THE CANCER LETTER

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MED-C
Molecular Evidence Development Consortium

Nascent Group Points to a Way To Validate, Pay for Genomic Tests

By Paul Goldberg

How is this for a plan:

Replace the U.S. system for validation and payment for cancer genomic tests with something that actually makes sense.

Dane Dickson, a doctor in Idaho, who until recently had the distinction of being the only oncologist working under the roof of Centers for Medicare and Medicaid Services, would like to do just that—and some important players in cancer research are betting on his success.

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Conversation with The Cancer Letter

A Doctor's Plan to Save Personalized Medicine

Dane Dickson would like to change the U.S. system for validation and coverage of molecular tests, thereby opening the road to development of complex tests and comprehensive genomic assays.

Recently, Dickson formed a nonprofit public-private partnership, called MED-C and published a white paper, which is posted here.

In an interview with Paul Goldberg, editor and publisher of The Cancer Letter, Dickson described his rationale for trying a new approach to solving this fundamental problem in personalized medicine.

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Duke Settles with Potti's Patients; Misconduct Probe Now in Fifth Year

By Paul Goldberg

Duke University has settled the suits filed by patients who were enrolled in clinical trials that were testing the technology developed by Anil Potti and his mentor Joseph Nevins.

By settling, Duke avoided having to confront embarrassing revelations about how much the university's deans knew about the problems in the genomic research organization.

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MED-C Seeks to Make Sense of Coverage of Genomic Tests

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Until recently, Dickson, who is 46, was setting cancer policy as a part-time employee of at Palmetto GBA, a CMS contractor which has pioneered a program for approval of genomic tests (The Cancer Letter, Jan. 23). This was an important position since Palmetto's MolDX program is likely to shape payment policy for the entire Medicare program.

Now, Dickson has struck out on his own, launching a nonprofit public-private partnership called MED-C, short for Medical Evidence Development Consortium, which aims to set policy on validation of genomic tests.

In his former job at CMS, Dickson had his finger on the pulse of the genomic industry:

"I could see a very disturbing trend, namely the end of personalized medicine before it could ever get started. I saw new technology with great promise, but very little direct application to patients," Dickson said in a conversation with The Cancer Letter. "I saw the exit of venture capital due to the unknown, and often labs couldn't find funding to finish the science they started. I also saw that the incredible savings that could be obtained from stopping ineffective treatments were also likely to never materialize.

"As I pondered how and when new promising technology could be introduced to patients with so many obstacles, I started to formulate a method to resolve the major concerns I had seen. The resulting solution required pulling together all stakeholders and focusing their energies into advancing molecular evidence and in return provides each group a tangible benefit. This would allow the introduction of not only NGS, but also build the infrastructure and procedures that would serve as a template to introduce other advances in personalized medicine. It was clear that there was no existing group that could accomplish this task and so a consortium was formed."

The text of the conversation, in which Dickson describes the landscape of genomic testing, appears on page 1.

MED-C received its 501(c)3 in April and has commitments of $1.2 million. The group has in-kind donations to help build the data structures and database of several million dollars. The goal is to raise $3.5 million for operations this year and $5 million next. The costs of construction of the IT structure would add up to much higher numbers, and would depend on the structure of relationships with potential IT partners, Dickson said.

"Precision medicine holds tremendous promise in cancer care, but rapid progress toward the goal of highly personalized, effective treatment combinations that are based on good evidence will require a much more rapid way of developing evidence based on the rapidly growing array of genomic tests used in actual practice," said Mark McClellan, director of the Health Care Innovation and Value Initiative at the Brookings Institution.

"Everyone—oncologists, payers, product developers, and most of all patients—wants to achieve that goal. This will require a different approach to payment for diagnostics, to develop knowledge on their use and impact based on sound scientific principles. MED-C is a broad-based, nonprofit coalition aiming to make it happen."

McClellan, a former FDA commissioner and a former administrator of CMS, serves on MED-C's board.

Brian Druker, director of the Oregon Health & Science University Knight Cancer Institute, has also joined the MED-C board.

"Right now, there are many problems with cancer panels. This includes lack of standardization and lack of consistent policies for insurance coverage driven in part by lack of clear evidence of clinical utility," Druker said to The Cancer Letter.

