

Response Form for the Final Performance Summary Report*

Instructions: Section A of the Response Form should be completed by a grant administration official. For each project Sections B, C and D of the Response Form should be completed by the project's PI.

1. Name of Grantee: Geisinger Clinic – Weis Center for Research
2. Year of Grant: 2011 Formula Grant

A. For the overall grant, briefly describe your grant oversight process. How will you ensure that future health research grants and projects are completed and required reports (Annual Reports, Final Progress Reports, Audit Reports, etc.) are submitted to the Department in accordance with Grant Agreements? If any of the research projects contained in the grant received an “unfavorable” rating, please describe how you will ensure the Principal Investigator is more closely monitored (or not funded) when conducting future formula funded health research.

See item C on pages 4 and 5.

Project Number: 1166101
Project Title: Reducing the Burden of Breast Biopsy with
Abnormal Screening Mammograms
Investigator: Vogel, Victor

B. To ensure that feedback provided in the Final Performance Summary Report is utilized to improve ongoing and future research efforts, briefly describe your plans to address each specific weakness and recommendation as noted in Section B of the Final Performance Summary Report and listed below. If no weaknesses are listed below, no response is required.

As you prepare your response please be aware that the Final Performance Summary Report, this Response Form, and the Final Progress Report will be made publicly available on the CURE Program's Web site.

SPECIFIC WEAKNESSES AND RECOMMENDATIONS

Reviewer 1:

The study objective, which was to evaluate auto-antigen-antibody complexes in women with mammographically-suspicious lesions with no clinical significance, women with diagnosed breast cancer and women with no history of cancer, was not accomplished during the award period. The data and information provided were unrelated to the project objectives listed in the strategic research plan. Although numerous *in silico* genetic experiments (SNP analysis, linkage disequilibrium and haplotype analysis, etc.) were conducted, these were unrelated to the original proposed specific aims of the project. Unfortunately, no reason was provided for this deviation from the original aims of the study.

Response: We agree that the study was poorly performed and deviated from the original study design. Institutional policies will be modified to provide greater oversight of future projects.

Reviewer 2:

1. The primary objectives were not clearly stated in the final project report. The investigators should have reproduced these objectives in the final report exactly as they appear in the funded application.

Response: The Investigators should have clearly stated the objectives in the final report. In the future progress reports will undergo greater internal scrutiny.

2. It was not clear how case status was determined. The risk of PMBC was modeled in genetic analyses; however, the definition of this particular outcome was not clear. Its role as biomarker for breast cancer was not established. Using PMBC or any function of it as a means to determine case-control status appears to be premature. We recommend that the investigators perform an external validation effort of this biomarker. They should not use the same data that was used to identify this biomarker.

Response: We agree that an external validation of the biomarker data should have been performed. This will be taken into account in any future studies.

3. The genetic data and results of the association study were not included nor discussed in the report while these analyses are apparently complete. It could be asked whether these analyses were even completed.

Response: The employment of the collaborating Investigator who was responsible for the analyses was terminated. The completeness of the analysis is unknown. We have implemented institutional policies to provide additional oversight of future PA CURE projects.

4. Use of ROC and AUC measures to judge predictive models can be misleading when the same dataset is used for both building and predicting data. This tends to lead to overfitting issues. We could not judge these results since (again) no data was shown. An external validation of any biomarker is recommended before efforts to identify genetic markers that are associated with it can be undertaken. Otherwise, results of the association studies could be hard to interpret.

Response: We agree that external validation of biomarker data is required for a rigorous study. We have implemented institutional policies to provide additional oversight of future PA CURE projects.

Reviewer 3:

1. The samples were not adequate.

Recommendation: The investigators should have provided at least some preliminary testing of the samples either before or early in the study. If the samples were not adequate, there could have been additional options. For example, the investigators might have made efforts to acquire appropriate samples. The investigators might have made efforts to acquire samples for some other source.

Response: We agree with the reviewer's comment and recommendation. We have implemented institutional policies to provide additional oversight of future PA CURE projects.

2. There was no training provided.

Recommendation: Even in failed experiments, there are learning opportunities. There is no indication that any training efforts were made.

Response: We agree with the reviewer's comment and recommendation. We have implemented institutional policies to provide additional oversight of future PA CURE projects.

3. No collaborations were developed.

Recommendation: The investigators might have sought to develop collaborations to acquire additional samples that could have provided at least something positive from this study and might have led to additional studies that were not as failed as the current study.

Response: We agree with the reviewer's comment and recommendation. We have implemented institutional policies to provide additional oversight of future PA CURE projects.

4. No infrastructure development.

Recommendation: The investigators could have sought development of new sources of sample collection to replace the samples that were inadequate.

Response: We agree with the reviewer's comment and recommendation. We have implemented institutional policies to provide additional oversight of future PA CURE projects.

C. If the research project received an "unfavorable" rating, please indicate the steps that you intend to take to address the criteria that the project failed to meet and to modify research project oversight so that future projects will not receive "unfavorable" ratings.

Response:

We agree that Project Number 1166101-"Reducing the Burden of Breast Biopsy with Abnormal Screening Mammograms" was poorly performed. As noted by the reviewers, the objectives of the study were not accomplished and the investigators provided no reason for deviating from the original aims of the study. Unfortunately, this lack of responsibility by the investigators was not identified by current grant oversight practices.

The existing grant oversight process at Geisinger Clinic depends significantly upon the PI to conduct projects as proposed or to contact the Office of Sponsored Projects for assistance in working with the sponsor to amend or revise the specific aims or deliverables. Investigators are provided an email reminder regarding the deadline for progress reports and follow up is initiated if the report is not provided in the appropriate time frame. However, there is no scientific review of the progress reports at the institutional level. The PI and collaborating PI in this project did not fulfill their responsibility for the conduct of the study. The PI will be barred from applying for PA-CURE funds for a period of 3 years. If after that period, the PI wishes to participate in PA-CURE funded activities, he will be subject to greater oversight as described below. Employment of the collaborating investigator, who was responsible for performing most of the analyses, has been terminated as a result of ongoing performance issues. This makes it difficult to provide detailed technical responses to the reviewer's criticisms.

The General Recommendations for Geisinger Clinic provided by the reviewers will be instituted at Geisinger Clinic for future projects funded by the PA-CURE.

Specifically,

- 1) Investigators will be required to submit intermittent internal progress reports every 6 months. The reports will be evaluated by the Associate Chief Research Officer (or designee) to confirm progress toward achieving stated milestone.
- 2) The relevant data will be required in all progress reports (intermittent internal and periodic sponsor required) to confirm that data is being collected and analyzed as appropriate.
- 3) In instances where internal progress reports indicate that the project is moving slowly or experiencing difficulty, the investigators will meet with the Associate Chief Research Officer to consider study revisions or alternatives. If revisions of the specific aims are needed, the sponsor will be contacted for advice and guidance.

The performance of this study did not meet Geisigner Clinic quality standards. We are committed to developing internal controls to prevent similar situations in the future.

D. Additional comments in response to the Final Performance Review Report (OPTIONAL):

Response: