude the same towards all? - in the Discussion part, the authors mention the lack of support. Could you discuss the availability of the ADPKD Route Map, freely available in English, German and French. - Table 1: please make a separate table for patients and caregivers. Now, it is difficult to interprete e.g. age of patients included. - In the introduction, in my opinion, it is important to stress the authors are discussing testing for a disease for which a cure is currently unavailble. Only slowing down disease progression is possible. Also, stressing the progressive character of the disease seems important for this study. - introduction l 16: complications: now it seems as if complications = extra-renal manifestations. Renal complications do occur (e.g. cyst infections,...). Please rephrase. - Fig 1: not all words are fitting - Ref 30 p15 l 46 incorrect; please check all ref - p15, l1: g testing ?

REVIEWER	Howard Trachtman NYU Langone Health
REVIEW RETURNED	26-Apr-2020

GENERAL COMMENTS	This is an excellent paper on an important topic that follows in the footsteps of similar work previous in nephrology and other subspecialities. The methods are sound nd the sample size is impressive. The investigative team is well recognized for expertise in this area. The following ae some suggestions that might improve the manuscript 1. The authors might want to explore whether attitudes varied by country, gender or age of the respondents 2. It might be interesting to compare approaches to preclinical testing for renal diseases that present earlier in life 3. it would be informative to add some detail about the focus group sessions per se

REVIEWER	Cheryl Stopford Department of Clinical Genetics Leeds Teaching Hospitals NHS Trust Chapel Allerton Hospital UK
REVIEW RETURNED	19-May-2020

GENERAL COMMENTS	This is a well written and thoughtful manuscript with the clear aim of presenting the experiences of people from ADPKD families. The authors can be commended on their recruitment of a large sample of

	individuals and providing a clear picture of their concerns around testing. The study is a good example of the need for genetic counselling support. The concerns of this patient group are similar to those living with a range of other conditions. I would like to make just a few comments. General: Primarily, I feel the manuscript might benefit from some clarity around the term 'testing'. Although this is provided in the introduction in paragraph 3, throughout the paper I found myself wondering what exactly participants were speaking of when comments were made (i.e. ultrasound versus genetic etc). It would be helpful if participants' diagnostic testing details could be summarised and added to the demographic characteristics, or more specifically referred to within the text. Methodology: The authors state that the participants were eligible if they were >18 and diagnosed with ADPKD (or a caregiver). Was there a reason that they were unable to recruit participants who were technically at risk but not diagnosed? It is indicated that 'patients were able to contact any other patients that would be interested to participate' suggesting that there was some element of self-selection? It would be helpful if the method of approach could be more clearly defined. The authors provide clear details of demographic characteristics. However when reading some of the quotations I felt it may be helpful to know more about the context, most specifically, how long had participants had a diagnosis (or known about the diagnosis in the family) prior to the interview. This could give the reader more information about when some of these conversations might have taken place. With reference to the COREQ checklist, it would be helpful to add some brief information about: • The prior relationship between participants and researchers • How data saturation was decided upon • Decisions around the make-up of focus groups (e.g. although participants were purposively sampled, were group dynamics considered? Was there a mix of diagnosed individuals/caregivers? Did focus groups have a mix of ages? Did groups have a mix of people who had more severe symptoms at younger age and less severe at older age etc or were participants chosen to be more similar? Were the groups entirely random?)

REVIEWER	Bettina Zimmermann University of Basel, Institute for Biomedical Ethics, Switzerland
REVIEW RETURNED	27-May-2020

GENERAL COMMENTS	The authors provide a very interesting, rich and international study on the challenges related to decision-making in autosomal dominant polycystic kidney disease. While the data seems to be rich, the study design appropriate and the data analysis rigorous and well done, my major concern is about the scope of the study. I don't understand why the authors use the general term "testing" instead of "genetic testing". I think the authors should elaborate a little more on how and why they generalised "testing" in their study, and the role of genetic testing in ADPKD diagnosis; especially because they seem to focus on the predictive component of testing. Also the question guide provided in the supplementary, the questions were directed towards

