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The Duke Scandal

IOM Committee Focuses On Studies Needed To Protect Patients In Omics-Based Trials

By Paul Goldberg

A committee of the Institute of Medicine is likely to recommend that researchers conduct prospective-retrospective studies before using genomic predictors to guide therapy in clinical trials.

Though the IOM Committee on the Review of Omics-Based Tests for Predicting Patient Outcomes in Clinical Trials was formed in the aftermath of the Duke genomics controversy, its most important task is to determine prospectively when it's appropriate to start testing genomic predictors for guiding patient care in the clinic.

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Drug Shortages

Obama's Executive Order Gives FDA Authority To Manage Shortages of Generic Cancer Drugs

By Lucas Thomas

President Barack Obama earlier this week signed an executive order aimed at reducing the shortages of prescription drugs—the government's first visible attempt to combat the problem that affects many areas, including oncology.

The executive order, signed Oct. 31, expands FDA early notification requirements. Before, manufacturers were only required to report a shortage if they were the exclusive provider of the drug. The executive order broadens that mandate, making it a requirement for manufacturers to "provide adequate advance notice of manufacturing discontinuances that could lead to shortages of drugs that are life supporting or life sustaining, or that prevent debilitating disease."

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In Brief

Cold Spring Harbor Laboratory Joins SWOG; First Basic Science Lab To Join Cooperative Group

COLD SPRING HARBOR LABORATORY has joined **SWOG**. This is the first time an NCI-designated basic science center has joined a national cooperative group. The center does not provide clinical care to patients.

"This collaboration will lead to many important discoveries," said SWOG Chair Laurence Baker. "Including the identification of predictive biomarkers, new therapeutic and perhaps prevention targets, and ultimately lead to the integration of modern cancer genetics and cancer clinical trials."

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Committee Seeks New Details On Moffitt's Short-Lived Trial

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The group's recommendations would likely determine the ground rules for guiding genomics and proteomics research for years to come.

"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 [Investigational Device Exemption] from the FDA," wrote committee chair Gilbert Omenn, professor of molecular medicine and genetics at the University of Michigan, in a letter to William Dalton, president, CEO and director of Moffitt Cancer Center, where an omics trial similar to Duke's was being conducted.

"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?" he wrote.

Omenn's IOM committee hasn't been making public statements, but it has been placing a remarkable amount of information in the IOM's "public access files," often shedding light on the direction of its thinking.

In addition to revealing the committee's thoughts on when genomic predictors are ready for testing in the clinic and the regulatory clearance that should be required, Omenn's letter and the exchange of correspondence it triggered provides an account of a previously unexplored aspect of the Duke controversy—a small, short-lived pilot prospective clinical trial of the technology in ovarian cancer conducted at Moffitt.

Funded in part by the Department of Defense, that trial was conducted at Moffitt (The Cancer Letter, Oct. 9, 2009). Sources said the Moffitt study accrued only four patients before it was stopped. By contrast, Duke accrued over 100 patients to its three phase II studies, and some of these patients and their survivors are now suing that institution.

FDA states that in cases when a new test is used to determine therapy for patients, researchers must obtain an Investigational Device Exemption, the device equivalent of an Investigational New Drug permit required for the vast majority of drug trials. The Duke trials were conducted without an IDE, and apparently no such license was obtained by Moffitt.

In his response to Omenn, Dalton agreed that such requirements are needed.

"Yes, such requirements are appropriate and somewhat inevitable," Dalton wrote. "We have already contacted the FDA for IDE guidance for the carbo-TCN TCC study…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."

Scientists who develop genomic and proteomic predictors say they are awaiting guidance from the IOM committee and, separately, from FDA.

"This side episode to the Duke situation represents one more example of the great complexities involved in the development of predictive clinical tests, not just with respect to the biology and the enabling technology, but also in the clinical research processes necessary to develop these tests," said David Parkinson, president and CEO of Nodality, a company that develops predictive tests to enable biologically-informed clinical treatment decisions in cancer and autoimmune disease.

"The new genomic and proteomic technologies permit the development of tests which allow clinical decisions regarding treatment to be based on the biology of an individual patient's malignancy," said Parkinson, who is not a member of the IOM panel. "It becomes ever more clear that the process required to develop these tests is as complex and requires as much rigor, as that involved in the development of therapeutics."

The committee's target date for releasing the final version of its report is slated for March. However, a "pre-publication" version could be made public earlier, perhaps in January.

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The exchange of letters sparked by the IOM committee, strikes down the view that the Duke scandal was limited to the work of one group of researchers at one institution, showing how the technology—which has since been retracted—was spread to another institution.

The case also points to the need for uniform standards across funding agencies. Correspondence triggered by Omenn shows that NCI was funding an R33 grant to validate the performance of the signatures in new samples once the signatures had been locked down.

In the R33, the signatures would not have been used to guide patient therapy. However, the researchers at the institution went to DOD to get sponsorship for the trial in which signatures were to guide therapy. This was done before the R33 validation was completed.

These details were revealed in a letter from NCI biostatistician Lisa McShane, a key figure in the controversy.

Copies of the Moffitt response to Omenn appears on p. 4, and McShane's letter expressing disagreement with that response appears on p. 7.

The letters show there were two studies being run concurrently at Moffitt.

In the first, an NCI-funded R21/R33 study, signatures were developed in the initial R21 phase (completed by 2007), and in the R33 phase the performance of the locked down signatures was to be validated using a prospective-retrospective evaluation similar to what the IOM is now considering.

Importantly, patient therapy is not being guided at this stage in the R33 grant-funded study; NCI's intent was that guidance would be considered after the signatures were validated. However, the second study being run at Moffitt was a DOD-funded clinical trial, in which signatures were being used to guide therapy.

"If Moffitt researchers had done the validation studies requested by NCI, they would have shown whether their technology works or doesn't work well enough to be validated in a clinical trial where it would be used to guide therapy," said Keith Baggerly, a biostatistician at MD Anderson Cancer Center.

The exchange between Omenn, Dalton and McShane is important because it shows that the impact of the Duke scandal reached outside Duke.

However, the Moffitt case was handled differently. "Once this problem was identified, there was not the shutting and reopening of trials," Baggerly said. "It stopped. The Moffitt example shows that these problems are neither unavoidable nor unfixable."

Baggerly and collaborator Kevin Coombes used the www.clinicaltrials.gov database to identify four studies where the signatures introduced by Potti et al. (Nature Medicine, 2006) to guide patient therapy. That paper has been retracted as part of the aftermath of the Duke scandal.

Three of these studies were conducted at Duke. These were: NCT00509366, NCT00545948, and NCT00636441. The fourth, NCT00720096, was conducted at Moffitt by gynecologic oncologists Johnathan Lancaster and Robert Wenham.

Wenham, the principal investigator on the Moffitt study, had trained at Duke. A sub-investigator on the study—Lancaster, also a gynecologic oncologist at Moffitt—had been a part of the Duke team, and his name is listed on Duke patents and publications.

The pilot study used "genomics-directed salvage chemotherapy with either liposomal doxorubicin or topotecan" technology to examine cancer genes to predict how individual women with recurrent ovarian cancer will respond to either liposomal doxorubicin or topotecan. Potti et al. had discussed the use of topotecan and paclitaxel as salvage therapy for ovarian cancer, which was the context of the Moffitt trial.

However, in the exchange of letters triggered by Omenn, Dalton wrote that the classifiers used in the Moffitt study weren't the same as the classifiers described in the now retracted Nature Medicine paper.

Versions of the trial protocol, however, which are also available as public access files from the IOM, do not make this distinction.

Version 13 (PAF 189, p.28) notes "The predictive models for Doxil and topotecan as defined in our previous work (Potti, et al. 2006) will be implemented to assess the predictive response of a clinical trial sample."

In his letter to Omenn, Dalton makes no comment on whether Moffitt had an IDE. "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," he wrote. "Four to five years ago, there was a much lower level of awareness than we have today on this topic."

Dalton's letter contains a caveat: "I, of course, consulted with Drs. Johnathan Lancaster and Robert Wenham, who were primary investigators for this trial, and the responses represent their views."

Moffitt officials said they would be unable to arrange an interview by deadline.

NCI officials, who wanted to see a validation of signatures before the start of a trial didn't know that the clinical study had begun under DOD sponsorship. The institute learned about it by running a search of www.clinicaltrials.gov and asked Moffitt to respond to

questions about its trial.

"NCI was not informed that a trial had already been initiated while NCI was funding the R33 grant to validate the predictors," wrote McShane, the institute's biostatistician that reviewed both the Duke and Moffitt grants, in a letter to Omenn.

"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," McShane wrote. "The following day, October 9, 2009, NCI was informed that the trial was closed."

On Oct. 23, 2009, The Cancer Letter reported the closing of the Moffitt trial:

"According to the database, the study was ended because 'funds for this project have been spent, and it is thereby terminated.' A Moffitt spokesman's description of the reason for closing the trial differed from one cited in the database. 'The trial was closed during extension of funding for low accrual,' Patricia Kim, a Moffitt spokesman, said in an email. The action, taken on Oct. 8, two days following suspension of the first two Duke trials, was not related to that controversy, Kim said."

The Duke trials were suspended and later restarted. The Moffitt trial was terminated outright.

The scandal escalated on July 16, 2010, when this publication reported that Duke researcher Anil Potti had misrepresented his credentials, claiming, among other things, to have been a Rhodes scholar.

Meanwhile, the industry awaits ground rules.

"The FDA has indicated its interest and the importance of this area with a series of meetings and public statements that it intends to regulate this area more closely," said Nodality's Parkinson. "The agency is also in the process of releasing a series of relevant draft guidances which will be particularly useful to industry test developers. As represented in some of the comments related to these interchanges NCI is clearly on top of these issues as well.

"Furthermore, it appears that the IOM committee is tackling these issues directly and will soon provide important recommendations to which clinical researchers and other stakeholders in this field should pay close attention," Parkinson said. "The Moffitt response letter seems to me to indicate the maturation of an institution as it develops policy and safeguards in a dynamic and evolving field which represents an important focus of its research.

"We can all learn from these recent experiences as we explore how to use the new molecular technologies to improve patient care."

In a related development, The Chronicle, Duke's independent student newspaper, reported that the university is at the most a month away from concluding the process of determining which of the papers of researcher Anil Potti would be retracted.

So far, seven papers have been retracted. They include papers in Nature Medicine, The New England Journal of Medicine, The Lancet Oncology, The Journal of Clinical Oncology, Blood, the Proceedings of the National Academy of Sciences, and PLoS One.

Duke officials said in the past that they have focused on 40 papers to which Potti had submitted original data. About a third of these papers would be retracted and another third would be corrected. The story is posted at http://dukechronicle.com/article/potti-saga-near-end-road.

A list of the files available from IOM as well as the files themselves can be obtained by emailing http://iom.edu/Activities/Research/OmicsBasedTests.aspx

The text of a response to Omenn's letter by William Dalton, president and CEO of Moffitt, appears below:

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

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 [sic.] 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 stud 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 include 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.

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Responding to Dalton's letter, Lisa McShane, a biostatistician at the NCI Division of Cancer Treatment and Diagnosis Biometric Research Branch, wrote:

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.

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.

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.

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.

Drug Shortages

Executive Order Combats Gray Market For Generics

(Continued from page 1)

"This is a problem we can't wait to fix," said Obama. "That's why today, I am directing my administration to take steps to protect consumers from drug shortages, and I'm committed to working with Congress and industry to keep tackling this problem going forward."

In conjunction with the executive order, Obama announced his support of the Preserving Access to Life-Saving Medications Act (H.R. 2245, S. 296). If passed, this law would mandate early notification of all potential shortages, not just of drugs made by single providers.