"MED-C proposes to fill these gaps by working with insurance carriers to provide coverage in return for allowing physicians to treat a patient by a defined pathway with collection of data on the clinical outcome. The reality is that there is something for everyone in this. Patients and physicians clearly benefit by having access to novel agents, as do insurance carriers that want this data to make coverage decisions, NGS sequencing companies that struggle with insurance coverage for

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their testing, and pharma companies looking to collect data about the effectiveness of their medications.

"What is needed for this to work is sufficient scale and if MED-C is sufficiently well-funded, I am confident they can achieve these objectives and advance the field of precision medicine. Given the importance of this effort, I have agreed to serve as a member of MED-C's board of directors," Druker said.

Another board member, Jeff Allen, executive director of Friends of Cancer Research, sees promise as well.

"MED-C could be a paradigm shift in creating high-quality evidence about new drugs and molecular diagnostics," Allen said to The Cancer Letter. "This type of systematic approach will allow for large-scale data collection, enhance treatment decisions in the field of lung cancer, and ultimately improve the quality of care."

Dickson's nascent organization is trying to build a partnership of payers, regulators, pharma, industry, patients, providers and laboratories. The objective would be to define testing standards and clinical pathways.

According to the group's white paper, which is posted here, MED-C would:

• Use the combined resources of all stakeholders to accelerate personalized research and appropriate utilization.

• Perform research at lower costs by using innovation and existing infrastructure.

• Collect data of high quality in both testing and therapeutics thereby developing a path to coverage and regulatory decisions.

• Provide access to advanced molecular diagnostics and targeted agents to all patients.

"One of the crucial issues facing us is the rapid availability of specialized molecular diagnostics and the need to develop evidence for their utility," said Razelle Kurzrock, chief of the Division of Hematology & Oncology, Murray Professor of Medicine, deputy center director for clinical science, and director of the Center for Personalized Therapy & Clinical Trials Office at UC San Diego Moores Cancer Center.

"MED-C should bring multiple stakeholders together that will build a research initiative that will advance molecular research," Kurzrock said. "We have also formed a Medical Oversight Committee that will determine treatment protocols, review the data, publish results and introduce new testing models. This is a potentially very valuable initiative for CMS and other payers with the ambitious goal of bring genomic testing to thousands of patients and collect outcomes in a scientific rigorous manner, hence informing the future of this field. The first focus will likely be lung cancer, as this is a major killer of Americans."

Vincent Miller, chief medical officer of Foundation Medicine Inc., is a supporter as well.

"MED-C is a visionary yet achievable initiative that recognizes the value of integrating comprehensive genomic profiling and real-world evidence in the care of cancer patients," Miller said to The Cancer Letter.

"We believe innovative programs like MED-C will be catalysts for the broad adoption of precision medicine in oncology, particularly within the community practice setting. Dr. Dickson's skill set of community oncologist and clinical trialist and his experience in the payer world make him uniquely positioned to lead this initiative."

Conversation with The Cancer Letter

Dickson: Bad Genomic Science Can Lead to Patient Harm

(Continued from page 1)

Paul Goldberg: *I hear you stepped down from MolDX, where you were the director of clinical science, last week. Why?*

Dane Dickson: When I started working with the Medicare program a few years ago, first with Noridian [Healthcare Solutions] and then with Palmetto [GBA], it was because of a great desire to help advance patient care, protect the Medicare program, and yet also advance the science that was on the horizon.

While working at MolDX, I could see a very disturbing trend, namely the end of personalized medicine before it could ever get started.

I saw new technology with great promise, but very little direct application to patients. I saw the exit of venture capital due to the unknown, and often labs couldn't find funding to finish the science they started. I also saw that the incredible savings that could be obtained from stopping ineffective treatments were also likely to never materialize.

As I pondered how and when new promising technology could be introduced to patients, I started to formulate a method to resolve the major concerns I had seen.

The resulting solution required pulling together all stakeholders and focusing their energies into advancing molecular evidence. In return, each group would get a tangible benefit. This would allow the introduction of not only [next-generation sequencing], but also build the infrastructure and procedures that would serve as a template to introduce other advances in personalized medicine.

