Author's response to reviews

Title: Blood spots as an alternative to whole blood collection and the effect of a small monetary incentive to increase participation in genetic association studies

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Version: 2 Date: 13 July 2009

Author's response to reviews: see over
July 13, 2009

Melissa Norton, M.D.
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Dear Dr. Norton

We thank you and the reviewers for the thoughtful comments on our manuscript (1781158492241238) “Blood spot collection as an alternative for participation in genetic association studies”, which is newly titled, based on reviewer comments as “Blood spots as an alternative to whole blood collection and the effect of a small monetary incentive to increase participation in genetic association studies”.

As you indicated to us in your correspondence, we have responded point by point to the reviewer comments and have reformatted the manuscript in concordance with journal requirements. Our reply to the comments and revised manuscript are attached with this cover letter. Please note that my contact information has changed since this manuscript was first submitted for review.

Thank you again for your consideration of our manuscript.

Sincerely,

Parveen Bhatti
Reviewer 1

1) There appear to be 2 aims: 1) to see whether blood spots can be used to increase DNA collection in people who don’t want a venepuncture, and 2) to see whether the incentive makes a difference. However, these have not been clearly stated anywhere in the paper. The aims should be clearly stated in the Introduction, the Abstract and reflected in the Title. Also, the Results should be presented in a way that reflects these explicit aims. Not doing so detracts from the clarity of the paper.

We agree with the reviewers comment and have reworded and restructured the abstract and background to clearly reflect the aims of this study. In particular, we modified the Methods section in the Abstract (page 2), which now reads:

“To determine if offering blood spot collection would increase participation in genetic epidemiologic studies, we conducted a trial of collecting dried blood spot cards by mail from a sample of cancer cases (n=134) and controls (n=256) who were previously selected for a breast cancer genetics study and declined to provide a venipuncture blood sample. Participants were also randomized to receive either a $2.00 bill or no incentive with the blood spot collection kits.”

And paragraph 2 of the Background (page 3), which now reads:

“To determine if offering blood spot collection would increase participation in genetic epidemiologic studies, we conducted a randomized trial of collecting dried blood spot cards by mail among 390 USRT cohort participants selected for a nested case-control study of breast cancer who declined to provide a venipuncture blood sample. We also assessed the impact of an incentive by randomizing participants to receive either a $2.00 bill or no incentive with the blood spot collection kits.”

We have also changed the title of the manuscript to reflect the second aim of the study which was to examine the effect of an incentive. The previous title “Blood spot collection as an alternative for participation in genetic association studies,” has been changed to “Blood spots as an alternative to whole blood collection and effect of a small monetary incentive to increase participation in genetic association studies.” Though we did not edit the Results section, with the rewritten Abstract and Background, the presentation of the results now mirrors the aims as they are outlined in the Abstract and Background.

2) The numbers of subjects in the Study Population paragraph (p4) don’t add up to the totals given – please correct.

Since a random subset of the total controls that had declined to provide a venipuncture blood sample were included for this study, the numbers given in parentheses on page 4
were not intended to add up to the total number of cases and controls that declined to provide a venipuncture blood sample (343 + 814).

3) It is sufficient to state the %s or means and the p-value for the appropriate statistical test, or odds ratios and their confidence intervals. It is not necessary to make statements about ‘statistical significance’ as though this was a binary concept. It is the magnitude of the effect measure or difference in means / %s between the groups that is central to determining the importance of any observed association.

The reviewer raises an important issue with regard to interpretation of results. In keeping with current epidemiologic practice, we assessed statistical significance at p ≤ 0.05. This was not previously stated, but now appears in the manuscript (page 6, final sentence of the Methods). That being said, when making statements about significance in the manuscript, we assessed effect sizes, 95% confidence intervals and p-values in combination. However, as referred to by the reviewer, the phrase “statistical significance”, appeared twice in the manuscript and has now been removed.

4) Is collection of blood spots, whereby the subject has to use a lancet to draw blood, really ‘minimally invasive’? (p3) This should be addressed in the Discussion, and compared with the ‘invasiveness’ of venipuncture.

The reviewer raises an important point. Blood spot collection is certainly more convenient, but we can only speculate on the invasiveness. As such, we no longer use the term “minimally invasive” in the manuscript. In the Background (paragraph 1, page 3), we now state:

“As compared to venipuncture, blood spot collection is more convenient (i.e. can be done by oneself at home), and while this method is invasive, it may be considered less so among participants.”

We have also added the following paragraph to the Discussion (page 8, paragraph 2):

“Convenience of blood spot collection over venipuncture blood draw is the most likely reason for the increase in participation. Subjects were able to perform the procedure at home and return the blood spot card through regular mail. In comparison, venipuncture necessitated scheduling appointments at laboratories or clinics and then arranging to have the blood samples picked up by a courier service. In general, the collection of capillary blood by finger stick is considered to be less invasive than blood draw using venipuncture because there is lower risk of soft tissue injury. However, there may have been discomfort and difficulties in applying the finger stick procedure among study subjects, so we can only speculate as to whether relative invasiveness was a factor in increased participation.”
5) The Discussion is very limited and needs to be strengthened in several areas, including a more complete description of the study’s limitations.