Another component of the executive order is to expedite the approval process for new manufacturing sites, providers and manufacturing changes.

FDA will receive increased resources for the Drug Shortage Program by enabling what the White House calls a "surge team" to specifically monitor the potential of a drug shortage. When a shortage is identified, the program will work to precede it by encouraging other manufacturers to increase their supply.

The executive order also includes provisions to prevent price gouging on the gray market, directing FDA to work with the Department of Justice to determine

whether distribution practices are lawful. Anything deemed by the DOJ to be out of line with industry regulations could trigger "whatever enforcement actions…it deems appropriate," the order reads.

This is significant because there had been no previous regulation in place to prevent gray market vendors from stockpiling drugs and selling them at inflated prices. The executive order now introduces the potential for legal action to be taken against any supplier operating outside the realm of "applicable law."

"I commend the President for his actions today to help patients obtain lifesaving drugs that are in critically short supply," said Rep. Elijah Cummings (D-Md.), ranking member of the House Committee on Oversight and Government Reform. "In addition to ensuring that these drugs are available for patients who need them, we must ensure that so-called 'gray market' middleman companies are not gouging patients by charging exorbitant rates."

Cummings began publicly investigating the gray market on Oct. 5, when he sent letters to five companies—Allied Medical Supply Inc., Superior Medical Supply Inc., Premium Health Services Inc., PRN Pharmaceuticals, and Reliance Wholesale Inc.—who were suspected of price gouging. The letters requested purchasing, sales and storage documents from the companies (The Cancer Letter, Oct. 14).

"The idea that some companies may be taking advantage of cancer patients and others in such vulnerable positions is criminal, and we are taking action to get to the bottom of this," Cummings said.

On Nov. 2, two days after the president's order was signed, Cummings pressured one of the identified gray market company by sending a second letter to Superior Medical Supply.

The letter begins: "After receiving my letter, an attorney working for your company informed my staff that you would cooperate fully with this investigation and provide the requested documents. Since then, however, several calls to your attorney have been ignored, and calls directly to you have not been returned. I am concerned that your recent lack of cooperation may signal a decision on your part to reverse course and obstruct a congressional investigation that potentially could impact the health of millions of Americans."

This letter expands the concerns raised in the previous letter about Superior's questionable operating practices.

It adds that, in 2008, the company paid $200,000 to settle allegations from the Justice Department that said Superior held "inaccurate and incomplete records related to the receipt, delivery, sale, and disposal of controlled substances that it received and distributed to customers" on 58 different occasions between January and September of 2007.

It also mentions a 2009 disciplinary action from the Colorado Board of Pharmacy for buying drugs from unregistered sources.

Cummings reiterated his request for the documents, as well as "all documents and communications relating to any disciplinary or enforcement actions brought against your company by any local, state, or federal authority," due by Nov. 14.

The letter is posted at: http://democrats.oversight.house.gov/images/stories/EECLetter_to_Superior_11_02_11.pdf.

Bruce Chabner, director of clinical research at the Massachusetts General Hospital MGH Cancer Center and chair of the National Cancer Advisory Board, said in a perspective article in The New England Journal of Medicine that the executive order stops short of addressing the economic and production problems that have created the shortage.

"This action represents a step forward in addressing this issue," wrote Chabner. "The specific manner in which these orders will be implemented and the degree to which they will ameliorate the drug shortages are unclear. The executive order does not improve reimbursement for generic drugs or address the need for redundant production facilities or incentives such as rewarding past performance in the approval of new generics applications.

"It will be up to the community of cancer doctors, patients, and concerned citizens to demand further action at the federal level and by the private sector to ensure access to lifesaving and life-extending drugs. A license to market lifesaving products should entail a public obligation to meet demand. After all, if we can afford to spend billions of dollars on medical research, we should, as a society, enjoy the fruits of that investment by assuring the manufacture of generic drugs."

