PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Disentangling the determinants of interest and willingness to pay for breast cancer susceptibility testing in the general population: A cross-sectional Web-based survey among women of Québec (Canada)
AUTHORS	Blouin-Bougie, Jolyane; Amara, Nabil; Bouchard, Karine; Simard, Jacques; Dorval, Michel

VERSION 1 – REVIEW

REVIEWER	G Georgiou Faculty of Medicine, University of New South Wales
REVIEW RETURNED	16-Mar-2017

GENERAL COMMENTS	An interesting, topical subject – though issues contained within this manuscript which need to be addressed. One of your keywords is genomics, yet there is no specific discussion about genomic technology. There is some reference to SNPs (though this term is not mentioned, just the acronym) – it would be important to expand upon on this idea. You refer to BCST at length, and yet there is no specific explanation of what this type of technology looks at. Perhaps some mention and further description of specific genes being tested for? There must be more explanation of SNPs if you are to include this in the Introduction, particularly as this is what would be specifically used in the case of BC prevention. Page 4 Line 50-51 'given that some of them' – Which of them? Needs further explanation. Your focus on willingness-to-pay is interesting, and is an important part of the future application of this technology. However, you do not specify amounts in the discussion – where is the exploration of how much people would pay, if in fact they are willing to pay, given your analysis in Table 2? Can more efforts be made to provide further description of your analyses provided in these tables within the paper? This should probably have been explored more if this is your focus. This will also help to substantiate the data being presented, as otherwise, we are left with very little quantitative information. Word count of Introduction and Background – can there be efforts made to reduce this? Slightly confused as to your inclusion of the lengthy discussion in the Background about the 'Genetic Home Reference'.

	This whole section could be condensed? It reads at times more as a description of this particular paper, repeating somewhat similar points to what has been presented in the Introduction, instead of summarising, and exploring the more recent data on this subject. Reflection on more recent references would be useful here. Methods: can you expand on the net response rate? Was there any particular model used to calculate this, and any recognised factors lowering this rate given that this is in fact low? At times, the tense changes – can this be checked ? eg from Methods to Results, past to present. Good points in discussion in terms of real-world limitations. Discussion of limitations Page 13 line 48 onwards could also be explored in limitations section? However, there needs to be further explanation of the possible bias that may have resulted in this particular population group. Interesting points in implications section, page 14 paragraph 1 – but needs further referencing ? What specific interventions might be utilised to improve knowledge and awareness? This may assist in the implications section also. Good point in Page 14 last paragraph on how findings may help delivering these services. Furthermore, I think this article would benefit from the inclusion of more recent articles, given the surge in interest in this particular area over the past 12 months? Some grammatical issues: concerns with some of the use of English in this paper – examples included: - Abstract Line 34 'pointed out to several' should read 'pointed out several'? - Page 3 Line 10 'allowing to test' should read 'allowing testing of ..' - Page 3 Line 22 'allowed to measure' should read 'allowed the measurement of ..'? - Page 3 Line 26 (and again in repeated sentence Page 13 Line 7) 'real sum…in a realistic' – doubling of 'real', remove one ? - Page 4 Line 24 'to get insights on' might read as 'in order to gain insight into the …' - Page 4 Line 56 'directly to consumers (DTC)' – need to be more specific as this particular acronym is technically 'direct-to-consumer' - Page 6 Line 18 'did not allow to understand' – not reading properly, 'study results did not allow an understanding of how …' - Page 6 Line 45 'leads to explore' should read 'position leads us to explore' or 'has led to the exploration of …' - Page 9 Line 49 'inform on' should read 'inform us about..' 'inform us on' 'inform the signs..' - Page 9 Line 57 'which could be useful in targeting for intervention the' does not read correctly ? - 'which could be useful in targeting the most influential factors regarding an intervention..' - Page 10 Line 46 'models lead to conclude' .. 'models lead us to conclude ..' or 'lead to the conclusion that ..' - Page 11 Line 35 'specific factors associated to..' should read 'specific factors associated with interest in ..' ? - Page 12 Line 28 'associated to' .. 'associated with' - Page 13 Line 23 'its individual expect' ? What do you mean by this exactly? - Page 13 Line 45 'associated to' .. 'associated with' and 'factors are important factors' – try another word to reduce repetition?

	Some referencing concerns: - page 4 line 8 ‘2,3’ not ‘eg 2,3’ ? - page 6 line 40 ’30,35’ ‘34’ not ‘eg 30,35’ ‘eg 34’ ? - page 8 line 16 ’31,37,38’ not ‘eg…’ ? - page 14 line 3 ‘eg 21,28,32’ … " " - page 14 line 37-38 why is ‘fully encouraged’ in <>?

REVIEWER	C Protière INSERM - France
REVIEW RETURNED	04-Jul-2017

GENERAL COMMENTS	This article is about interest and willingness to pay for BCST among the French-speaking women of the general population in Quebec – Canada. Despite it is an interesting topic, the manuscript suffer of a lack of contextual and methodological rigor and precision. It would have been useful to better define the public health rational and the policy context. Some potential useful references are included at the end of this review. Specific comments Introduction Has stated by the authors, genetic tests desirability have been studied since more than two decades. To this respect, it is important to contextualize the study regarding both literature and public health context. What is the rational for surveying women of the general population rather than women with a huge familial cancer history? What is the expected benefit to provide genetic test to the general population? Did the authors considered there is a need for more genetic tests in Quebec? A general overview of the delivery of genetic tests in Quebec is needed: how are these tests proposed and to which target population? The development about the relationship between interest and WTP is not very useful and the introduction can be shortened (see below). Methodology All the development of the relation between interest and WTP seems a bit redundant as it is the premise of any contingent valuation: a good or a service has a value for someone if she has an interest/utility for it. Concerning the statistical analysis, the two steps approach (at least Heckman model) is very classical in the CV literature, some references should be added. Moreover the CV methodology is poorly described, what is the elicitation tool used? What is the payment vehicle? The lack of those basic information do not allow to be convinced by the survey and then the results. There is no mention of any pilot test, what is it about? Providing and justifying the framing of the scenario should be useful. Why the genetic test was presented as an hypothetical existing one whereas they are already on the market? Discussion There is a lack of comparison of the resulys with the ones of the litterature Minor comments P3. ‘Strenghts and limitations of this study’: The highlighted points are very general and then not very informative.