	genetic screening and genetic counselling. Related to this issue, the authors should elaborate and consider how they defined "diagnosis" in their study – and distinguish, for example, between presymptomatic diagnosis (through screening), early diagnosis (when symptoms had started but no treatment) and late diagnosis (when treatment became necessary). I think the study would benefit if the authors would consider their results in line with disease progression. In that context, it would also be more clear when the authors refer to genetic testing and when to other kinds of tests. The characteristics of participants seem to allow for such distinctions; and it would also allow for more directed practical implications. I also have a number of minor issues and open questions: Title: The quote "A sword of damocles" paired with an autosomal dominant disorder let me expect a study about predictive genetic testing. It also seems like the predictive component of testing is the main concern in the findings of the study. That should be made more transparent. Also, if the authors use this quote in the title, they should please refer to it in the text and provide the context in which this quote was given. Abstract: The conclusions do not seem to bring any new findings – please be more specific Introduction: 1. "In some countries in Europe and Asia, access to asymptomatic or predictive testing is very restricted or not available" – Please be more specific here and outline how access is restricted and which European and Asian countries are meant here. Also, please add a reference to this statement for Asian countries. 2. "For the scope of this paper, testing may include any strategy used to identify the presence of ADPKD prior to symptom onset (including genetic tests, blood tests, imaging such as ultrasound, CT, MRI, etc.)" – Please elaborate a bit more on these different tests – for example, since ADPKD is a heritable autosomal dominant disorder, why is genetic testing not the gold standard for diagnosing ADPKD? Why is this study focussing on that many different tests, and not on genetic testing in particular? Are all of these tests having a predictive component, as the title and the results suggest? Methods: 1. Please provide more detailed information on patient recruiment: how were they recruited, who recruited them? What did the "information packages" include? Was there only written information, or was oral information given and the opportunity of participants to ask questions about the study before giving informed consent? 2. "Patient and public involvement": I do see the patient involvement, but where is the public involved? 3. Data collection: How was data saturation assessed? 4. Data analysis: o Was the analysis started during data collection or afterwards? o Were the whole transcripts translated or just the codes from the line-by-line coding? How was the quality of the translations ensured? o What "principles from grounded theory" were specifically used? Because the authors mentioned having used a combination of qualitative data analysis methods (grounded theory, thematic analysis), this needs more detailed elaboration. o Please specify what is meant by "investigator triangulation" Results:

	1. How many participants were in each focus group? Did the authors aim for diverse or similar demographics within the focus groups? Were the caregivers interviewed separately from the patients or were they mixed up? Were several members from the same family involved in the same focus groups? 2. "Medicalizing family planning" and "Judging the value of life with ADPKD" seem to overlap importantly – please explain the difference better or consider merging those themes 3. "Medicalizing family planning": did preimplantation genetic diagnosis not come up at all? If not that is a noticable point to raise in the discussion, as it would uncover an information gap that seems to be consistent in all three countries Discussion 1. " We are uncertain about the transferability of the findings to other countries with different healthcare policies on testing." – I think the authors can be a little more confident regarding the transferability of findings, because they included participants from three different continents. As pointed out nicely in the discussion, some findings were depending on policy, but if I understood correctly, the themes and general theory (as illustrated in Figure 1) came from the merged experience from many different settings. 2. " We acknowledge that testing can be a sensitive topic and some views may have been suppressed in the focus group setting which may also explain why there was limited variation in the perspectives of caregivers vs. patients." – Were there any signs of suppression, did the authors notice themes that were suppressed or not that easy to cover? Having examples here would be very interesting.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1 -

1. “The used selection process inevitably leads to selection bias. In this paper, testing for disease presence is discussed only in patients diagnosed with the disorder and of whom up to 40% has ESKD. The opinion of those refusing to be tested would of course be very meaningful, but including those at-risk persons is (ethically) impossible. Nevertheless, this should be clearly mentioned as a major limitation. To have a better view on the included patients: please add the following: what was the reason for diagnosis (all asymptomatic at diagnosis, testing at the request of the patient?); what was the used method for diagnosis? Do you have data on genetics? (PKD1 vs 2: perhaps PKD1 patients are less reluctant towards testing given they in general more severely affected)”

