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

RE: RESPONSE TO QUESTIONS - "Genomic-directed salvage chemotherapy with either liposomal doxorubicin or topotecan"

Dear Gil,

I am writing in response to the additional questions regarding the above mentioned trial, posed by your IOM Committee that we discussed by phone earlier this month. The Committee is doing very important work in an area that is critical to the future of personalized medicine. As such, we are pleased to be of any assistance to your work. I, of course, consulted with Drs. Johnathan Lancaster and Robert Wenham, who were primary investigators for this trial, and the responses represent their views.

Your questions, and our responses are reflected below:

1. ***Were any review bodies at Moffitt (and Duke) responsible for reviewing the science underpinning the Moffitt trial to ensure that the predictor for the genomics-directed therapeutic decision was sufficiently validated?***

RESPONSE: This trial went through reviews by the Moffitt Cancer Center (MCC) Scientific Review Committee and University of South Florida (USF) Institutional Review Board (IRB), as well as required Department of Defense (DoD) reviews since it was funded via the National Functional Genomics Center (NFGC). Furthermore, prior to the transition of Dr. Johnathan Lancaster's R21 to an R33, NCI mandated that the signatures that were to be prospectively validated in the R33, be evaluated by a senior NCI statistician, working with Dr. Steven Eschrich from our Biomedical Informatics Core. Dr Eschrich and the NCI statistician were able to reproduce Dr. Lancaster's findings and reported such to the NCI who approved the R21 to R33 transition.

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2. ***Were scientific leaders and the IRB at Moffitt made aware of the published criticisms of the Nevins/Potti classifiers relevant to this study?***

RESPONSE: There were no "published criticisms of the Nevins/Potti classifiers relevant to this study" as the predictors used in the MCC study were derived at MCC, and not at Duke. MCC was made aware of the published criticisms of the Nevins/Potti classifiers as the criticisms were published and through communication by Dr. Lancaster himself.

3. ***Was anyone aware that enrollment in the trial proceeded while Dr. Lancaster was receiving funding through an NCI grant to develop what might have been this or a similar predictor? If yes, were there efforts to determine if the grant background information provided helpful insights into the readiness of the predictors being used in the trial? If not, what mechanisms might ensure such information be shared in the future?***

RESPONSE: This dox and topo predictors were developed as part of an NCI-funded one-year R21, the objective of which was to develop signatures predictive of primary platinum-based therapy and salvage therapy with topo and dox for patients with platinum-resistant recurrent disease. Following a LONG NCI review (which coincided temporally with Keith Baggerly's presentation at NCI about the Duke data problems) and subsequent approval, the R21 transitioned to a 4-yr R33, which was designed to prospectively validate the R21-developed predictive signatures (observational study without any patients allocated on the basis of signatures). The overlap with the clinical trial now in question, was with the prospective R33 (validation), not the R21 (development) phase of the NCI study. Thus, at the time of the NFGC-funded clinical trial Dr. Lancaster was not receiving NIH funds to develop the signatures; that had already been done, and was memorialized as such in the required 82-page R21 final report/R33 transition application (available on request). The temporal overlap was with the R33 prospective observational validation.

We hope it is recognized that there was in no way, at any point, an effort to conceal the facts of either the NFGC-funded genomic-directed therapy trial, or the NCI-funded R33, were open and enrolling patients at the same time. There was no reason to hide such information as we recognized they were very different studies: one was a prospective observational validation (the R33) of signature predictive accuracy, the other was a feasibility study evaluating whether it is possible to consent/enroll/ biopsy/ array/ analyze data/allocate therapy/treat patient in a clinically-acceptable timeframe (the NFGC-funded clinical trial). In fact, both the NFGC-funded trial and the R33 concepts were presented at multiple venues (NFGC meetings, MCC mentorship dinner meetings, Grand Rounds, etc). We have no reason to believe that there was any lack of awareness (intentional or otherwise) about the existence of the two parallel studies.

As to how to avoid signatures being used prematurely: importantly, the signatures in the MCC clinical trial were used to select between two essentially equivalent drugs; drugs that are selected somewhat "flip of coin" in clinical practice in the broader gynecologic oncology community. The questions in focus in the study were the feasibility of the process, rather than the performance of the signatures. The study was not powered to achieve anything close to the latter.

Currently MCC relies on the Scientific Review Committee evaluation, which includes bioinformatics/biostatistics, however, the process is not designed to execute deep-dives into specific signatures or to assess "readiness". As time has evolved, we have all become more aware of the regulatory aspects associated with these sorts of studies, including the CLIA and FDA/IDE issues. Four to five years ago, there was a much lower level of awareness than we have today on this topic.

4. ***Are Drs. Wenham and Lancaster conducting other trials with a strategy similar to this trial? We realize that the subject trial was started 3 years ago and there may be many learnings for present trials.***

RESPONSE: Drs. Wenham and Lancaster are not conducting other trials with a similar strategy. Neither currently have studies that use signatures to allocate therapy, however, they do plan to conduct them in the future. Ongoing planning is currently underway for a similar study with industry, and Dr. Lancaster has recently submitted an invited application to the DoD to fund a Platinum-TCN study that will select patients from Moffitt's Total Cancer Care study who have profiles consistent with activation of the BAD apoptosis pathway. Both investigators have discussed opportunities for several additional similar studies. We agree there are many learnings.

5. ***We are considering recommending that genomics-directed therapy trials be conducted only after performing prospective-retrospective analyses of appropriate archived specimens, if feasible, and only after obtaining an IDE from the FDA. Would you consider such recommendations desirable and helpful going forward? Would you recommend that certain kinds of information be shared between funders, in this case DoD and NCI.***

RESPONSE: Yes, such requirements are appropriate and somewhat inevitable. We have already contacted the FDA for IDE guidance for the carbo-TCN TCC study mentioned above. The ability of different funding agencies to evaluate/track/coordinate/communicate such information is questionable, however, the concept does perhaps have some merit. Of concern would be the possible additional hurdles it might generate.

I would also like to highlight some new services we have introduced at Moffitt to assist investigators in using patient-derived data for "omics" studies, which we hope will also serve as a means of providing a system to promote data provenance and data governance. This new service was created approximately one year ago and is called the Department of Information Shared Services (ISS). We started this effort as part of a large prospective observational study called the Total Cancer Care Protocol (TCCP). This protocol involves the collection of clinical data and tumor specimens for research purposes, and an information technology platform that provides a robust "warehouse" for clinical and molecular profiling data. To-date, over 76,000 cancer patients from Moffitt and consortium medical centers have been enrolled in the protocol.

As mentioned earlier, ISS administers release of data from the central data warehouse and ensures standardization of data release, regulatory compliance and resource efficiency. Within the ISS Department resides the Data Concierge, which receives and processes requests

for data, and the Project Management Office (PMO) that coordinates the aggregation of data across sources systems when the requested data do not reside entirely in the central data warehouse.

The process by which data requests are fulfilled begins with the Data and Biospecimen Request Form, a web-based tool that solicits specific information from the requestor. The form also includes a section for uploading regulatory approvals when appropriate. All requests for patient-level data must have undergone review by both the Moffitt Scientific Review Committee and the USF IRB, our IRB of record for the protocol. The Data Concierge reviews the IRB-approved protocols to ensure that the requestors have received approval to obtain the information being requested and in close collaboration with the requestor, Moffitt's Tissue Core and the Departments of Biomedical Informatics, Data Quality and Standards, and Information Technology, the data sources are identified and data quality checks are performed prior to the final release of the data. All data releases are logged into a central tracking system to support project management and data usage reporting.

To facilitate the above process, several honest brokers have been established within Moffitt, including the ISS Data Concierge, Tissue Core, and Cancer Informatics Core. Individuals working within these groups have access to patient protected health information residing in multiple source systems. However, the release of information through the source systems is coordinated by the ISS Department, as described above. Given that some research programs are active users of the data, a program-specific honest broker policy has also been established, whereby a data concierge residing within ISS is dedicated specifically to the program. The program-specific honest broker is intimately familiar with data residing within the "hub," as well as the specific program or "spoke" in which he or she is working. While the program-specific or "spoke-level" honest broker's daily activities are directed by the research program leader, he or she officially reports to the Director of ISS and logs all data spoke-level data requests into the central ISS data request tracking system. The spoke-level honest broker may also contribute subject matter expertise during database development and integration of spoke-level data back into the hub.

The data release process and honest broker policies outlined above comprise an efficient approach to providing high-quality patient-level data to requestors. However, investigators often require aggregate data or "counts" in preparation for research. Enabling the investigators to directly query de-identified data residing in the central database is the most efficient approach toward "cohort identification." As such, Moffitt has configured a front-end tool that allows investigators to identify groups of patients based on a set of parameters defined by variables residing in multiple source systems. Once the investigator identifies a cohort and receives regulatory approval, he or she completes the Data and Biospecimen Request form to gain access to the patient-level data.

To effectively address the multitude and complexity of issues that arise in conjunction with the storing and dissemination of data, Moffitt has instituted a data governance structure emanating from a Steering Committee of leadership and stakeholders, and function-specific subcommittees that address various aspects of operational decision-making. The subcommittees are defined around foci of subject matter expertise and meet monthly to discuss topics including information technology support of TCC, data acquisition, data

standards and release, biobanking standard operating procedures, and management of the TCC protocol itself. Recommendations made by each subcommittee are reviewed for approval by the TCC Steering Committee, which authorizes action, allocates resources when necessary and ensures that the overall activities of each committee are well-coordinated and collectively advance the institution toward its goals of personalized medicine.

Data provenance is maintained throughout this process, beginning with the Scientific Review Committee evaluation requiring appropriate study design, data management plans, complete statistical analysis plans and detailed power calculations for all study protocols. Studies involving "omics" also require involvement of a bioinformatician and, in some cases, a biostatistician. Protocols are reviewed for the integrity of the study design, including proposed training and test sets; thus resulting in high internal validity of the research.

Biostatisticians work with time-stamped data files for analyses, with nearly all analyses executed by statistical software coding (e.g. SAS, R, Matlab). For all published work, both the program code and data files are retained, thus allowing any analysis to be re-run.

Biomedical Informatics documents transformation algorithms in the data dictionary, as well as utilize software tools that capture physical metadata, including transformations, as the data is moved from source to target system. A reconciliation occurs between each uniquely barcoded specimen, its related CEL file and the study participant.

Gil, I hope we have been able to clarify the outstanding questions posed by the Committee. If, however, additional information is warranted, please feel free to contact me to discuss.

Best regards,



William S. Dalton, PhD, MD
President & Chief Executive Officer

cc: Christine Micheel, PhD, IOM
Johnathan Lancaster, MD, PhD
Robert Wenham, MD
L. David delaParte, Esq.