	Moreover using marginal effects is just a better way to present the results but clearly not Background, p5: the variability in WTP values regarding population or health state seems to be considered as a problem, whereas it was an expected result according to the internal validity of CV. Data collection, p8: the data are quite ancient (2012) it could be explained. Statistical analysis: choosing a level of significance higher than 5% should be argued (in particular knowing the sample size). Results: income is presented p11 and p 12. Julian-Reynier C, Welkenhuysen M, Hagoel L, Decruyenaere M, Hopwood P; CRISCOM Working Group. Risk communication strategies: state of the art and effectiveness in the context of cancer genetic services. Eur J Hum Genet. 2003 Oct;11(10):725-36. Review. Julian-Reynier CM, Bouchard LJ, Evans DG, Eisinger FA, Foulkes WD, Kerr B, Blancquaert IR, Moatti JP, Sobol HH. Women's attitudes toward preventive strategies for hereditary breast or ovarian carcinoma differ from one country to another: differences among English, French, and Canadian women. Cancer. 2001 Aug 15;92(4):959-68. 1 Protière C, Chanel O, Nogues C, Coupier I, Mouret-Fourme E, GENERPSO cohort I, et al. How Can Contingent Valuation Inform the Bioethics Debate? Evidence from a Survey on Hereditary Cancers in France. Rev Econ 2017; 68:333–354. Protière C, Chanel O, Nogues C, Coupier I, Mouret-Fourme E, GENERPSO cohort I, et al. How Can Contingent Valuation Inform the Bioethics Debate? Evidence from a Survey on Hereditary Cancers in France. Rev Econ 2017; 68:333–354.

REVIEWER	Eliza Courtney National Cancer Centre Singapore 11 Hospital Drive Singapore 169610
REVIEW RETURNED	12-Jul-2017

GENERAL COMMENTS	1) Methods: 1a) This study is based on an assumption that interest is a prerequisite of willingness to pay, however, you didn't justify why you used this assumption. Please address this (lines 40-42). 1b) Can you please explain why the cut off for objective and perceived risk of breast cancer is 15%? Given the population risk is 11-12%, would it not make more sense to use a cut off around population risk to delineate between those who are at or above population risk? 2) Ethics: I cannot see mention of ethics approval or the consent process for the included participants. 3) STROBE table: page numbers and table numbers seem to be incorrect. E.g. for item #14 (descriptive data), it states page 9 and Table 2 - I believe it is page 10 and Table 1. 4) Grammar, wording and abbreviations: 4a) Please ensure 'BCST' is correctly abbreviated throughout the document (it sometimes is written 'BSCT'). 4b) Please refer to line 12 on page 5 - please explain this sentence regarding cost-effectiveness and recent literature. 4c) Please refer to line 42 on page 5 - please explain why adding the GHR webpage here is necessary.

	4d) Please check through document for English grammar/wording - there are a few mistakes. 5) Results - Please add 'Family history of BC' as a demographic variable to Table 1. I understand this will typically correlate with 'Objective risk of BC', but not always. It would be an important variable for comparing with other studies. 6) Discussion 6a) Please refer to line 31 on page 13 in the Discussion - as you are discussing participants from a population who have access to universal healthcare schemes, it may be worthwhile to discuss how they may be similar/different in populations lacking universal healthcare schemes. 6b) Please refer to line 40 on page 15 - I think this point regarding the association between income and interest/WTP needs further thought and comment based on the literature. Is it that, people with higher incomes may overestimate their risk? In other words, are there other confounding variables that are associated with income, that mean that it appears to be correlated with interest/willingness to pay? It would be worthwhile to just expand on this further, as it would be an interesting area to explore in further research.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

An interesting, topical subject – though issues contained within this manuscript which need to be addressed.

One of your keywords is genomics, yet there is no specific discussion about genomic technology.

Response: We chose «genetics and genomics» as the primary subject heading at first on the list provided in the submission system as our article concerns genetic susceptibility testing for breast cancer. We were then more precise with the secondary subject headings available in including: oncology, public health, and health services research.

As we understand your concern about genomic technology, we propose to change our primary subject heading to «Public Health» given that BCST is discussed for this particular population, and place «Genetics and genomics» as the secondary subject heading.

«Genomics» is however not one of our keywords, which are: «Interest; Willingness-to-pay; Breast cancer susceptibility testing; Women of the general population». We think that these keywords clearly represent what the subject of our article is, given that they respectively correspond to the two dependent variables assessed, the type of genetic test discussed and the disease for which it is used as well as to whom it may possibly be proposed.

Comment: There is some reference to SNPs (though this term is not mentioned, just the acronym) – it would be important to expand upon on this idea.

Response: We added brief information on what SNPs are (vs mutations) in the Introduction:

«Fourthly, several mutations (i.e., rare genetic variations) on different genes and polymorphisms (i.e., SNPs: common genetic variations present within particular sub-populations) are now known as BC susceptibility risk factors and can be detected simultaneously with recent technologies (e.g., next-generation sequencing, panel-gene testing).» 21-24

Comment: You refer to BCST at length, and yet there is no specific explanation of what this type of technology looks at.

Response: We added more information on what we mean by BCST in the Introduction:
«In this paper, we refer to BCST as genetic tests (i.e., carrier or predictive testing) that lead to the identification of genetic variants that substantially increase BC risk.»

Comment: Perhaps some mention and further description of specific genes being tested for?
There must be more explanation of SNPs if you are to include this in the Introduction, particularly as this is what would be specifically used in the case of BC prevention. Page 4 Line 50-51 'given that some of them' – Which of them? Needs further explanation.

Response: We added some information on this type of genetic test in the Introduction of the paper and provided some examples of genes that confer various BC risk levels:
«Some genetic variants are associated with greater risks than others. For instance, a mutation on BRAC1, BRCA2, TP53 or PTEN confers a high risk, as a mutation on CHECK2, PALB2 or ATM confers a moderate risk of developing BC. »22-24
We also provided useful references to readers who may want to know more about genetic variants, recognized as being involved in the development of BC (i.e., Couch et al., 2014 and Evans & Howell, 2015; Easton et al., 2015).
However, we do not think that adding more detailed information about genetic markers may provide more comprehensiveness to readers. We really want to focus on the fact that the genetic knowledge base about BC allows to more precisely assess BC risk and opens the door to genetic stratification population-based screening, which might be partly possible because particular genetic markers confer different risk levels.
We do not propose to assess the interest or the WTP of a specific and new genetic test, given that which genetic variants (BRAC 1 or 2 PT53, CHECK2, ATM, PALB2, RAD51C, etc.) should be included in this test are still under evaluation for the general population. However, there is a particular interest for personalized medicine through a risk stratification approach from public health authorities as well as scientists. We think that, before moving on with the development of population-based screening or the expansion of genetic tests dedicated to assess BC susceptibility in the general population, getting the point of view of the end-user is necessary and useful.