We confirm that the participants included patients and their caregivers (family members involved in the care and support of patients). In the revised manuscript, we have now clarified that the inclusion criteria and sampling strategy were intended to elicit a broad range of perspectives (Page 6, paragraph 3). The participants included caregivers who were family members who did not have a diagnosis of ADPKD but were potentially genetically at-risk. As suggested, we have now added in the limitations: “We discussed testing for disease presence only in patients diagnosed with ADPKD and 31% were receiving kidney replacement therapy. We also acknowledge that the findings may not include views of at-risk persons because of ethical reasons.” (Page 15, paragraph 1 – marked copy). The question regarding different behaviour patterns in patients with variants for PKD1 is an interesting suggestion. We did not have ethics approval to collect information about the reason for diagnosis, the method for diagnosis or the genetic diagnosis and cannot provide these data.

2. Could you give more details about the caregivers? Are they all nephrologists? Are there pediatricians involved? Other disciplines? It would be very interesting to have multiple disciplines involved here, however given the small number of caregivers it would be hard to draw conclusions"

In the revised manuscript, we clarify caregivers refer to family members involved in the care of the patients (not health professionals including nephrologists) and have now defined this in the manuscript (page 6, paragraph 3 – marked copy). We have provided data on their relationship with the patient (page 8, paragraph 2 – marked copy).

3. Please make subdivisions on testing of adults (their own decision) and testing of minors (parents' decision). Now this is discussed as entirety in contrast to the bio-ethical/legal implications. Moreover, in the current consensus statements (KDIGO, EAF) testing in adults is overall accepted and encouraged in contrast to testing in minors. In this light, please rephrase l39 introduction."

Our study included participants from 18 to 79 years old and we did not collect information to determine if the decision was their own and/or their parents'. However, we have reported that parents were concerned for their children and what a positive diagnosis could mean for their child. For example: "Parents considered how the risks of early diagnosis through testing may jeopardize work opportunities for their children" (Page 9, paragraph 1 – marked copy). As advised, we have now rephrased the section on consensus statements to: "Typically, countries used to offer testing when a diagnosis is needed to be confirmed in young patients with unknown family history, for family planning, to determine eligibility for kidney donation, or when the disease presents in childhood or adolescence but testing in adults is overall accepted and encouraged". (Page 5, paragraph 2 – marked copy)

4. As discussed in the introduction part, l46, testing includes all possible methods: genetics, radiology, etc. However, in some parts testing only includes genetic testing (cfr. Sup Table 1; in discussion about testing in Korea and its funding. This created the impression the authors only discuss genetic testing of asymptomatic patients and not other methods. Please clarify into detail and in case multiple testing methods, please subdivide. Moreover, do patients or caregivers have different opinion on the different possible ways to test for disease presence? Is their attitude the same towards all?"

We sought to collect information specifically on genetic testing, but participants also discussed other methods of diagnostic evaluation. Because of this, we have used the term 'testing' broadly to include all methods. To clarify the distinction between genetic testing and other types of diagnostic tests raised by the participants, we have added: "The diagnosis of ADPKD using methods other than genetic testing is routinely offered as the latter is not readily available or accessible in many countries." (Page 14, paragraph 3 – marked copy). We did not collect information on the testing method that patients used. Participants spoke about all methods of testing and confirming a diagnosis interchangeably and did not highlight any specific method.

5. "In the Discussion part, the authors mention the lack of support. Could you discuss the availability of the ADPKD Route Map, freely available in English, German and French."

As suggested, we have now added: "Lack of support has been recognized and, through discussions with specialists and patient advocates, this led to the development of a route map for ADPKD (available in three languages) intended to help patients and all stakeholders navigate through the services available to them (including genetic testing, diagnostic, management and treatment options) (1)." (Page 13, paragraph 2 – marked copy).

6. Table 1: please make a separate table for patients and caregivers. Now, it is difficult to interpret

e.g. age of patients included.

As clarified in our response to Point #2 above, caregivers refer to family members involved in the care of patients. We presented the participant demographic data together as the demographics were similar within the two groups. Both patients and caregivers ages ranged from 18 to 79 years. Additionally, we have marked the data that pertains only to the patients in the footnote.

