Pennsylvania Department of Health
Final Performance Summary Report
Formula Grants

Overview of the Health Research Project Performance Review Process and Criteria

An applicant that receives a health research grant under Tobacco Settlement Act / Act 77 of 2001, Chapter 9, is subject to a performance review by the Department of Health upon completion of the research project. The performance review is based on requirements specified by Act 77 and criteria developed by the Department in consultation with the Health Research Advisory Committee.

As part of the performance review process, each research project contained in a grant is reviewed by at least three experts who are physicians, scientists or researchers. Reviewers are from the same or similar discipline as the research grant/project under review and are not from Pennsylvania. Reviewers use the applicant's proposed research plan (strategic plan), the annual progress report and final progress reports to conduct the review. A grant that receives an unfavorable performance review by the Department may be subject to a reduction in funding or become ineligible for health research funding in the future. The overall grant evaluation rating is based on the ratings for the individual research projects contained in the grant.

This performance review report contains the outcome of the review for the grant as a whole (outstanding, favorable, or unfavorable), strengths and weaknesses of each research project, as well as recommendations for future improvement.

The following criteria were applied to information submitted by research grant recipients:

- **Criterion 1 - How well did the project meet its stated objectives? If objectives were not completely met, was reasonable progress made?**
  o Did the project meet the stated objectives?
  o Were the research design and methods adequate in light of the project objectives?
  o Consider these questions about data and empirical results: Were the data developed sufficiently to answer the research questions posed? Were the data developed in line with the original research protocol?
  o If changes were made to the research protocol, was an explanation given, and, if so, is it reasonable?
  o Consider (only for clinical research projects) the extent of laboratory and clinical activities initiated and completed and the number of subjects relative to the target goal.
  o Were sufficient data and information provided to indicate or support the fact that the project met its objectives or made acceptable progress?
  o Were the data and information provided applicable to the project objectives listed in the strategic research plan?

- **Criterion 2 - What is the likely beneficial impact of this project? If the likely beneficial impact is small, is it judged reasonable in light of the dollars budgeted?**
    - What is the significance of this project for improving health?
    - Consider the value of the research completed towards eventual improvement in health outcomes.
    - Consider any changes in risk factors, services provided, incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of impact and effectiveness of the research being conducted.
    - Consider any major discoveries, new drugs and new approaches for prevention, diagnosis and treatment, which are attributable to the completed research project.
    - What are the future plans for this research project?

- **Criterion 3 - Did the project leverage additional funds or were any additional grant applications submitted as a result of this project?**
    - If leveraging of funds were expected, did these materialize?
    - Are the researchers planning to apply for additional funding in the future to continue or expand the research?

- **Criterion 4 - Did the project result in any peer-reviewed publications, licenses, patents, or commercial development opportunities? Were any of these submitted/filed?**
    - If any of the above listed were expected, did these materialize?
    - Are the researchers planning to submit articles to peer-reviewed publications, file for any licenses, or patents or begin any commercial development opportunities in the future?
    - Consider the number/quality of each.

- **Criterion 5 - Did the project enhance the quality and capacity for research at the grantee's institution?**
    - Were there improvements made to infrastructure?
    - Were any new investigators added or were any researchers brought into the institution to help carry out this research?
    - Were funds used to pay for research performed by pre- or post-doctoral students?

- **Criterion 6 - Did the project lead to collaboration with research partners outside the institution, or new involvement with the community?**
    - Are the researchers planning to begin any collaborations as a result of the research?
    - For clinical research only: consider the number of hospitals and health care professionals involved and the extent of penetration of the studies throughout the region or the Commonwealth.

Overall Evaluation Rating

An overall evaluation rating is assigned to each research project. The rating reflects the overall progress the project attained in meeting the stated goals and objectives. The rating is based on a scale of 1–3, with 1 being the highest. An average rating is obtained from all the reviews (minimum of 3) of each project and is the basis for the determination of the final overall rating for each project as follows:

1.00 – 1.33 = *Outstanding*
1.34 – 2.66 = *Favorable*
2.67 – 3.00 = *Unfavorable*

The grant level rating is an average rating from all projects as above. The numerical rating appears in parentheses for the grant and each project in the ***Overall Grant Performance Review Rating*** section of the report.