Comment: Your focus on willingness-to-pay is interesting, and is an important part of the future application of this technology. However, you do not specify amounts in the discussion – where is the exploration of how much people would pay, if in fact they are willing to pay, given your analysis in Table 2? Can more efforts be made to provide further description of your analyses provided in these tables within the paper? This should probably have been explored more if this is your focus. This will also help to substantiate the data being presented, as otherwise, we are left with very little quantitative information.

Response: We did not want to be redundant as we detailed this information in Table 1. We however expand a little further on how much people would pay in the discussion:
«Indeed, nearly 35% of the women of our sample would pay up to $100, 15% up to $250, and only 7% more than $250. It is however important to note that a great proportion of them were not willing to pay (24%) or did not provide information on the survey item assessing their WTP for BCST (18% of missing data).»

Comment: Word count of Introduction and Background – can there be efforts made to reduce this? Slightly confused as to your inclusion of the lengthy discussion in the Background about the 'Genetic Home Reference'. This whole section could be condensed?

It reads at times more as a description of this particular paper, repeating somewhat similar points to what has been presented in the Introduction, instead of summarising, and exploring the more recent data on this subject. Reflection on more recent references would be useful here.
Response: We have substantially reduced the background section as proposed while adding, as suggested by reviewers, information on context and BC susceptibility risk factors. Overall, the Introduction and background sections are ~ 1060 words as the first version was of 1340 words.

We notably used two streams of studies, one on WTP for Dx technologies and another on interest for genetic testing that have drawn conclusions for diverse populations, diseases, and tests (including genetic testing). They helped us identify gaps in the literature on interest and WPT for genetic tests. The classification of explanatory variables, identified for cancer susceptibly testing specifically, is inspired by the findings of these two streams (see the literature review in Appendix 1). We revised this section and proposed numerous specifications on individual variables assessed for cancer genetic susceptibility testing in Appendix 2.

Comment: Methods: can you expand on the net response rate? Was there any particular model used to calculate this, and any recognised factors lowering this rate given that this is in fact low?

Response: We prefer to leave this point on risk perception in the potential implications sub-section for space constraints but, especially, for its link with the other results and the implications for more education about the familial and genetic component of BC within the general population.

Comment: However, there needs to be further explanation of the possible bias that may have resulted in this particular population group.

Response: We added more information on a possible bias as requested in the Discussion (Potential implications second paragraph). It now reads as:
«It is worth mentioning, firstly, that women's interest in and WTP for BCST should be analyzed in light of another important finding: women greatly overestimated both their personal lifetime risk of developing BC and that of women of the general population. Similar results were also found in other populations.58-60 This overestimation may be due to a lack of knowledge, a low level of numeracy or otherwise unrealistic worries about BC.58-60 In addition, as reported by other studies,26 52 more anxious, less optimistic women and those with poor numeracy skills are more interested in BCST and thus, will probably more extensively use such services. This may suggest that some moderating psychosocial variables enacted throughout the women's decision process to get tested or not. Moreover, it could result in a biased level of interest in and WTP for BCST…»

Comment: Interesting points in implications section, page 14 paragraph 1 – but needs further referencing ? What specific interventions might be utilised to improve knowledge and awareness? This may assist in the implications section also. Good point in Page 14 last paragraph on how findings may help delivering these services.

Response: We provided examples and more references in the Discussion (Potential implications fourth paragraph). It is now read as follows:
«These facts lead, as others proposed,11 26 33 to reiterate the necessity to put a stronger emphasis on popular education, and to develop educational material toward genetics and the notion of risk to ensure that the choice of getting tested for BC susceptibility is made following an informed decision-making process, and based on more objective and realistic risk perceptions of BC. As a starting point, we suggest that some lessons learned from public health and charity organization messages and decision aids (e.g., information from leaflet or web page, communication campaigns, and other health promotion strategies) about cancer screening65 66 may serve as a building block for the dissemination of BCST information among the general population.

Moreover, the literature on BC risk communication may provide important cues on the most comprehensive ways risk and genetic information should be transmitted to women of the general population.67 68 For instance, explaining to women how family history impacts on their risk among other risk factors, stating clearly the prevalence and risk of BC from a genetic point of view, or clarifying the benefits and consequences of being tested for BC susceptibility, might improve women's awareness and knowledge of BCST, may reduce anxiety or worries about BC risk or even motivate some of them to seek out more information about their BC risk. Interventions improving knowledge and awareness, as well as fostering objective BC risk evaluation, have the potential to improve ethical and informed decision-making,65 66 but may also slightly decrease interest in and WTP for BCST.11 33 34 »

Comment: At times, the tense changes – can this be checked ? eg from Methods to Results, past to present.

Response: We have harmonized verb tenses as requested.

Comment: Some grammatical issues: concerns with some of the use of English in this paper – examples included:
Thanks a lot for helping us with some English wording issues. The manuscript has been entirely revised.