Rep. Joe Pitts (R-Pa.), chairman of the House Energy and Commerce Health Subcommittee, which recently held a hearing about the drug shortages, issued a statement in response to the executive order:

"I am bewildered as to how the administration can claim that they can't wait for Congress to address drug shortages since we have been anxiously awaiting a report promised by the administration at our hearing over a month ago. The issue is complex and witnesses, including HHS, testified at our hearing that there are multiple causes and as a result, it will require multiple

solutions. I am disappointed that the administration has spent more time strategizing a press rollout to politicize this deadly issue than working with Congress to resolve the problem."

In a related development, FDA issued a lengthy report on the drug shortages. The document is posted at http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm275051.htm

The text of the executive order follows:

By the authority vested in me as President by the Constitution and the laws of the United States of America, it is hereby ordered as follows:

Section 1. Policy. Shortages of pharmaceutical drugs pose a serious and growing threat to public health. While a very small number of drugs in the United States experience a shortage in any given year, the number of prescription drug shortages in the United States nearly tripled between 2005 and 2010, and shortages are becoming more severe as well as more frequent. The affected medicines include cancer treatments, anesthesia drugs, and other drugs that are critical to the treatment and prevention of serious diseases and life threatening conditions.

For example, over approximately the last 5 years, data indicates that the use of sterile injectable cancer treatments has increased by about 20 percent, without a corresponding increase in production capacity. While manufacturers are currently in the process of expanding capacity, it may be several years before production capacity has been significantly increased. Interruptions in the supplies of these drugs endanger patient safety and burden doctors, hospitals, pharmacists, and patients. They also increase health care costs, particularly because some participants in the market may use shortages as opportunities to hoard scarce drugs or charge exorbitant prices.

The Food and Drug Administration (FDA) in the Department of Health and Human Services has been working diligently to address this problem through its existing regulatory framework. While the root problems and many of their solutions are outside of the FDA's control, the agency has worked cooperatively with manufacturers to prevent or mitigate shortages by expediting review of certain regulatory submissions and adopting a flexible approach to drug manufacturing and importation regulations where appropriate. As a result, the FDA prevented 137 drug shortages in 2010 and 2011. Despite these successes, however, the problem of drug shortages has continued to grow.

Many different factors contribute to drug shortages, and solving this critical public health problem will require a multifaceted approach. An important factor in many of the recent shortages appears to be an increase in demand that exceeds current manufacturing capacity.

While manufacturers are in the process of expanding capacity, one important step is ensuring that the FDA and the public receive adequate advance notice of shortages whenever possible. The FDA cannot begin to work with manufacturers or use the other tools at its disposal until it knows there is a potential problem. Similarly, early disclosure of a shortage can help hospitals, doctors, and patients make alternative arrangements before a shortage becomes a crisis.

However, drug manufacturers have not consistently provided the FDA with adequate notice of potential shortages.

As part of my Administration's broader effort to work with manufacturers, health care providers, and other stakeholders to prevent drug shortages, this order directs the FDA to take steps that will help to prevent and reduce current and future disruptions in the supply of lifesaving medicines.

Sec. 2. Broader Reporting of Manufacturing Discontinuances. To the extent permitted by law, the FDA shall use all appropriate administrative tools, including its authority to interpret and administer the reporting requirements in 21 U.S.C. 356c, to require drug manufacturers to provide adequate advance notice of manufacturing discontinuances that could lead to shortages of drugs that are life supporting or life sustaining, or that prevent debilitating disease.

Sec. 3. Expedited Regulatory Review. To the extent practicable, and consistent with its statutory responsibility to ensure the safety and effectiveness of the drug supply, the FDA shall take steps to expand its current efforts to expedite its regulatory reviews, including reviews of new drug suppliers, manufacturing sites, and manufacturing changes, whenever it determines that expedited review would help to avoid or mitigate existing or potential drug shortages. In prioritizing and allocating its limited resources, the FDA should consider both the severity of the shortage and the importance of the affected drug to public health.

