

**Response Form for the Final Performance Review Report—
National Disease Research Interchange 2009F***

1. Name of Grantee: National Disease Research Interchange
2. Year of Grant: 2009 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.

Future health research grants and projects will be completed and required reports (Annual Reports, Final Progress Reports, Audit Reports, etc.) will be submitted to the Department in accordance with Grant Agreements, exactly as they have been previously. NDRI’s policies and procedures and oversight process in this regard have ensured timely submission of all reports to date using the required formats.

For each research project contained in the grant, please provide a response to items B-D as listed on the following page(s). When submitting your response please include the responses for all projects in one document. The report cannot be submitted as a ZIP file, because the Department’s exchange server will remove it from the email. If the report exceeds 2MB, please contact the Health Research Program for transmittal procedures: 717-783-2548.

* Please note that for grants ending on or after July 1, 2007, grantees’ Final Performance Review Reports, Response Forms, and Final Progress Reports ***will be made publicly available on the CURE Program’s Web site.***

Project Number: 0990201
Project Title: Fine Mapping of Genetic Susceptibility for Microvascular
Complications in Patients with Type 1 Diabetes
Investigator: Lonsdale, John

B. Briefly describe your plans to address each specific weakness and recommendation in Section B using the following format. As you prepare your response please be aware that the Final Performance Review Report, this Response Form, and the Final Progress Report will be made publicly available on the CURE Program's Web site.

Reviewer 1:

1. The scope of the project is too broad. It would be ideal if the focus were narrowed down to one complication at a time while adjusting for the effects of other correlated traits or complications.

Response

We would agree with this except that, in fact, the most frequent complication is retinopathy. Thus, most of our findings will be related directly to retinopathy. Nephropathy is next most frequent and our subsequent findings with that complication have been more uncertain than with retinopathy. We believe this recommendation will be carried out by default, but given the impact of nephropathy on the lives of patients, we are reluctant to give up trying to discover what affects susceptibility.

2. In Aim 3, "continue the annual program of participant follow-up using an updated family questionnaire to track any development or progression of microvascular complications among patients with both T1D and T2D to enhance the sample size and maintain the scientific value of the dataset," it is not clear how type 1 and type 2 diabetic subjects are going to be analyzed. It may be helpful to provide more details on this.

Response

We are at the moment working exclusively with T1D subjects and families. The scientific question, and one that has a direct impact on population risk assessment, is: "are our findings exclusively related to the genetics of T1D-related complications or are those findings generalizable to T2D?" This is important because if it is the high levels of blood glucose *alone* that triggers complications then our findings should be replicable in T2D patients. If not, then complications risk may have differing causes in T1D and T2D. However, we do not intend to collect T2D patients because NIH data bases and repositories have sufficient patients for us to tap in the future when the research is more advanced.

3. In association studies, replication of a disease association in one or more samples is very critical for publication, so is there any plan to conduct replication analysis?

Response

HBDI cannot conduct another data collection effort of the magnitude that led to our current collection. Also, due to the emphasis on case-control studies over the past decade, few new *family* data collection efforts on complications have been carried out. Our results thus far indicate that certain HLA alleles *protect* from complications and that there are loci that are linked to complications (from family data). These could be major breakthroughs in our understanding of complications' origins and we believe that, once these are published, there will be replication attempts galore.

Reviewer 2:

1. The major weakness, as outlined above, is still recoverable by delivering a final analysis of the data that was acquired, which would enable an assessment of whether there would be a future for this work.

Response

We are preparing publications now that will report on this work. One has been submitted and is now in revision.

2. It seems likely that the dataset would be most useful in meta analysis with other similar efforts-- this should be encouraged.

Response

We agree that the work on complication such as we are doing should be done in other laboratories and we would welcome cooperation with others.

3. The greatest value is the HBDI resource. A plan for its continued support and expansion would give some hope for the future of the project.

Response

We completely agree. Almost all of the resources of this grant go to verifying and expanding the data set.

Reviewer 3:

From a clinical standpoint, the project is highly significant, since it focused on diabetic complications.

Recommendation: The outcome and results of this important project should be published and further expanded in new proposals supported by strong and compelling data obtained by this pilot study. If the results are not published and shared with the scientific community to advance the field, all the work that has been done is futile and funds were misspent.

Response

As noted above, we are now preparing publications of our work.

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: The project received a favorable rating.

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

Response: N/A