- Abstract Line 34 'pointed out to several' should read 'pointed out several'? Done.
- Page 3 Line 10 'allowing to test' should read 'allowing testing of ..' Done.
- Page 3 Line 22 'allowed to measure' should read 'allowed the measurement of ..'? Done.
- Page 3 Line 26 (and again in repeated sentence Page 13 Line 7) 'real sum…in a realistic' – doubling of 'real', remove one ? Done.
- Page 4 Line 24 'to get insights on' might read as 'in order to gain insight into the …' Done.
- Page 4 Line 56 'directly to consumers (DTC)' – need to be more specific as this particular acronym is technically 'direct-to-consumer' Corrected.
- Page 6 Line 18 'did not allow to understand' – not reading properly, 'study results did not allow an understanding of how …' Done.
- Page 6 Line 45 'leads to explore' should read 'position leads us to explore' or 'has led to the exploration of …' Removed.
- Page 9 Line 49 'inform on' should read 'inform us about..' 'inform us on' 'inform the signs..' Done.
- Page 9 Line 57 'which could be useful in targeting for intervention the' does not read correctly ? - 'which could be useful in targeting the most influential factors regarding an intervention..' Done.
- Page 10 Line 46 'models lead to conclude' .. 'models lead us to conclude ..' or 'lead to the conclusion that ..' Done.
- Page 11 Line 35 'specific factors associated to..' should read 'specific factors associated with interest in ..' ? Done.
- Page 12 Line 28 'associated to' .. 'associated with' Done.
- Page 13 Line 23 'its individual expect' ? What do you mean by this exactly? Changed as requested. The sentence now reads as:
«The findings of this study provide a proxy for the readiness of women of the general population of Québec to get genetically tested for BC susceptibility and the amount they expect to be acceptable to pay for such services in private settings and DTC genetic testing.»
- Page 13 Line 45 'associated to' .. 'associated with' and 'factors are important factors' – try another word to reduce repetition? Changed as requested. The sentence now reads as : « Furthermore, the results suggest that many psychosocial factors are associated with women's interest in and WTP for BCST.»

Response: Furthermore, I think this article would benefit from the inclusion of more recent articles, given the surge in interest in this particular area over the past 12 months?

Comment: We added several references and most of them were published in the last 3 years. See those in yellow in the list of references.

Response: Some referencing concerns:
- page 4 line 8 ‘2,3’ not ‘eg 2,3’ ?
- page 6 line 40 ’30,35’ ‘34’ not ‘eg 30,35’ ‘eg 34’ ?
- page 8 line 16 ’31,37,38’ not ‘eg…’ ?
- page 14 line 3 ‘eg 21,28,32’ … " "
- page 14 line 37-38 why is ‘fully encouraged’ in <>?

Comment: All changes were made according to your recommendations.

Reviewer 2

Comment: This article is about interest and willingness to pay for BCST among the French-speaking women of the general population in Quebec – Canada. Despite it is an interesting topic, the manuscript suffer of a lack of contextual and methodological rigor and precision. It would have been useful to better define the public health rational and the policy context. Some potential useful references are included at the end of this review.

Response: We agree that public health rationale and policy context would have been relevant to include and to detail. At first, we opted for a general introduction as Canada faces some similar challenges regarding personalized medicine as other developed countries in the context of BC. Important reasons are:
- Mutations and SNPs that should be tested and included in a genetic test offered to the general population are still under evaluation.
- No country has currently implemented such a test and determined the modalities needed to support its offering in the general population.

Nevertheless, we revised this section to provide more specifications and references on the Québec/Canadian context.
For the second part of your comment: We added numerous methodological elements through the paper (see below and the references in yellow).

Comment: Has stated by the authors, genetic tests desirability have been studied since more than two decades. To this respect, it is important to contextualize the study regarding both literature and public health context. What is the rational for surveying women of the general population rather than women with a huge familial cancer history?

Response: We added precisions about the Canadian context as proposed and why it is of interest for the general population (Please, see the Introduction). Some of the important reasons are:
- «Secondly, beside the identification of at-risk women, BCST aims to provide suitable risk-management recommendations adapted to women’s BC risk level and preferences (e.g., type and interval of screening - mammograms or MRI - or consideration of prophylactic interventions - mastectomy or chemoprevention)».10 17 18
- «Stratifying healthy women’s BC risk is thus viewed, in Canada and overseas, as an opportunity to adapt BC screening programs for maximizing benefits and minimizing drawbacks in the general population and the health care systems in a foreseeable future»7 9 12 21 25

Other arguments and precisions would have been added, but reviewers also asked to shorten the Introduction. So, we present the main aspects only.

Comment: What is the expected benefit to provide genetic test to the general population?

Response: This point is, in our view, more clearly explained throughout the Introduction that we have revised.

Comment: Did the authors considered there is a need for more genetic tests in Quebec?

Response: The need or the cost effectiveness issues for more genetic tests in Québec or Canada, targeting the general population, is not finally stated yet, but it is being discussed by scientists and decision makers; we added references. (see, for example: RSSPQ, 2013; Gouvernement du Canada, 2015; Foulkes et al., 2016; Dent et al., 2013; Burton et al,. 2014; Easton et al,. 2015)

Comment: A general overview of the delivery of genetic tests in Quebec is needed: how are these tests proposed and to which target population?

Response: These types of tests are not proposed to the general population while it is anticipated in a relatively near future. Information regarding genetic tests delivery in Québec and Canada was added in the paper where relevant. See the revised introduction. Here are specific elements as examples :

- «…these genetic tests are currently used in highly-specialized genetic clinics…»
- «… in Canada - as in other countries - BCST are only offered to some newly diagnosed BC patients and their relatives, and to those with a strong BC family history.»
- «… fees would not necessarily be charged as genetic tests requiring blood testing are generally covered by the public health insurance system in Canada once approved by authorities»
- « In Canada, health care services are managed at a provincial level, and health care systems are publicly-funded, while there are some private health care delivery channels (e.g., private clinics, complementary private insurance market).»

We shortened the Background section as much as possible, without omitting relevant information on the conceptual and methodological basis that guides the rationale of the empirical part of the paper.

Comment: Background, p5: the variability in WTP values regarding population or health state seems to be considered as a problem, whereas it was an expected result according to the internal validity of CV.

Response: We agree with this comment. In fact, the problem we raised is about the theoretical foundation available for the particular topic of our article. Recent reviews on interest and WTP underlined variability between populations, diseases, and tests. They were also informative in identifying gaps for genetic testing in general. However, we cannot just extrapolate their results for the target population in our study.
As we are interested in the particular case of cancer susceptibility tests, we realised a literature review on this particular topic (Appendix 1) and used it to identify variables that should be included in the analysis (Appendix 2). We have modified the Introduction and the Background section. In our view, it is clearer now.

Comment: All the development of the relation between interest and WTP seems a bit redundant as it is the premise of any contingent valuation: a good or a service has a value for someone if she has an interest/utility for it.