Sec. 4. Review of Certain Behaviors by Market Participants. The FDA shall communicate to the Department of Justice (DOJ) any findings that shortages have led market participants to stockpile the affected drugs or sell them at exorbitant prices. The DOJ shall then determine whether these activities are consistent with applicable law. Based on its determination, DOJ, in coordination with other State and Federal regulatory

agencies as appropriate, should undertake whatever enforcement actions, if any, it deems appropriate.

Sec. 5. General Provisions.

Nothing in this order shall be construed to impair or otherwise affect:

• authority granted by law to an agency, or the head thereof; or

• functions of the Director of the Office of Management and Budget relating to budgetary, administrative, or legislative proposals.

(b) This order shall be implemented consistent with applicable law and subject to the availability of appropriations.

(c) This order is not intended to, and does not, create any right or benefit, substantive or procedural, enforceable at law or in equity by any party against the United States, its departments, agencies, or entities, its officers, employees, or agents, or any other person.

In Brief

Cold Spring Harbor Joins SWOG; Korc Joins Indiana University

(Continued from page 1)

Bruce Stillman, president of Cold Spring Harbor Laboratory and director of the CSHL Cancer Center, said "CSHL is pleased to be the first basic science NCI-designated cancer center to join the SWOG cancer clinical trials group. I hope that this initiative helps to break down barriers between discovery science and clinical research."

The idea for the collaboration began in a meeting at Cold Spring Harbor last June, called by SWOG's Genomic Medicine Task Force. All cooperative group chairs were invited to attend.

The meeting focused on developing strategies for making better use of the collections of biospecimens held by SWOG and other cooperative groups.

Baker also announced at the June meeting that SWOG would consolidate its multiple specimen banks into a single biorepository, making it easier for researchers to answer vital questions using those specimens.

By the end of this year, SWOG will have consolidated nine distinct specimen banks all across the country into a single biorepository at Nationwide Children's Hospital, in Columbus, Ohio. The biorepository will hold more than 300,000 specimens from more than 20,000 patient volunteers on SWOG cancer treatment trials.

MURRAY KORC joined the **Indiana University Melvin and Bren Simon Cancer Center** as the first Myles Brand Professor of Cancer Research.

Korc was the scientific leader of the Pancreatic Cancer Group at the Dartmouth-Hitchcock Norris Cotton Cancer Center in Lebanon, N.H.

The Myles Brand Professorship was created to help physicians and scientists at the IU Simon Cancer Center to continue investigating malignancies, such as pancreatic cancer, which claimed the life of Brand, the 16th president of Indiana University.

Korc is one of the first researchers to receive funding from the Physician Scientist Initiative. The initiative was created by the IU School of Medicine, and is supported by a $60 million grant from the Lilly Endowment.

Korc's focus is on aberrant growth-factor signaling in pancreatic cancer and genetic mouse models of pancreatic cancer. He has published more than 250 peer-reviewed manuscripts, and is recognized for his contributions to the understanding of the EGF receptor and transforming growth factor-beta in pancreatic cancer.

Korc was the Joseph M. Huber Professor of Medicine and a professor of pharmacology and toxicology at The Dartmouth Institute for Health Policy and Clinical Practice at Dartmouth Medical School. Since 2003, he has served as chair of the Dartmouth Hitchcock Medical Center Department of Medicine and as a member of the Section of Endocrinology. From 2008 to 2010, he was the associate dean for clinical and translational research.

THE PANCREATIC CANCER ACTION NETWORK named seven new members to its scientific advisory board.

They are: **Christine Iacobuzio-Donahue** and **Anirban Maitra** of Johns Hopkins University; **Anil Rustgi** and **Robert Vonderheide** of the University of Pennsylvania; **Frank McCormick**, University of California, San Francisco; **Diane Simeone**, University of Michigan; and **Craig Thompson** of Memorial Sloan-Kettering Cancer Center.

The Scientific Advisory Board provides advice, scientific expertise, and leadership to the network, with regards to the research and scientific program goals and initiatives of the organization.