It was clear that there was no existing group that could accomplish this task, and so a consortium was formed.

As it gathered momentum and started to grow, it was clear that I could not do both, and so, with great sorrow, I stepped down to focus my time on building the Molecular Evidence Development Consortium.

PG: *Before we get too deep into MED-C, can you give me some background on the current state of affairs in molecular testing?*

DD: Sure.

PG: *There are lots of molecular tests out there. Do you know how many there are overall, and how many are in oncology? Here's the main question: Does anyone really have this information?*

DD: I don't think anyone knows how many molecular tests are out there.

It's a constantly changing and evolving area. We don't know how many of them are out there, we don't know what they are doing, we don't know what they're looking for, we don't know how they were validated, we don't know how they were shown to have any benefit—or if they have been shown to have any benefit whatsoever.

PG: *Overall, is Medicare, as a federal program, able to determine what it's paying for under the CPT codes? And, let's broaden this question: do private insurers know what they pay for?*

DD: Is Medicare aware of what they are paying for? The answer is no.

For example, if I am looking at an EGFR mutation for lung cancer, Medicare at the current time does not look and ask what sort of methodology you use to analyze for that EGFR mutation—whether it's PCR, whether it's FISH testing, whether it's Sanger sequencing, or whether it's next-generation sequencing.

Payers are using traditional CPT codes; they do not know what they are paying for, and they don't know in some cases if what they are paying for is useful.

Let's take, for example, HER2 testing, which is one of the better-understood areas. It took years for people to realize that not all HER2 testing was created equally. And that even though a lab may say, "I am doing HER2 testing as good as anyone," it later came out that many of the labs that were doing HER2 testing were not doing it in a way that the results would have been validated by an independent lab.

It took years to standardize HER2 testing in a way that we could trust the results between labs. We are now on the brink of thousands of molecular tests that are like the HER2 analysis. Many have the same therapeutic implication as HER2, namely a treatment that is directly associated with the biomarker.

And yet we have many laboratory-developed tests that have never been validated to show that they get the same answer as the FDA-approved companion diagnostics.

This is a major reason why the FDA has made the announcement about LDTs—they are worried, as others have been worried. Can we be sure that someone's analysis of a driver mutation, for which there is a therapy, has been tested in such a way that a true answer has been given?

What's scaring me is that there could likely be a group of patients that are EGFR-negative by a LDT that would have been EGFR-positive by the FDA companion diagnostic kit, and these patients are not being treated by a very effective and reasonable non-toxic treatment compared to the standard chemotherapy.

This is exactly what we saw happen with HER2.

PG: *You're talking harm?*

DD: I'm talking harm.

PG: *Is the chance of harm from a test larger than the chance of harm from a drug?*

DD: Well, it's equivalent in many ways, and that's the problem. This is where there's been a great disconnect.

Whereas the FDA tells a pharmaceutical company that it can only advertise its drug according to the information that is included in the package insert, and they had to show that the drug was safe and useful to receive approval, and the package insert strictly describes how and where that drug could be used.

The laboratory industry often does not need to go through the FDA—and yet they can come into a physician's office and they can say this is exactly how you need to use the test. And, in many ways, they misrepresent the value of their test, just tying into the belief of the physician that, well, if the FDA does this for pharmaceutical companies, obviously the lab industry would be the very same.

What I learned early in my career is that some individuals that would come into my office and talk about the value of their lab test, and explaining why this test is clinically beneficial to patients.

I didn't have the time to drill into their data to determine how they determined their value and its benefit to patients. And in many cases, I would feel like they are talking about a "new" standard of care that I had not seen, and a yet when I did have time to dive deeper, it was clear that their standard of care isn't supported by any of the mainstream literature.

I recognized these individuals weren't even close to under the same scrutiny as the pharmaceutical companies. And, their "selling of a test" could misguide treatment for patients, or in some ways potentially harm patients.

PG: *What's the best-case scenario in the way these tests are used by oncologists, and what's the*

worst-case scenario?