We agree with the reviewer and have expanded the discussion, including the limitations. Please see responses to comments 4 and 6.

6) The first sentence of the final paragraph of the Discussion has not been substantiated in the paper. The study has shown that blood spots may be a feasible method for blood collection when venepuncture is not possible. However, the authors need to comment on two important issues relating to this. Firstly, how generalisable are the results to the wider population, given that this study was conducted in a cohort of non-Hispanic female radiographers? Secondly, what quantity of DNA was collected and what could it be used for? What were its limitations?

We understand the reviewer’s concern. As such, the first sentence of the Discussion which formerly read “This study demonstrates that collection of dried blood spot cards in addition to venipuncture blood samples can substantially increase overall participation in genetic case-control studies.” has now been modified to read:

“This study demonstrates that collection of dried blood spot cards in addition to venipuncture blood samples may be a feasible method to increase overall participation in genetic case-control studies.”

We also agree with the reviewer that generalizability of the results is a potential limitation of the study. Furthermore, assessment of the quality and quantity of the DNA in the blood spots that we obtained was beyond the scope of this study and is another limitation. However, blood spots have been shown to be a effective source of high-quality DNA for genetic association studies. We have commented on both of these issues in the Discussion (page 10, final paragraph):

“Generalizability of our results to other populations is another limitation of this study given that participants were predominantly non-Hispanic women that worked as medical professionals. Furthermore, we were unable to assess the quantity or quality of the genetic material obtained from the blood spot cards collected for this study; however, it has been previously demonstrated that blood spots are a stable source of high quality DNA that, when coupled with whole genome amplification, can be effectively used to conduct genetic association studies (Steinberg et al, 2002; Mas et al, 2007).”

7) Could the ‘brief questionnaire’ sent out with the blood spot card have influenced the response fraction? This should at least be addressed in the Discussion.
The same questionnaire that was sent out previously with the venipuncture kits was sent out with the blood spot cards. To avoid confusion, the word “brief” has been removed (Methods, page 5, paragraph 2).

8) It would be useful to present the participation fractions for the main breast cancer case-control study, and what % (as well as the number) of these women declined to provide a blood sample by venepuncture.

On page 4, paragraph 2 of the methods (Study population) we have now added a detailed description of the participation fractions from the main breast cancer case-control study:

“Study participants were selected from eligible cases and controls identified as part of a genetic case-control study of breast cancer nested in the USRT cohort who had declined to provide a venipuncture blood sample. Of 1402 eligible breast cancer cases, 871 (62%) agreed to participate in the original study. One-hundred and fifty-five cases could not be located or were unable to participate, and 376 refused to participate, of which 343 had declined to provide a venipuncture blood sample. Of the 2,268 breast cancer controls that were identified, 1093 (48%) agreed to participate in the genetics study. Three-hundred and thirty-six controls could not be located or were unable to participate; 839 controls refused to participate in the study of which 814 declined to provide a venipuncture blood sample.”

9) The Journal requires a structured abstract, but this requirement has not been complied with. The authors should also ensure that their References and Section titles conform to Journal requirements.

The appropriate changes have been made.

- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

10) When describing the results, it is not clear why the authors have presented percentages and chi-square p values in the text, but odds ratios in the Table referred to in the text. There is no mention of odds ratios in the results section.

Odds ratios have now been included in the text of the Results section (pages 6 and 7)

11) There are several unnecessary spaces (eg. p4 line 4 and 3rd last line) that need to be removed.

These spaces have been removed.

- Discretionary Revisions (which are recommendations for improvement but
which the author can choose to ignore)

12) Table 2 adds little to the paper and could be deleted.

We agree with this comment and the table has been removed.

13) I would prefer to see the term ‘fraction’ used for response, as it not really a ‘rate’ (which involves a time component)

We understand the reviewer’s reasoning and have removed the term “rate” and replaced it with “proportion” where necessary.

Reviewer 2

The author gives an account of the factors which might affect the willingness of patients in participation in the dried blood spot genetic study. However, the findings in this study give little impact on the current clinical practice.

We appreciate the reviewer’s comment and agree that the findings of this study may have little direct impact on clinical practice. However, the focus of this study was to examine blood spot collection as a means to increase participation in molecular epidemiologic studies, and in these settings, we believe our findings are of value and may be useful to investigators planning these studies.

The author concluded in page 9 that "this study demonstrates that dried blood spots are an acceptable and effective method for collecting blood samples for genetic studies". However, the author did not give an account of the "quality" of the dried blood spots and any discomfort/difficulties experienced by the patients.

We understand the reviewer’s concern with this conclusion, which is too general a statement given the limitations of our study. As such, we have modified the sentence (page 10, Conclusion) to read:

“This study demonstrates that dried blood spots may be a feasible method for increasing participation rates for genetic studies.”

In terms of quality of the specimens and the discomfort/difficulties experienced by patients, please see responses to comments 4 and 6 above.