Response: Again, we agree with your comment about the fact that interest is a premise of WTP. For this reason, we adopted a two-step sample-selected model. As mentioned previously, we significantly shortened the Background section without omitting relevant information on the conceptual and methodological basis that guides the rationale of the empirical part of the paper.

Comment: Concerning the statistical analysis, the two steps approach (at least Heckman model) is very classical in the CV literature, some references should be added.
Response: We added some references regarding sample-selected models we used : Greene et al., 2010; Hanmer et al., 2013; Saha et al., 1997; D'este et al., 2016)

Comment: Moreover the CV methodology is poorly described, what is the elicitation tool used? What is the payment vehicle? The lack of those basic information do not allow to be convinced by the survey and then the results.

Response: We add more information on this point in the survey section, notably on the description of the scenario presented to women: « A hypothetical scenario is presented to women indicating that a new genetic test now available on the market could be used to assess their BC risk, and to adapt their screening modalities if their risk level is higher than the one of the general population. The respondents are also advised of its hypothetical nature, and that fees should not necessarily be charged as genetic tests requiring blood tests are generally covered by the public health insurance system in Canada, once approved by authorities. No specifications on the modalities under which this test could be offered or on the genes being assessed by this test was provided to the participants as more research is needed, regarding variants that should be included in a BCST targeting women of the general population.8 24 Following that, respondents are firstly asked to rank their level of interest to get this test on 5-point Likert scale. They were thereafter asked how much they would be willing to pay out of their pocket for this test on an ordinary scale. Detailed information regarding operational measures of outcomes and explanatory factors, including coding and main references, is presented in Appendix 2.
We also added some limits in the discussion regarding the measurement of WTP.

Comment: There is no mention of any pilot test, what is it about?

Response: The questionnaire was pre-tested with eligible women, as mentioned in the Methods section when describing the data collection.

Comment: Providing and justifying the framing of the scenario. Why the genetic test was presented should be useful as an hypothetical existing one whereas they are already on the market?

Response: Breast cancer susceptibility testing is currently offered to high-risk women only (those with a strong family history of breast cancer) within oncogenetic clinics, and especially ill patients and their relatives. The tests proposed within these settings mostly assessed high (e.g., BRAC1/2) and some moderate penetrant genes (e.g., CHEK2 or PT53). However, we know that some low penetrant genes (polymorphisms, i.e., SNPs), taken together, could have an impact on the likelihood of developing BC. And, given that all these genetic markers are associated with different levels of risk, it is possible to propose some genetic tests (e.g., panel genes testing) that would allow identifying mutation carriers within the general population and assessing more precisely BC risk, and then propose some adapted risk management strategies as exposed at the beginning of the paper. This type of genetic tests could be offered into a public health care program that is, for example, harmonized with the current breast cancer screening program. Up to now, those services are in development and are not offered to the population, but health care authorities are interested in knowing more about this possibility. Which combination of genetic variants should be included in BCST dedicated to women in the general population, if we go further in this way, is not yet determined.
Moreover, despite a few private companies offering BC genetic tests, they only test some particular variants and genes, and these may vary from company to company. Some of them are among a panoply of low penetrant genes (SNPs) that taken alone are not very informative of one's BC risk and for risk management recommendations. That is why we proposed a hypothetical scenario. We added information about those elements in the Introduction of the paper.

A hypothetical scenario was often used in previous studies. We added this information in the Discussion section.

Comment: Data collection, p8: the data are quite ancient (2012) it could be explained.

Response: Even if the data were collected 4 years ago, we think that they are still relevant, given that BCST is not yet implemented nor provides to women of the general population. Moreover, BC risk management recommendations have not changed since the time we have collected those data.

Comment: Statistical analysis: choosing a level of significance higher than 5% should be argued (in particular knowing the sample size).

Response: We understand this concern that is, as contended by Noymer (2008), more serious in large data sets (thousands of observations or more). In such data sets, it is not uncommon for nearly every test to be significant at the alpha '0.05' level; therefore, the more stringent level of '0.01' is often used (or even '0.001' in some instances). In our paper, the number of valid cases included in the econometric models are not very large (i.e., INTER n= 635; WTP n = 544). Thus, it may make sense to choose '0.1' for alpha,
Moreover, there is no authoritative reference for using 5% as a significance level. There are eminent statisticians as Neyman & Pearson (1933) and Fisher (1956) who contended that the level of significance has to be chosen based on the whole context (scientific, academic, aims, limitations..).
Other reasons that support our choice of a less stringent level of significance are:

- The psychosocial nature of the majority of the variables included in the models and the complex interaction they have together. A more conservative alpha might hinder some significant results that might be interesting for further empirical investigation.
- 10% is widely accepted in social sciences empirical literature.

Nevertheless, we reported, for each variable, the level of significance commonly used in the empirical literature (.10, 0.05, and 0.01), and the majority of the results reported are significant at 0.01. We added a comment and references under Table 2 regarding this concern for the readers who want to know more about that still ongoing debate (Lispey, 1990; Fisher, 1956; Noymer, 2008)

Comment: Results: income is presented p11 and p 12.

Response: On page 11, we presented the common explanatory factors of interest and WTP (based on the significant coefficients in the two models), whilst on page 12, we presented the most impactful factors on WTP (marginal effects, which were calculated only for significant variables). We presented our results according to the objectives of our research.

Comment: There is a lack of comparison of the resulys with the ones of the literature

Response: We added references and elements of discussion in this particular section (see text in yellow). Moreover, a reader can easily use the synthesis of the literature review in Appendix 1. See also the references added (in yellow, in the Reference section).

Comment: P3. ‘Strenghts and limitations of this study’: The highlighted points are very general and then not very informative.

Response: We added more details in this section as requested.

Comment: Moreover using marginal effects is just a better way to present the results but clearly not

Response: Given that we did not receive your full comment on this point, we are not sure what you mean. Here is a tentative answer to your potential concerns regarding elasticities and marginal effects:
We removed the expression «hierarchization» in order to avoid confusion. Moreover, we added more information («Marginal effects can be an informative means for summarizing how change in a response is related to change in a covariate») as well as references on marginal effects and the econometric models used as mentioned above, in the Methods section.

