October 23, 2011

Gilbert S, Omenn, MD, PhD
Chair, Institute of Medicine Committee on the Review of Omics-Based Tests for Predicting Patient Outcomes in Clinical Trials
500 Fifth Street, NW
Washington, DC 20001

RE: Moffitt response to questions on the trial "Genomics-directed salvage chemotherapy with either liposomal doxorubicin or topotecan"

Dear Dr. Omenn,

I am writing to comment on some issues that were raised in the letter sent to you by Dr. William Dalton, President & Chief Executive Officer of Moffitt Cancer Center, concerning interactions between NCI and Moffitt investigators regarding the Moffitt ovarian cancer genomics-directed therapy trial NCT00720096. I am the "senior NCI statistician" referenced in Dr. Dalton's letter, and I was the statistician on the transition review team for Dr. Johnathan Lancaster's NCI-funded R21-R33 grant # CA110499. This letter is written to clarify my role in reviewing the gene signatures, as I don't feel Dr. Dalton's letter reflected NCI program staff's position regarding several key points.

1. **Response to question 1:**

The statement that the NCI statistician was "able to reproduce Dr. Lancaster's findings" is inaccurate. Dr. McShane (the "senior NCI statistician") was provided computer code and validation data for *one* of the five predictors mentioned in the grant progress report. That predictor was not one of the two predictors used in the Moffitt trial. The reason that NCI initially made the request for Moffitt to send data and computer code is that information about the validation data and predictor accuracy estimates had been observed by NCI transition team reviewers to *change during the course of the review.* It took several weeks for Moffitt and Duke to produce this operational and stable version of code for the platinum/taxane sensitivity predictor, which was the *only one* evaluated by Dr. McShane. The NCI could not evaluate from the information it had been given at that time the accuracy of the data provided or whether the predictor model had been developed using appropriate methods. NCI could only confirm that the predictor examined by Dr. McShane existed in locked down form.

The NCI review team considered the R33 phase of the grant as the place where the predictors would be retrospectively validated to determine their readiness for use in guiding patient therapy. The patient tumor samples were collected prospectively in the R33 study, but the calculation of the predictions and correlations of the predictions with actual clinical response took place after patients had been treated and follow-up for clinical response was complete, i.e,. patients in the R33 grant-based study were not to be assigned to treatment based on the predictors. The NCI insisted on changes in the grant workflow to establish an honest broker system so that the validation would be blinded and rigorous. NCI staff on the grant transition review team did *not* consider the predictors to have been sufficiently validated to be ready for use in guiding patient therapy. Such retrospective validation was the purpose of the R33 grant work.

In order for the validation in the R33 grant to be meaningful, the predictors had to be fully locked down. It was the locked down status that Dr. McShane had been able to verify for the platinum/taxane predictor, the single predictor for which she received computer code and data. The Moffitt investigators were

advised to appropriately lock down the remaining predictors after Dr. McShane had interacted with the Moffitt statistician, Dr. Eschrich, about the platinum/taxane predictor to be certain NCI's expectations for locked down status were understood. Dr. McShane did not receive data or computer code that would have allowed her to "reproduce" findings for the topotecan and liposomal doxorubicin predictors being used in the trial, nor even to establish that those predictors were locked down.

2. **Response to question 2:**

The response letter states that "the predictors used in the MCC study were derived at MCC, and not at Duke." Because the Moffitt trial protocol identifies the Potti et al., 2006 *Nature Medicine* paper as the source of the trial predictors, NCI does not know whether the predictors used in the trial were those derived at Duke as might be indicated by the reference to the Potti paper or if the statement in the protocol was in error. Consequently, NCI does not know if the statement in the retraction notice for the Potti et al., 2006 *Nature Medicine* paper concerning the inability to reproduce the validation results for the topotecan predictor applies to the topotecan predictor used in the Moffitt trial. .

3. **Response to question 3:**

The response letter references a "LONG NCI review (which coincided temporally with Keith Baggerly's presentation at NCI about the Duke data problems)." The length of the review was driven in large part by the time required by the Moffitt investigators to correct numerous errors in the different versions of their progress report and to produce operational locked down versions of their predictors. The relevance of the comment about Keith Baggerly's presentation at NCI is not clear; however it should be noted that Dr. Baggerly gave his talk at NCI in November 2007. The grant transition review had already been going on for at least four months by then, and the numerous inconsistencies in the information provided in the grant progress report (two versions by then) had already been identified by the NCI reviewers.

The response denies an "effort to conceal the facts of either the NFGC-funded genomic-directed therapy trial . . .". We are not aware of evidence that Moffitt tried to actively conceal the relationship between the trial and the validation study conducted as part of the grant while the trial was open, but NCI was not informed that a trial had already been initiated while NCI was funding the R33 grant to validate the predictors. As stated above, NCI believed that the predictors would be evaluated retrospectively for their validity in the R33 portion of the grant, and would not be used to direct patient therapy. NCI program staff called Dr. Lancaster to voice concerns about using the predictors in an ongoing trial to guide patient care. The following day, October 9, 2009, NCI was informed that the trial was closed.

We hope that your committee finds these clarifications helpful to gain a better understanding of the process followed by NCI during the review of these genomic predictors developed as part of Dr. Lancaster's NCI-funded R21-R33 grant.

Best regards,

Lisa M. McShane, Ph.D.

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