DD: The best-case scenario is that the testing is reliable and consistent, so that we can identify a driver mutation or a biomarker of some significance that reliably allows us to treat a patient in a very specific way and collect data to know if they marker and associated treatment are beneficial.

For example, this would be like finding a HER2 mutation in a breast cancer patient that allows me to use the drug trastuzumab, or an EGFR mutation in lung cancer that allows me to use erlotinib. These are the best-case scenarios—that we can identify a true driver mutation that allows us to target the disease with, in many cases, a therapy that is much less toxic than their carpet-bombing counterparts, which, often times, are how traditional chemotherapy drugs can be considered.

The worst-case scenario is that we convince a physician to act upon an erroneous test that puts a patient at increased risk of being shunted away from a standard of care therapy, or it takes a patient away from further diagnostics or further clinical trials that could be introduced to that patient—but they were not, because they were given erroneous information upfront.

Now, that erroneous information may not be that the test is wrong; it might be that the test has never been shown to have any benefit. I have also seen where individuals in trying to show that their test has value, may recommend a very toxic course of treatment based on very limited clinical data.

Let me give you an example:

We had a test in melanoma that we were evaluating, and the laboratory said they had identified a group of patients that may benefit from interleukin-2 therapy. When we looked at the data, and knowing how toxic interleukin-2 is, and knowing how very few patients on average will benefit from the treatment, we found that this recommendation was based on a less-than-30-patient retrospective case report that came out of one institution—that was collected over many years—and they only looked at a very selective group of patients.

They were basing their entire recommendation, or their theoretical recommendation, on one retrospective data-mining experience. Had this been applied wholesale to the 65+ medical population, there would have been severe toxicity or death.

PG: *And when you are looking at costs, by which I mean costs and toxicity, what's the highest-priced panel of tests you have ever seen?*

DD: What is intriguing to me is that most of these tests cost the same amount of money.

There's a difference between a single multiplex test—for example, if I go through and order basically an adjuvant chemotherapy benefit prognostic model, such as Oncotype DX, which is a multiplex study, even though it's looking at 21 genes, it's a multiplex test that gives one answer basically. Those tests can usually run thousands of dollars, somewhere between $3,000 and $5,000.

Now, this is where it gets more complicated.

If a company goes through and they say, "OK, we are going to analyze gene after gene after gene. And we are going to use different methodologies, different validation, different techniques," then they can stack codes in such a way that, in one specimen, you could have tens of thousands of dollars in costs.

PG: *Since you aren't giving me the number, I will give you one: $30,000, which I've seen for one particular company's test. Is it similar to what you have seen?*

DD: That is an extreme example, but there are groups that identify a certain tumor type, and they want to look at every mutation that has ever been described in any tumor type, whether or not that mutation has been shown to have any prognostic or therapeutic benefit.

They say they are looking at all those genes, because maybe it may allow someone to do research on that patient…

PG: *Medicare is paying, and it doesn't know what it's paying for. Is that how it works?*

DD: Before, a lab could come in and say they were going to order this test, this test, and this test. And it's all medically necessary. This continued until the MolDX program came in and started trying to define exactly how this works. It is likely that many of these things did sneak through.

PG: *What happens outside MolDX?*

DD: Outside MolDX, it's almost certain that a lot of self-covered companies and private insurers are not even sure what they're paying for.

And a lot of these labs have decided not even to deal with the MolDX program, because they recognize there may be easier routes through groups that don't have the expertise or skillset to completely determine what is useful and what is beneficial. But this is changing.

PG: *The reason we're talking now is because that is changing, in the way molecular tests are approved by the FDA and Medicare.*

Do you know when the change is coming, and what the new world will look like?

DD: The change is already taking place. The first step was the building of the MolDX program, which was a pilot program that started in 2011. Its initial idea was to identify what CMS was paying for.

Its second step, which is what I was brought on to do a year and half ago, was to define what is useful by looking at the clinical utility of testing.

Then, in the recent PAMA legislation [Protecting Access to Medicare Act of 2014] that took effect, Congress enacted legislation that included a nod to the MolDX project.

"The secretary of HHS may designate between one and four Medicare administrative contractors to either establish coverage policies or establish coverage policies and process claims." These groups would help unify policy for coverage and/or payment for these molecular tests.