Overall Grant Performance Review Rating

Grant Rating: Unfavorable (3.00)

Project Rating:

Project	Title	Average Score
1166101	Reducing the Burden of Breast Biopsy with Abnormal Screening Mammograms	Unfavorable (3.00)

Section A. Project Evaluation Criteria

Criterion 1 - How well did the project meet its stated objectives? If objectives were not completely met, was reasonable progress made?

STRENGTHS AND WEAKNESSES

Reviewer 1:
The objective of the study is to test the specificity and sensitivity of circulating serum auto-antibodies against a panel of breast cancer-associated antigens with the goal of distinguishing women diagnosed with breast cancer from: a) women diagnosed with mammographicly-suspicious lesions of no clinical significance, and b) women with no history of cancer with "normal" mammography. The applicant posits that this relatively non-invasive approach will be more accurate, rapid, less expensive, and reduce the rate of false negative and false positive results associated with current mammography screening.

The study will evaluate archived serum samples from three patient groups: 1) women diagnosed with breast cancer, 2) women diagnosed with mammographicly-suspicious lesions of no clinical significance, and 3) women with no history of cancer with "normal" mammography.

Two specific aims are proposed: Aim 1 will seek to improve the performance of an already developed and validated panel of anti-tumor antibodies for distinguishing women with breast cancer from those without breast cancer, and Aim 2 will validate the accuracy of the improved panel in a group of women with screening mammographic outcome of "normal" (BIRADS^{TM}1), suspicious lesions (BIRADS^{TM}4) and highly-suspicious lesions (BIRADS^{TM}5).

The study objective, which was to evaluate auto-antigen-antibody complexes in women with mammographicly-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.

Reviewer 2:
The final progress report was hard to grasp because the primary objectives of the project were not stated. The summary of progress reported for 01/2012-06/2012 period suggests that the main

objective was to identify biomarkers that could help identify breast cancer cases without a biopsy, a procedure that could be risky, pricey, and lead to bad outcomes (disfiguration) in some cases. Although the specific aims were not stated in the final report, it appears that a case-control genetic association study was the main objective pursued in this project. Based on that annual report, it appears that PMBC was the outcome used to determine case-control status. In the end, an association study was conducted, but its results were not included in this report.

With the objective of the study not clearly stated, it became harder to judge other aspects of the proposal. For example, if the ultimate goal is to identify biomarkers then association analyses with a specific biomarker would have been premature. The investigators would be required to first establish that the proposed biomarker does have the ability to identify breast cancer cases before efforts to detect genetic variants that are associated with it could be initiated. It is also hard to evaluate the results because the data were not shown.

Reviewer 3:
Strengths: None.

Weaknesses: The study did not meet the stated objectives. This suggests that there were problems with the research design. If the blood samples were inadequate, this should have either been identified before the study began or very early on in the study. The investigators should have taken more responsibility to seek samples that were adequate. If the samples from the stored bank were not competent, the investigators should have taken efforts to seek another source of samples or to acquire additional samples. No new information was derived from this study that was useful, which is very disheartening and perhaps could have been prevented.

Criterion 2 - What is the likely beneficial impact of this project? If the likely beneficial impact is small, is it judged reasonable in light of the dollars budgeted?

STRENGTHS AND WEAKNESSES

Reviewer 1:
Due to the fact that the project objectives were not realized, it is concluded that the likely benefit for the dollars budgeted is negligible. Were the study to have been conducted and completed as originally proposed, it had potential to contribute to improvement of health outcomes of breast cancer patients.

Reviewer 2:
It was also hard to evaluate the likely benefits of this project. An effort to identify relevant biomarkers that could help identify breast cancers without the need for a biopsy would have been greatly valued. Also, assuming that a biomarker was identified, efforts to identify genetic variants that govern the levels of these biomarkers would have also been of great interest to the scientific community. However, as presented, the final report was not useful. It did not state the main objectives of the project, used undefined abbreviations, contained no data, and was not clear about the choice of outcome.

Reviewer 3:
Strengths: None.

Weaknesses: There is no beneficial impact of this project, unfortunately. There is no significance derived from the study. There are no discoveries. There are no future plans for this study by the investigators.

Criterion 3 - Did the project leverage additional funds or were any additional grant applications submitted as a result of this project?