Comment: Julian-Reynier C, Welkenhuysen M, Hagoel L, Decruyenaere M, Hopwood P; CRISCOM Working Group. Risk communication strategies: state of the art and effectiveness in the context of cancer genetic services. Eur J Hum Genet. 2003 Oct;11(10):725-36. Review
Julian-Reynier CM, Bouchard LJ, Evans DG, Eisinger FA, Foulkes WD, Kerr B, Blancquaert IR, Moatti JP, Sobol HH. Women's attitudes toward preventive strategies for hereditary breast or ovarian carcinoma differ from one country to another: differences among English, French, and Canadian women. Cancer. 2001 Aug 15;92(4):959-68.
Protière C, Chanel O, Nogues C, Coupier I, Mouret-Fourme E, GENERPSO cohort I, et al. How Can Contingent Valuation Inform the Bioethics Debate? Evidence from a Survey on Hereditary Cancers in France. Rev Econ 2017; 68:333–354.
Protière C, Chanel O, Nogues C, Coupier I, Mouret-Fourme E, GENERPSO cohort I, et al. How Can Contingent Valuation Inform the Bioethics Debate? Evidence from a Survey on Hereditary Cancers in France. Rev Econ 2017; 68:333–354

Response: Thanks, we used one of these.

Reviewer 3

Comment: 1) Methods:
1a) This study is based on an assumption that interest is a prerequisite of willingness to pay, however, you didn't justify why you used this assumption. Please address this (lines 40-42).

Response: We added this information in the Background section as requested: « Consistent with the economic theory,33 36 37 which supposes that a person’s decision is a sequential process «where the decision of whether or not to consume a particular commodity is followed by the choice of how much to consume»,37 we propose a two-step model where WTP is conditional on interest.»

Comment: 1b) Can you please explain why the cut off for objective and perceived risk of breast cancer is 15%? Given the population risk is 11-12%, would it not make more sense to use a cut off around population risk to delineate between those who are at or above population risk?

Response: We chose this cut-off risk for the following reasons:
- Respondents were more inclined to provide a round up BC risk estimate than a really specific one such as 11 or 12%.
- 15% is still in the range of the risk of the population.
- Objective risks calculated with risk prediction models do not use absolute risk, but instead pure cumulative risk (when no competing mortality risk exists). The pure risk is often higher than the absolute risk. 15% pure cumulative risk corresponds, approximately, to 11 to 12% absolute risk
- The objective risk measure was not included in our analysis, but we think that this information is relevant to readers for comparison with the perceived risk measure.
- The perceived risk measure presented in Table 1 was presented with the same cut-off of objective risk (15%) as it seems to us more intuitively comparable with the measure of objective risk. However, perceived risk was included in our analysis as a continuous measure (See Appendix 2).
We added a note and a reference for readers regarding the cut-off of objective risk under Table 1.

Comment: 5) Results - Please add 'Family history of BC' as a demographic variable to Table 1. I understand this will typically correlate with 'Objective risk of BC', but not always. It would be an important variable for comparing with other studies.

Response: Done. We added this information in Table 1.

Comment: 6) Discussion
6a) Please refer to line 31 on page 13 in the Discussion - as you are discussing participants from a population who have access to universal healthcare schemes, it may be worthwhile to discuss how they may be similar/different in populations lacking universal healthcare schemes.

Response: We provided, in the first version of the manuscript, some useful insights, though general, to interpret the results (openness to copayments, payment in private settings and DTC genetic testing, insights on the willingness to collectively pay…). In this revised version, we added more information in the discussion about the Canadian health care system that might be helpful for the interpretation of the results on the women's WTP.
See the text in yellow - first paragraph in the Potential implications section.

Comment: 6b) Please refer to line 40 on page 15 - I think this point regarding the association between income and interest/WTP needs further thought and comment based on the literature. Is it that, people with higher incomes may overestimate their risk? In other words, are there other confounding variables that are associated with income, that mean that it appears to be correlated with interest/willingness to pay? It would be worthwhile to just expand on this further, as it would be an interesting area to explore in further research.

Response: We added more information on this point as requested. (Potential implication last paragraph)
It now reads as : « Lastly, considering that the study's results indicated that interest in and WTP for BCST increased with income, which was also pointed out by previous studies on genetic testing,33 57 interventions designed for women from lower-resourced neighbourhoods or targeting physicians with a large panel of women with low income could prevent some inequalities in the uptake of BCST (e.g., health or life insurances and employment discrimination, limited access to health services given the cost (if the test is pay out of pocket or partially reimbursed by private insurances) or the way the risk assess, i.e., the risk factors considered, notably age, ethnicity, and family history).72 73 Moreover, the link between income and interest in BCST should be deeply assessed in future studies as inconsistent findings are underlined in the literature on cancer susceptibility testing with relating concepts. For instance, previous authors found mixt results regarding its association with the socio-economic status.33 61 62 As this concept reflects more broadly family or household resources, including education, employment, goods and revenues, one hypothesis may be that some confounding or moderating variables are involved into the decision-making process of women opting or not for BCST. »

Comment: 2) Ethics: I cannot see mention of ethics approval or the consent process for the included participants.

Response: We added, at the end of the manuscript ,the following sentences:
«This study was approved by the Comité d'éthique et de la recherche du CHU de Québec-Université Laval (#2012-1584/2012-HSS-300-05).»

Comment: 3) STROBE table: page numbers and table numbers seem to be incorrect. E.g. for item #14 (descriptive data), it states page 9 and Table 2 - I believe it is page 10 and Table 1.

Response: We totally agree with you and we apologize! We revised this table as requested and we made the necessary adjustments in the manuscript.

Comment: 4) Grammar, wording and abbreviations:
4a) Please ensure 'BCST' is correctly abbreviated throughout the document (it sometimes is written 'BSCT'). Done
4b) Please refer to line 12 on page 5 - please explain this sentence regarding cost-effectiveness and recent literature.

Response: We removed this sentence as we revised and shortened the Introduction as requested by other reviewers. This sentence meant to reflect the idea that most studies have assessed WTP values in relation with treatment options. However, in the case of cancer susceptibility testing, if the women's risk level was not high enough, they could just get information on their risk with no adjustment or recommendation of risk management strategies.
This sentence was replace by:
« Previous studies have shown that women might demonstrate interest in and willingness to pay for genetic testing even it is not associated with treatment options, as genetic test results may reduce uncertainty, offer some reassurance, guide life or family planning decisions, and may be useful to other family members.» 11 30-32

Comment:
4c) Please refer to line 42 on page 5 - please explain why adding the GHR webpage here is necessary.