7. “In the introduction, in my opinion, it is important to stress the authors are discussing testing for a disease for which a cure is currently unavailable. Only slowing down disease progression is possible. Also, stressing the progressive character of the disease seems important for this study.”

Page 5, paragraph 1, we stated “Early phase of ADPKD is often asymptomatic but the development of kidney cysts leads to increased kidney volume, reduced kidney function and eventually follows a relentless course towards end-stage kidney disease (ESKD)(2-8)”. This indicates that the disease is progressive and there is no cure.

8. introduction l16: complications: now it seems as if complications = extra-renal manifestations. Renal complications do occur (e.g. cyst infections,...). Please rephrase.

As noted, we have now clarified this: “Clinical management involves pharmacological and lifestyle interventions to control hypertension, slow the progression of cysts, manage complications (kidney and extra-kidney manifestations), and maintain quality of life (QoL) (9-11).” (Page 5, paragraph 1 – marked copy).

9. Fig 1: not all words are fitting

We have corrected the wording in Figure 1.

10. Ref 30 p15 l 46 incorrect; please check all ref

We have corrected and updated this reference(12). (Page 13, paragraph 3 – marked copy)

11. p15, l1: g testing ?
We have corrected this, the ‘g’ has been removed. (Page 13, paragraph 1 – marked copy)
Reviewer #2 –
12. The authors might want to explore whether attitudes varied by country, gender or age of the respondents

In the analysis, we investigated for differences by demographic and clinical characteristics and confirm that we did not find substantial differences. This has been outlined in the third paragraph of the discussion, particularly surrounding the cost of testing; “Korean patients were particularly concerned about the cost burden of the disease and expressed that they did not understand the added value of paying for a pre-symptomatic ultrasound test if cysts may develop later in life.” (Page 14, paragraph 2 – marked copy)

13. It might be interesting to compare approaches to preclinical testing for renal diseases that present earlier in life
This is an interesting idea, but unfortunately, we did not collect data on how or when participants were tested.

14. it would be informative to add some detail about the focus group sessions per se

Details about the focus group sessions can be found in the methods section: “The two-hour focus group discussions were conducted from June to November of 2017 until data saturation. We developed the question guide from the literature and with input from the research team (supplementary material and methods) (22, 25, 26). Focus groups were convened in a venue external to the hospital and facilitated by one investigator (English – A.T. (researcher), T.G. (researcher), Y.C (academic nephrologist); French – B.S (academic nephrologist); Korean – Y.K.(academic nephrologist)). A co-facilitator recorded field notes. All discussions were audio-recorded and were transcribed.” (Page 7, paragraph 2 – marked copy).

Reviewer #3 –

15. Primarily, I feel the manuscript might benefit from some clarity around the term ‘testing’. Although this is provided in the introduction in paragraph 3, throughout the paper I found myself wondering what exactly participants were speaking of when comments were made (i.e. ultrasound versus genetic etc). It would be helpful if participants’ diagnostic testing details could be summarised and added to the demographic characteristics, or more specifically referred to within the text.

We have intentionally used a broad definition of testing because the participants had different notions around the term and concept of testing, which we wanted to capture. For example, some participants referenced ultrasounds not just for monitoring reasons but also for diagnostic purposes. This is also mentioned in comment 4 and 12. Korean participants were particularly concerned about the cost burden of pre-symptomatic testing and this was done through ultrasounds. This is because they did not feel like it would give them a definitive answer. Few participants had direct experience of genetic testing. We did not collect data on participants’ diagnostic tests.

16. The authors state that the participants were eligible if they were >18 and diagnosed with ADPKD (or a caregiver). Was there a reason that they were unable to recruit participants who were technically at risk but not diagnosed? It is indicated that ‘patients were able to contact any other patients that would be interested to participate’ suggesting that there was some element of self-selection? It would be helpful if the method of approach could be more clearly defined.

Participants were encouraged to invite caregivers (family members). These family members may have been at-risk. In this study, we did not have approval from the human research ethics committee clearance to identify potential participants from the community who may be at-risk (we could not approach individuals considered at-risk who may not be aware of the risk). We used purposive sampling to maximize diverse demographic and clinical characteristics and have expanded details on the approach: “Recruiting clinicians identified patients with ADPKD who could also invite their caregivers.” (Page 6, paragraph 3 – marked copy). As mentioned in our response to Point #1 above, an additional limitation has been added regarding the lack of known participation of participants who were at-risk.