"I am pleased to welcome these distinguished researchers to the Scientific Advisory Board. They bring a great wealth of cross-disciplinary expertise to the organization and their active participation will further

strengthen our scientific and research agenda," stated Julie Fleshman, president and CEO of the Pancreatic Cancer Action Network.

The terms of three members of the advisory board ended in June of this year, including: **Ralph Hruban**, Johns Hopkins University; **Margaret Mandelson**, Fred Hutchinson Cancer Research Center; and **Selwyn Vickers** of the University of Minnesota.

Two members—**Teri Brentnall** of the University of Washington and **Elizabeth Jaffee** of Johns Hopkins University—completed their terms in October.

All past members will transition onto the network's Emeritus Scientific Advisory Board.

DAMON PAPAC and **JOSEPH MURPHY** joined the **Southern Research Institute** to lead two departments in its Drug Development Division.

Papac will be the director of Bioanalytical Sciences. He was formerly director of Discovery ADME from Myrexis/Myriad Pharmaceuticals in Salt Lake City.

He has held bioanalytical ADME, mass spectroscopy, pharmacokinetic and pharmaceutic positions for more than 17 years. He served on the editorial board for Analytical Biochemistry, and was an ad hoc reviewer for the Journal of American Society of Mass Spectrometry, Analytical Chemistry, and the Journal of Pharmaceutical Sciences. He is a member of the American Society of Mass Spectrometry and the American Association of Pharmaceutical Scientists.

Murphy will lead efforts in Cancer Therapeutics and Immunology. He joins Southern Research from Trinity College at the University of Dublin in Ireland, where he was a lecturer and senior research scientist.

Previously, he served as founder and managing director of Emmerex Limited, a company focused on developing an immune-based therapy for cancer. He has served as a reviewer for Clinical Medicine/Oncology, Prostate Cancer Foundation of Australia, Clinical Medicine/Cardiology, International Journal of Cancer, and the Journal of Medical Genetics and Genomics.

MOFFITT CANCER CENTER and **THE US ONCOLOGY Network** announced a joint effort to expand access to patient services in Florida and will collaborate to develop and operate community-based cancer centers throughout the state.

Initially, US Oncology and Moffitt will develop a cancer center in New Port Richey, Fla., where independent physicians will be able to treat patients while supported by both organizations.

Over time, the collaboration will expand to other sites across the state. This will complement the Moffitt Affiliate Network of 15 Florida hospitals and more than 400 oncologists.

FDA Approvals

Agency Approves HPV Test That Detects 14 High-Risk Strains

FDA approved the **Aptima HPV assay**, an amplified nucleic acid test that detects 14 types of high-risk strains of human papillomavirus associated with cervical cancer and precancerous lesions. The test has been approved to run on the Gen-Probe Incorporated TIGRIS instrument system.

Testing is performed from ThinPrep liquid cytology specimens routinely used for Pap testing. Unlike other FDA-approved, DNA-based HPV tests, the APTIMA HPV assay detects messenger RNA over-expressed from two viral oncogenes that are integral to the development of cervical cancer.

"We believe our Aptima HPV assay will offer physicians and patients a more accurate screening test for cervical cancer, and significantly improve testing efficiency for our laboratory customers," said Carl Hull, Gen-Probe's president and chief executive officer. "FDA approval represents a major milestone for the company, since developing the Aptima HPV assay was the largest and most complex diagnostic R&D program we have ever completed."

"Most HPV infections clear up on their own, so it's important to identify those persistent, high-risk infections that are most likely to lead to cervical cancer," said Tom Wright, professor of pathology and cell biology at the Columbia University Medical Center.

The assay is approved to test women age 21 and older whose Pap tests showed atypical squamous cells of undetermined significance, and to screen women age 30 and older as an adjunct to Pap testing.

Approval was based on data from the CLEAR (CLinical Evaluation of Aptima HPV RNA) trial, which analyzed approximately 11,000 women undergoing routine Pap testing at 18 U.S. clinics.