Right now, MolDX is the only group that's doing this.

There's not any legislation right now that says another contractor has to follow what MolDX is doing, but there has been a tendency from Medicare to standardize LDTs across jurisdictions, because it doesn't make sense that a patient can get a treatment paid for in New Jersey that he can't get paid for in Texas.

Medicare recognizes that coverage decisions should be made on a region-based level, and they don't want to lose that— but there is also a need for unified services on a national level. Yet the cumbersome process of doing national coverage decisions is such that it would be impossible to handle but only a few policies per year.

What has happened is that Medicare has recognized that they need to use the expertise that exists in some of their contractors to help define this space, and that's what the MolDX program is doing.

Most people don't know this, but MolDX has probably the most robust team for determining benefit that exists in this nation. There's no other group that has the combination of subject-matter experts, clinicians, pathologists and molecular pathologists to determine whether tests are valuable and whether these tests are useful to the clinical community.

In some ways, the MolDX program is analogous to the role that the FDA has done for drugs, but its role is to determine what is "Reasonable and Necessary," and not statutorily excluded by the legal basis for CMS.

PG: *Has MolDX reviewed most testing that is out there?*

DD: MolDX reviews only the tests of companies that have registered and submitted a complete dossier to MolDX for review. A lot of groups have not registered their tests.

Once again, unlike something like the FDA, which was started with national and congressional direction, the MolDX program was started as a demonstration project and it is gathering steam as time goes on.

What we were seeing initially was people were coming in and thinking, "Well, MolDX is over the Palmetto region of the Carolinas and Virginias, and they also have a relationship with California, so I don't need to worry if I'm out of that region…"

But now, companies that are coming to that are frequently outside of those jurisdictions, who are looking to get approval from MolDX because they're starting to recognize that the MolDX approval probably has the greatest weight for approval nationwide.

MolDX follows strict guidelines of looking at analytical validity, clinical validity, and clinical utility (the ACCE criteria developed by the CDC)—and while the economics that come into play are important, it is not considered as a large portion of the decisions.

In other words, MolDX basically determines if the test is beneficial to the patient and they look at every single component to determine if a test has value.

PG: *Do they pay for something like Oncotype DX or Mammaprint?*

DD: Yes they do. There are certain tests that are paid for by the Medicare program that have been determined to have this benefit.

Because the MolDX program is somewhat new—I was only brought in as the clinical utility expert a year and a half ago—there are some molecular tests, such as the Oncotype test and the Mammaprint test that were approved prior to the full policies and directives of the MolDX program.

One of the arguments that some labs have is that MolDX raised the bar dramatically to allow entry into this space. Those who are familiar with scientific standards would say that all MolDX has done is held greater accountability for good science—or in other words, what determines good evidence that a test has value in a defined set of patients. And when I'm saying value, I'm not talking dollars and cents—I'm talking about impacting patient care in a positive way.

PG: *When FDA was announcing its plans to regulate these tests last summer, I was having a difficult time discerning what level of proof would be required. Now, how much evidence would CMS require to start coverage?*

DD: The FDA looks at the analytical and clinical validity of testing. They do not look at the clinical utility of these tests. For example, the FDA will make sure that a test is reproducible and reliable in looking for the effect that you are looking for, but they will not go through and say that this is something that is useful in the clinic.

That's what the MolDX program is doing.

PG: *But in the future? We are talking about the new era...*

DD: Well, in the new era, it's likely that the FDA is going to take a bigger role.

What may happen is that the FDA may require all complex testing to go through them, then, payers will likely only allow testing that had shown analytical and clinical validity in an FDA approval process. This would not be alone however, they will also have gone through an independent clinical utility process such as the MolDX program is doing.

So the MolDX program is still going to be looking at the clinical utility of a test. Or, in other words, what is reasonable and necessary to be covered by the Medicare program. With this said, it is still unclear what role the FDA will play, and how new regulation swill have effects on patient care.

Now, you asked what level of evidence has MolDX uses to determine that a test is ready to go forward. Medical evidentiary standard cannot be altered, and so generally benefit is shown through well-designed clinical trials. Yet, one of the biggest things, I learned when working as clinical utility expert for MolDX was recognizing that sometimes we would have to think outside the box and extrapolate benefit.