17. The authors provide clear details of demographic characteristics. However, when reading some of the quotations I felt it may be helpful to know more about the context, most specifically, how long had participants had a diagnosis (or known about the diagnosis in the family) prior to the interview. This could give the reader more information about when some of these conversations might have taken place.

We did not collect information about how long a participant had since been diagnosed or how long the participant knew about the diagnosis within the family.

18. With reference to the COREQ checklist, it would be helpful to add some brief information about: 1) The prior relationship between participants and researchers, 2) How data saturation was decided upon, 3) Decisions around the make-up of focus groups (e.g. although participants were purposively sampled, were group dynamics considered? Was there a mix of diagnosed individuals/caregivers?

Did focus groups have a mix of ages? Did groups have a mix of people who had more severe symptoms at younger age and less severe at older age etc or were participants chosen to be more similar? Were the groups entirely random?)

We have added the following details to the manuscript.
1) Participants and researchers had no prior relationship. (Page 6, paragraph 3 – marked copy)
2) Data saturation was decided upon when no new ideas or perspectives were emerging in subsequent focus groups. We have now indicated that “data saturation was achieved when C.L, Y.C, and A.T agreed that little or no new concepts were arising from subsequent focus groups.” (Page 7, paragraph 2 – marked copy)
3) Focus groups were designed with the intent to have a broad range of demographic and clinical characteristics (including patients/caregivers, age). We did not consider severity of symptoms a priori. We did not separate patients from a caregiver as they preferred to participate in the same group. (Page 7, paragraph 2 – marked copy)

Reviewer #4 –
19. I don’t understand why the authors use the general term "testing" instead of "genetic testing". I think the authors should elaborate a little more on how and why they generalised "testing" in their study, and the role of genetic testing in ADPKD diagnosis; especially because they seem to focus on the predictive component of testing. Also, the question guide provided in the supplementary, the questions were directed towards genetic screening and genetic counselling.

We used the general term because, as noted in our response to Point #15 above, participants had different notions around the term and concept of testing, which we wanted to capture. Most participants were not aware of the availability of genetic testing. We wanted to include perspectives on any pre-symptomatic method of screening or diagnosing ADPKD. Predictive testing done either by genetic testing or pre-symptomatic testing done using ultrasounds, arguably raises the same ethical dilemmas. This has also been expanded on in our response to Point #15.

20. Related to this issue, the authors should elaborate and consider how they defined "diagnosis" in their study – and distinguish, for example, between pre-symptomatic diagnosis (through screening), early diagnosis (when symptoms had started but no treatment) and late diagnosis (when treatment became necessary). I think the study would benefit if the authors would consider their results in line with disease progression.

This study focuses on pre-symptomatic diagnosis: “For the scope of this paper, testing may include any strategy used to identify the presence of ADPKD prior to symptom onset (including genetic tests, blood tests, imaging such as ultrasound, CT, MRI, etc.)”. (Page 5, paragraph 3 – marked copy)

21. In that context, it would also be more clear when the authors refer to genetic testing and when to other kinds of tests. The characteristics of participants seem to allow for such distinctions; and it would also allow for more directed practical implications.

For the scope of this paper, “test” refers to any test. Participants had a wide understanding, knowledge and accessibility to differing tests. For this reason, we have left the term broad to capture all perspectives.

22. Title: The quote "A sword of damocles" paired with an autosomal dominant disorder let me expect a study about predictive genetic testing. It also seems like the predictive component of testing is the main concern in the findings of the study. That should be made more transparent. Also, if the authors use this quote in the title, they should please refer to it in the text and provide the context in which this quote was given.

This study is focused on pre-symptomatic and predictive testing. This has been clarified in comment 20. Regarding the quote “A sword of Damocles”, this quote is referred to on page 10, paragraph 1: “a sword of Damocles over [their] head causing worry, anxiety, depression and even posttraumatic stress disorder” (France)”. We found this quote to be extremely powerful in describing the sense of worry that so many participants described with knowing their diagnosis. It is for this reason that we have included it in the title.