Response: We removed this link as we revised and shortened the Introduction section.

Comment: 4d) Please check through document for English grammar/wording - there are a few mistakes.

Response:
The paper was revised for English.

VERSION 2 – REVIEW

REVIEWER	Protiere, Christel INSERM, SESSTIM
REVIEW RETURNED	25-Oct-2017

GENERAL COMMENTS	General comments The manuscript improved compared to the previous version. However, I always have a few points for the authors to consider, in particular regarding the methodological aspects. Specific comments Abstract: To be more balanced Introduction 2nd §: Please distinguish between points specific to Quebec (Canada) to the not specifics ones.

	The three lasts sentences are not very informative for the scope of the manuscript. Background A lack of theoretical foundation, from previous surveys, is pointed out. Please specify this point. Did really Lin et al. (2013) considered that “previous study results did not allow an understanding of how preferences and WTP values vary according to individual factors, nor tried to present the magnitude of their impact”. What about some more recent surveys? Perhaps the assumption should be more qualified and specified. Methods Data collection: Has the pilot survey conducted to any change? Measure: Please can you provide in appendix 2 the exact framing of the WTP question (including the way respondents were informed “that fees would not necessarily be charged as genetic tests requiring blood testing are generally covered by the public health insurance system in Canada, once approved by authorities”, and of the payment vehicle (out of pocket). Please clearly state, the protocol used: including if respondents who answered “not interested at all” were or not asked the wtp question, the way you have considered wtp values for this specific population (missing value or equal to zero) and please discuss the implication of the rule you have adopted. Statistical analysis Please rewrite your model: Z is not present in your equations As written, the model does not allow to understand whether you have or not used an Heckman approach. More over it looks like you have performed two independent (logit) models and not a conditional analysis. Please explain why you presented marginal effects and not aOR (adjusted Odds Ratio), knowing you have used logit and not probit for example. Please specify the software you have used and the command. The two last § do not present particular interest, and may be suppressed to better explain your statistical analysis Please explain the rational of using only 3 class for the WTP, and of not using the middle of the class for example. Please add in the discussion section a point regarding the impact of not taking into account the censured nature of the WTP data. Results Descriptive statistics A cross tab between INTER and WTP could be informative Please detail the distribution of the 191 missing value for the WTP variable Ordered logit regressions The first § is not very instructive and should be included in the legend of the tables. Discussion Some interpretations of the results are expected, the 1st paragraph is too descriptive and similar to the paragraph in the result section. If there is a large number of references, there is a lack of theoretical and methodological perspective between the literature and the results. For example, what are the implication of the impact of the BC family history, or what should be the interpretation of the lowest interest in for women with a lower income.

	Did economic theory said anything between income and WTP values? Potential implication If the authors are interested in a collective payment, why did they chose an out of pocket payment and not an insurance premium or a contribution? I'm not clear with the argument saying that the results can provide insight about a collective payment.

VERSION 2 – AUTHOR RESPONSE

General comments
The manuscript improved compared to the previous version. However, I always have a few points for the authors to consider, in particular regarding the methodological aspects.

Response: Thank you once again for your comments. They help us very much to improve the manuscript, and especially to clarify the methodological section.

Comment: Abstract:
To be more balanced

Response: Done: We revised and shortened the abstract.

Comment: Introduction
2nd §: Please distinguish between points specific to Quebec (Canada) to the not specifics ones.

Response: Done: We proposed more finely tuned information on the Canadian context in the introduction by adding a sub-section entitled: BC Prevention in the Canadian context.
We tried to gather all information on the Canadian context that was presented through out the different sections of the paper into this new section to avoid, as much as possible, redundancy in other sections of this manuscript.

Comment: The three lasts sentences are not very informative for the scope of the manuscript.

Response: Done: The last three sentences were removed.

Comment: Background
A lack of theoretical foundation, from previous surveys, is pointed out. Please specify this point.

Response: Done: We added more information on this point in the background section. It is worth noting that other reviewers have asked to shorten this section in the previous version. We tried to be as concise as possible while explaining the main elements identified in previous studies that have guided our analysis.

Comment: Did really Lin et al. (2013) considered that "previous study results did not allow an understanding of how preferences and WTP values vary according to individual factors, nor tried to present the magnitude of their impact". What about some more recent surveys?
Perhaps the assumption should be more qualified and specified.

Response: We used some parts of the text (discussion) of Lin et al. to build that argument. For example: «Despite numerous cost-utility analyses demonstrating good value for money of many laboratory diagnostic tests, relatively little has been published characterizing preferences for test information in detail—specifically, how preferences vary by patient factors, the condition being evaluated, or the diagnostic modality. Our review suggests that at the individual level, differences in risk perception, risk tolerance, and personal or family/acquaintance history may make some individuals more willing to pay larger amounts of money to identify whether they have a disease or risk factor. … Our findings also shed light on discrepancies in preferences for and value of test information with respect to individual characteristics, the disease in question, as well as the performance characteristics of the test.»
(Lin et al., 2013: 803)
We revised the formulation of this idea to be more specific, and as the background section was slightly modified.

Comment: Methods
Data collection: Has the pilot survey conducted to any change?

Response: Done: We added more information related to this point in the methods section. The questionnaire was validated by experts in familial BC and genetics, and pre-tested by the survey firm with 20 eligible women in February 2012. Their comments were collected in-person or by telephone and minor changes were made to the questionnaire to improve understanding.

Comment: Measure:
Please can you provide in appendix 2 the exact framing of the WTP question
(including the way respondents were informed “that fees would not necessarily be charged as genetic tests requiring blood testing are generally covered by the public health insurance system in Canada, once approved by authorities”, and of the payment vehicle (out of pocket).
Please clearly state, the protocol used: including if respondents who answered “not interested at all” were or not asked the wtp question, the way you have considered wtp values for this specific population (missing value or equal to zero) and please discuss the implication of the rule you have adopted.

Response: Done:
We added more information in this section regarding the measure of interest and WTP, as well as the presentation of the scenario used in the analysis in this article (either in the text and the appendix).

We mentioned clearly that all respondents who have indicated to be “Not at all interested” in BSCT were not asked about their WPT, and therefore they were not included in the second model (WTP model).