STRENGTHS AND WEAKNESSES

Reviewer 1:
The project did not leverage additional funds related to the project or to continue/expand the project. No additional grants were submitted as a result of the project. This outcome is not totally unexpected, given the short duration of the award (1 year) and the amount of compelling preliminary data needed for a grant application to be competitive for funding

Reviewer 2:
The project did not leverage funds. However, the investigators indicated in the annual report for the period 07/2012-06/2013 that they used preliminary data to apply for an NIH grant.

Reviewer 3:
Strengths: None.

Weaknesses: There was no additional leveraging of funds. There are no plans to continue or to expand the research according to item 11 in the final report.

Criterion 4 - Did the project result in any peer-reviewed publications, licenses, patents, or commercial development opportunities? Were any of these submitted / filed?

STRENGTHS AND WEAKNESSES

Reviewer 1:
The project did not result in any peer-reviewed publications, licenses, patents or commercial development opportunities due in part to the fact that the stated research objectives were not pursued.

Reviewer 2:
According to the annual report for the period 07/2012-06/30/2013, there is a manuscript under preparation. It would have been useful to include some of the observed data in this report, but that was not done.

Reviewer 3:
Strengths: None.

Weaknesses: According to the final report, there are no peer-reviewed publications, no submitted articles, and no plans to submit articles. There are no plans to file for any licenses or patents. There are no plans for commercial development opportunities in the future. Based on this report, the study was unproductive.

Criterion 5 - Did the project enhance the quality and capacity for research at the grantee's institution?

STRENGTHS AND WEAKNESSES

Reviewer 1:
To the extent that the health research grant funds were used to pay the salaries of individuals who contributed to the research effort, the project enhanced the capacity for research at Geisinger Clinic. The investigator lists two collaborators (Dr. Stark, Epidemiologist; Dr. Yan, Biostatistician) that were paid salaries from the formula grant funds.

Reviewer 2:
No infrastructure improvement could be linked directly with this project. All 3 investigators on this project are from the same institution.

Reviewer 3:
Strengths: None.

Weaknesses: There were no improvements to the infrastructure. No new investigators were brought into the system. There was no training provided. Here also, there was no apparent value to the study according to the report submitted by the investigators.

Criterion 6 - Did the project lead to collaboration with research partners outside of the institution or new involvement with the community?

STRENGTHS AND WEAKNESSES

Reviewer 1:
The health research funds did not lead to collaboration with research partners outside of the institution nor did it result in commercial development of research products. It also did not lead to new involvement with the community. This is not unexpected given the laboratory-based nature and duration (1 year) of the project.

Reviewer 2:
This project did not lead to collaboration with outside researchers.

Reviewer 3:
Strengths: None.

Weaknesses: In this case also, there are all weaknesses. There are no plans to begin any collaborations as a result of the research.

Section B. Recommendations

SPECIFIC WEAKNESS AND RECOMMENDATIONS

Reviewer 1:
The study objective, which was to evaluate auto-antigen-antibody complexes in women with mammographicly-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.

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.

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.

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.

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.

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.

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.

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.

4. No infrastructure development.

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

Generic Recommendations for Geisinger Clinic

Reviewer 1:
Intermittent (e.g., every 6 months) evaluation of funded projects should be performed to monitor progress towards achieving stated milestones.

Reviewer 2:
Investigators should be required to show at least a portion of their data in these reports. This could at least confirm that described analyses were in fact conducted.

Reviewer 3:
It is regrettable that this project report is of very little value to the scientific community or to the general community. The investigators apparently ran into an obstacle of poor samples. They could have made more effort to turn this project around.

ADDITIONAL COMMENTS

Reviewer 1:
The study objective, which was to evaluate auto-antigen-antibody complexes in women with mammographicly-suspicious lesions with no clinical significance, women with diagnosed breast cancer and women with no history of cancer, was not performed during the award period. The data and information provided were unrelated to the project objectives listed in the strategic research plan. No explanation was provided in the final report to justify this deviation from the originally proposed specific aims of the project.

Reviewer 2:
The primary objectives were not clearly stated in the final project report.
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.

The genetic data and results of the association study were not included nor discussed in the report while these analyses are apparently complete.

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 issue. We could not judge these results since (again) no data was shown.

Reviewer 3:
This progress report did not meet the goals originally delineated. Those weaknesses are presented in my comments.