23. Abstract: The conclusions do not seem to bring any new findings – please be more specific

We have summarised the key findings in the conclusion: For patients with ADPKD, pre-symptomatic testing provides an opportunity to take ownership of their health through family planning and preventive measures. However, these decisions can be wrought with tensions and uncertainty about prognostic implications, and the psychosocial and financial consequences of the burden of testing. Person-centered genetic counseling and education that addresses patients’ concerns may support informed decision-making about testing in ADPKD. Healthcare professionals should focus on genetic counselling, mental health and providing education to a patient’s family to support informed decision-making. Policymakers should consider the cost-burden and risk of discrimination when informing government policies. Finally, patients are recommended to focus on self-care from an early age. (Abstract)

24. "In some countries in Europe and Asia, access to asymptomatic or predictive testing is very restricted or not available" – Please be more specific here and outline how access is restricted and which European and Asian countries are meant here. Also, please add a reference to this statement for Asian countries.

This is further expanded on in the discussion section; “A recent study showed that more than 70% of Korean patients believed that genetic testing should be included in Korea’s national health testing program so these services can be provided at little expense (13). In Australia, access to dialysis and transplantation is provided to all citizens via government funded Medicare system (14). Transplantation is primarily limited due to insufficient kidney donors available to meet the number of potential recipients on the organ waiting list (14). Dialysis in Korea has also been covered since 1989 and this is similar in France (15, 16). In France, genetic testing is not routinely offered to patients, although some could have free access to genetic testing (for example if they were enrolled in the GENKYST observational cohort study) (17). In regard to legislative protection, Australia, France and Korea have comprehensive provisions pertaining to consent, autonomy and integrity of the person tested (18). In France, refusal of fetal testing for ADPKD may be due to fear of genetic transmission and the illegality of termination of pregnancy after 12-weeks conception due to ADPKD (19).” (page 15, paragraph 2 – marked copy. Additional references have been added.

25. "For the scope of this paper, testing may include any strategy used to identify the presence of ADPKD prior to symptom onset (including genetic tests, blood tests, imaging such as ultrasound, CT, MRI, etc.)" – Please elaborate a bit more on these different tests – for example, since ADPKD is a heritable autosomal dominant disorder, why is genetic testing not the gold standard for diagnosing ADPKD? Why is this study focusing on that many different tests, and not on genetic testing in particular? Are all of these tests having a predictive component, as the title and the results suggest?

We have addressed this in our response to Points #15 and #19 above. Historically, genetic testing has not been the first-line test for diagnosis whereas ultrasound has been widely available with validated criteria. Accessibility and cost of genetic testing have also been barriers, and historically there have been questions about whether it would alter clinical management if the diagnosis has been

revealed by ultrasound. Thus, this study does not focus solely on genetic testing because the participants were not all aware of genetic testing. This was limited by the participants' awareness of genetic testing. This study focuses on a diagnosis that is made pre-symptomatically. Depending on the stage of the disease, all of these tests can confirm a diagnosis prior to symptoms.

26. Please provide more detailed information on patient recruitment: how were they recruited, who recruited them? What did the "information packages" include? Was there only written information, or was oral information given and the opportunity of participants to ask questions about the study before giving informed consent?

Patients were recruited from three centres. Patients were referred by their respective nephrologists and we provided written standard information and consent forms. Patients were contacted by phone from the local investigative team and they were given opportunities to ask questions about the study prior to giving informed consent to attend the session. Patients could invite caregivers to attend the focus groups. This included contact information for participants to ask questions prior to giving consent.

27. "Patient and public involvement": I do see the patient involvement, but where is the public involved?

The project aims to elicit the perspective of patients and caregivers (family members). We have now made explicit that "The general public were not involved." (Page 7, paragraph 1 – marked copy).

28. Data collection: How was data saturation assessed?

This is expanded on in comment 18. We have now indicated that "data saturation was achieved when C.L, Y.C, and A.T agreed that little or no new concepts were arising from subsequent focus groups." (Page 7, paragraph 2 – marked copy)

29. Was the analysis started during data collection or afterwards?

Data analysis began after the data had been collected.

30. Were the whole transcripts translated or just the codes from the line-by-line coding? How was the quality of the translations ensured?