We had to recognize that in some cases, technology that dramatically could meet an unmet need should be introduced even without the same level evidence that was needed in the past. This was especially important in areas such as early prostate cancer, where doing traditional trials is near impossible.

In addition, there is not as much money in the laboratory testing space as there is in the pharmaceutical space.

The reality was that the MolDX program had to recognize other pathways that could strongly suggest utility. One of the pathways—and which has been one of the most significant changes—is the pathway that allows a partner society to recommend a new promising technology.

If a society with a formal relationship with MolDX recommends a test that they feel is important for early adoption to improve patient care and if there are good preliminary data, and MolDX agrees that the test is likely to have significant impact on clinical care, MolDX may allow it to be covered, but may require data collection to confirm the believed benefit.

PG: *So randomized trials are not going to happen?*

DD: They should and need to happen.

But sometime the costs and clinical hurdles make these near impossible to run. In these cases, the MolDX program may have to look at much more modest clinical utility studies and put together guidelines on how the test should be utilized for safety given the more modest data.

PG: *Could I ask you to describe the intellectual journey that led you to the MolDX job, and now to your new responsibilities as CEO of MED-C? I understand that at least part-time you are seeing patients… How did it happen?*

DD: When I was in my internal medicine training at Washington University in St. Louis, the finest internal medicine training program I could ever imagine, they wanted us to understand evidenced-based medicine from its origins and so we were expected to know medical literature very well.

In addition we had frequent journal clubs, where we would do exhaustive critiques of studies not only to understand the results of the studies, but the design and operation of the trials. We were encouraged to go through studies and dissect the trials into their respective parts.

Then, as I started my fellowship at the Huntsman Cancer Institute, I recognized that you could take a clinical trial and extract the essential information and put it in a very concise graphical format.

I proposed that the core literature base of oncology be converted into a rapid learning tool graphic format and proposed the building of this as part of my research time of my fellowship. As you can imagine, it was considered as an unusual project and was frankly a few years ahead of its time. But as a research project, because it was more informatics research, so the university didn't exactly know what to do with this project as part of an oncology fellowship.

So, in 2001, I decided to leave the university and I started a private, solo practice in rural Idaho, and as I started seeing patients. I developed a small company that was called the Summarius Corp. With a small team, we would take a clinical trial that's 12 of 15 pages and extract its component parts and put into a graphical format that would allow a clinician in 30 seconds to find on the page what they wanted to know from that clinical trial.

Eventually we were able to work with some major pharma companies, and in one converted their entire training library over to our format. We renovated their entire training material.

During that time, I worked very closely with clinical trial conversion teams, and I ended up reviewing hundreds if not thousands of oncology trials, including schemas, endpoints, background material and outcomes. I became an expert in clinical trial design, not because I

designed the clinical trials, but because I have reviewed so many trials.

As this was growing, one of the cancer physicians in our region was diagnosed with a brain tumor and abruptly shut his practice. With this unfortunate event, I became much busier clinically overnight. If I was a pure entrepreneur, I would have curtailed my clinical practice and would have grown Summarius, but I was happy taking care of the wonderful people of southeast Idaho, and so was content to keep Summarius small.

One other thing I learned as I was working with Summarius was that no one wanted to see someone spinning information from the clinical trial in such a way that it could be misconstrued as overstepping the value of the data in the trial. Much of this learning was through working with legal and regulatory teams from pharma that were assigned to review what Summarius was doing.

PG: *It still exists?*

DD: It has been mothballed, but you can go on the Summarius website right now and see what we've done in the past. I haven't updated it in many years. I am hoping that it can be resurrected one day—but not now.

PG: *This wasn't for diagnostics or other tests…*

DD: Mainly, this was for pharmaceutical testing. But, when this started in 2001 and 2002, this was also the starting of the hotbed of molecular subtyping, and so much of our reviews did focus on molecular subtyping.

PG: *Where is your practice?*

DD: My practice started in a little town called Rexburg, Idaho, as a solo practice.