All information on missing data was available in Appendix 2. We also added information on this measure under the new Table 2, notably for the distribution of the 191 missing on the WTP measure.

Comment: Statistical analysis
Please rewrite your model: Z is not present in your equations

Response: Done: We provided a better-detailed statistical description of ordered logit models.

Comment: As written, the model does not allow to understand whether you have or not used an Heckman approach. Moreover it looks like you have performed two independent (logit) models and not a conditional analysis.

Response: You are absolutely right! To avoid any confusion, we clarified our analytical approach that consists of the estimation of two independent ordered logit regressions. We also provided justification to why we did not use Heckman's two-step sample selection procedure in a note at the bottom of the corresponding page.

This justification reads as follows: « The two models were estimated separately even though our approach might resemble Heckman' two-step sample selection procedure. This is mainly because the types of the dependent variables of our two models do not allow an appropriate use of Heckman's procedure. Indeed, as contended by Dubin and Rivers (1990: 411), ''the Heckman two-step estimator is specifically a probit model followed by a linear regression, and there is no simple analog for the Heckman method for discrete choice models despite the logical appeal of the process.'' In the same vein, Bushway et al. (2007: 153) consider that the use of models other than OLS in the second stage of Heckman's two-stage method is a frequent error in studies using this method.

Comment:
Please explain why you presented marginal effects and not aOR (adjusted Odds Ratio), knowing you have used logit and not probit for example.

Response: We agree that Odds Ratios (OR) can be calculated in ordered logit models, when the link function is logit. They are given by the EXP of the coefficients. Nevertheless, we choose marginal effects (ME) as an alternative measure to OR for the following reasons:
We think that ME are more intuitive and easier to interpret than OR. Indeed, OR in an ordered logit model gives the change in odds for a unit increase in a continuous predictor or when changing levels (classes) of a categorical predictor, whilst ME interpretation refers directly to the percentage of change in Y when X varies, all other things remaining equal. Moreover, OR is often misunderstood and interpreted as relative risk (RR).
OR does not directly reflect the effect of independent variables on an outcome, as it also considers the unobserved heterogeneity of the data, inherent to qualitative variables or incompleteness of variables included in the models, which in turn, limits the interpretation of this metric (effect across groups, across models…). One alternative proposed in the literature is to use a measure based on percentage as ME.
More details about these points are available in: Mood, C. (2010). Logistic Regression: Why We Cannot Do What We Think We Can Do, and What We Can Do About It, European Sociological Review, 26(1) : 67-82)

Comment:
Please specify the software you have used and the command.

Response: The softwares used are now clearly presented for each type of analysis. We are not sure about the added value of specifying the command for the readers if we already have presented the statistical tests performed in the text.
Here are some specifications on commands:
- ANOVA and Post-hoc analysis (Tamhanes' tests): ONEWAY command in SPSS (i.e., compare means – ANOVA)
- Ordered logit models: PLUM Command in SPSS (Ordinal regression)
- Marginal effects: MARGINAL EFFECT$ command in LIMPMED (Discrete choice models – ordered display marginal effects)

Comment: The two last § do not present particular interest, and may be suppressed to better explain your statistical analysis

Response: Done: The last two paragraphs were removed and we added information on our statistical analysis as requested.

Comment: Please explain the rational of using only 3 class or the WTP, and of not using the middle of the class for example.

Response: Our WTP question initially offers 6 ranges of potential answers to participants (excluding the option “do not know” and “do not want to answer”, which were recoded in missing data for multivariate analysis) that we thereafter recoded in three to reach a sufficient N in each range that allows adequately performing the statistical tests (i.e., “even” and sufficiently large distribution within and across categories). There were some categories with only 3 or 13 respondents – see Table 1 for initial descriptive statistic on this particular measure.
We agree that it is possible to transform original data to use other econometric analysis (e.g., OLS). However, we used the model that better fits our measure. For example, as contented by Fullerton (2009, p. 310) while discussing the use of ordered logit models: «If the dependent variable is an ordinal scale that represents an underlying continuous measure (e.g., income intervals representing income in dollars), then the cumulative approach makes the most sense».
This information was not added into the text.

Comment: Results
Descriptive statistics
A cross tab between INTER and WTP could be informative

Response: Done: We added a crosstable as requested. We also presented the results of a bivariate analysis between Interest and WPT measures.

Comment: Please detail the distribution of the 191 missing value for the WTP variable

Response: Done: We added information on 191 missing data below Appendix 2.

Comment: Ordered logit regressions
The first § is not very instructive and should be included in the legend of the tables.

Response: Done: We removed this paragraph and place some complementary information below Table 3 (regression models, previously Table2) as recommended.

Comment: Discussion
Some interpretations of the results are expected, the 1st paragraph is too descriptive and similar to the paragraph in the result section. If there is a large number of references, there is a lack of theoretical and methodological perspective between the literature and the results. For example, what are the implication of the impact of the BC family history, or what should be the interpretation of the lowest interest in for women with a lower income. Did economic theory said anything between income and WTP values?

Response: We added a column in Appendix 1 in order that readers can quickly compare previous study results on interest in and WTP for cancer susceptibility testing with our results on BCST. We also added more information on prior studies in the discussion, notably regarding family history and income.

Comment: Potential implication
If the authors are interested in a collective payment, why did they chose an out of pocket payment and not an insurance premium or a contribution? I’m not clear with the argument saying that the results can provide insight about a collective payment.

Response: Québec and other provinces of Canada have publicly funded healthcare systems. However, there exist private health delivery channels and it is possible to buy genetic tests directly from privates companies and laboratories. The general objective of this study was to better understand interest in BCST and to gain insight into the readiness of women of the general population of Québec (Canada) to use genetic information for BC prevention. The possibility of implementing a risk stratification approach is more and more discussed. This argument, added to those on DTC genetic tests, urged in knowing the interest and obtaining a proxy of the value attributed by women to such test. Moreover, the implication indicating “WTP to collectively pay” is presented as an insight only. We revised the formulation of this implication while indicating clearly in the discussion that the items used to measure WTP did not consider various payment methods to avoid confusion.

VERSION 3 – REVIEW

REVIEWER	Protiere, Christel INSERM, SESSTIM
REVIEW RETURNED	08-Dec-2017

GENERAL COMMENTS	The authors have successfully responded to the comments. I'm happy with the final version of the manuscript