We have now made clearer that the analysis (including coding) were conducted in the original language of the transcripts by bi-lingual researchers who were fluent in the respective languages of the transcripts. This ensures that linguistic nuances are identified and captured in the analysis. The bi-lingual researchers (C.L, Y.C, B.S.) discussed the findings. Only the quotations presented in the manuscript were translated into English by bi-lingual researchers.

31. What "principles from grounded theory" were specifically used? Because the authors mentioned having used a combination of qualitative data analysis methods (grounded theory, thematic analysis), this needs more detailed elaboration.

As suggested, we have expanded the methods (analysis) section to include these details: "From grounded theory, we conducted initial coding (memoing) and line-by-line coding of the data, used constant comparison within and across the transcripts, and inductively identified concepts and themes. In accordance with thematic analysis, we identified initial concepts and grouped similar concepts into themes." (Page 8, paragraph 1 – marked copy).

32. Please specify what is meant by "investigator triangulation"

Three investigators (C.L., Y.C, B.S) identified concepts and coded the data and discussed the findings to ensure that the themes reflected the full breadth and depth of the data.

33. How many participants were in each focus group? Did the authors aim for diverse or similar demographics within the focus groups? Were the caregivers interviewed separately from the patients or were they mixed up? Were several members from the same family involved in the same focus groups?

We have now provided the number of participants in each focus group in a supplementary file. We aimed for diverse focus groups to ensure as broad an exchange of perspectives as was feasible, given that this also depended on the availability of the participants to attend the session at the scheduled time/date. Patients and caregivers were given the option to participate in separate/same groups; all preferred to participate in the same focus group together. Participants were invited to only invite one caregiver, and this was the case in multiple focus groups.

34. "Medicalizing family planning" and "Judging the value of life with ADPKD" seem to overlap importantly – please explain the difference better or consider merging those themes

We prefer to keep the themes separate as they have distinct concepts. Medicalizing family planning refers to how participants believed that clinicians communicated options for family planning options with a medical focus without consideration of the patient's personal priorities and circumstances. Patients reported that some clinicians advised against starting a family and instead wanted clinicians to discuss options. Judging the value of life with ADPKD refers to participants' perspectives on whether living with ADPKD could be fulfilling and worthwhile, which they considered in their decisions to start a family.

35. "Medicalizing family planning": did preimplantation genetic diagnosis not come up at all? If not that is a noticeable point to raise in the discussion, as it would uncover an information gap that seems to be consistent in all three countries

Preimplantation genetic diagnosis was not mentioned in the focus groups, but prenatal testing was mentioned, particularly by patients living in France. We have added that no participants mentioned preimplantation genetic diagnosis; "No participants mentioned pre-implantation genetic diagnosis which highlights an information gap between countries." (Page 15, paragraph 2 – marked copy). Nothing further was raised by the participants.

36. " We are uncertain about the transferability of the findings to other countries with different healthcare policies on testing." – I think the authors can be a little more confident regarding the transferability of findings, because they included participants from three different continents. As pointed out nicely in the discussion, some findings were depending on policy, but if I understood correctly, the themes and general theory (as illustrated in Figure 1) came from the merged experience from many different settings.

We will retain the statement as we recognize that it is not possible to include all countries and we cannot claim complete transferability of the findings globally. We confirm that the findings (themes) reflect the full range of experiences and perspectives from the different settings included.

37. " We acknowledge that testing can be a sensitive topic and some views may have been suppressed in the focus group setting which may also explain why there was limited variation in the perspectives of caregivers vs. patients." – Were there any signs of suppression, did the authors notice

themes that were suppressed or not that easy to cover? Having examples here would be very interesting.

The focus groups were facilitated in a way to encourage open and frank discussion (e.g. assurance of anonymity and confidentiality, respect for difference in opinion) and to allow all participants to voice their opinion. Based on verbal and non-verbal cues, we did not notice censorship from participants.

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VERSION 2 – REVIEW

REVIEWER	Howard Trachtman NYU Grossman School of Medicine USA
REVIEW RETURNED	23-Jul-2020

GENERAL COMMENTS	This is well done study and clearly written manuscript.