I left fellowship, came to a small town, at that time it was around 20,000 people, not including the Brigham Young University Idaho campus, which was the biggest claim in the Rexburg area.

We would see patients that would come from 200 miles of either side of us. Last time I calculated, we had 200 by 200 miles as our area. Patients I see come from southern Montana, western Wyoming, and central and southern Idaho. Some of my patients will travel two-and-a-half hours.

My practice location is bigger than many states.

PG: *Is it still a solo practice?*

DD: I hired a partner around eight years ago, and then we merged with a hospital four years ago, and then we brought in another group, so we're a group of four oncologists; four mid-levels.

Then we have another group that's two oncologists south of us that we're friends with, but they're not affiliated with us, who cover a similar area. So it's really six oncologists covering this huge geographic area.

PG: *What got you involved with the Medicare program?*

As my practice started to expand regionally, I saw there was a need in the state of Idaho to have a stronger unified voice to help drive oncology direction. So I went across the state to Boise, where the majority of the oncologists practice and asked, "What we were doing with our state oncology society?"

And next thing you know, I was president of the Idaho Society of Clinical Oncology. Then, next thing you know, I was working very carefully with Noridian to help determine what interventions should be introduced into the Medicare population. I think Noridian turned to me, because they recognized that I was someone who wanted to help

I worked with Noridian for a few years. And then, when the MolDX program started, Noridian put me in contact with the Palmetto. While I was working with Palmetto, it became clear a need for someone who understood oncology clinical trials, that could help Palmetto in a visible fashion.

They didn't have anyone with my skill set and the background in clinical trials, nor how they should be applied in practice. And one day I asked them if they needed more help, and would it help if I could talk directly to the labs? They made me the director of clinical science and gave me a great deal of support. That continued until last week, when I sadly stepped down to do something I believe could help healthcare (and payers like CMS) even more than I could working inside of Palmetto—namely MED-C.

PG: *So tell me about MED-C.*

DD: Let me give you some background first.

In 2013, the National Comprehensive Cancer Network published something in their non-small cell lung cancer guidelines that was exciting and concerning at the same time.

In the NSCLC guideline, they suggested that a standard of care option was to look for genetic alterations other than the EGFR mutations and ALK rearrangements. And, to do so, use next-generation sequencing to identify these genes.

I found out about this change when my partner, who is trained as both a pediatric and adult oncologist, called me as said, "Where do I send the specimen for testing?"

I had just been reviewing all the literature on NGS in NSCLC, and I knew that the outcomes of these

patients were case reports—and in many cases in only a few patients. And yet the NCCN strongly stated that this was the direction of where medicine needed to go.

When I saw that, I recognized that we could get into deep, deep trouble.

And the reason why is because we could see that next-generation sequencing, had not (and still is not) standardized. We had some labs that were doing it one way, some labs were doing it another way. Some labs were doing hotspot testing and only looking for very specific mutations in very specific genes and others were doing comprehensive genomic profiling and looking at all the genes and everything that could happen in those genes. So there's a great disparity between the labs.

And what we heard from the industry and academics is that not all testing by the methodology of NGS will give you the same answer. So we had two big hurdles: one, non-standardization of testing, and two, preliminary clinical data promising great results, but not with enough outcome data to confirm this belief.

Initially some individuals felt that this was a overstepping of evidence by the NSCLC panel, but after questioning and when further versions of guidelines came out without only minor modification of the recommendation, it was clear that this was something NCCN felt strongly about.

PG: *I hear that there is a white paper that describes its principles and direction, what's its current status?*

DD: While confronting these problems, I started to explore scenarios to allow this technology to be introduced in a way that would address the concerns of the many stakeholders impacted by this technology.

Out of this came a concept that was presented in various multi-stakeholder groups such as the Tapestry SpotDX group and subsequently Friends of Cancer Research/Brookings meetings. The idea was shared in a preliminary "living white paper," or in other words a document that would be continually updated to allow it to evolve with the rapid changing environment.

Now, after further vetting it has been updated and will be released through the MED-C website in the next two weeks as the operational prototype for MED-C's first project.

In short, the white paper outlines three basic principles:

1) Standardize the new testing and compare it back to the old standard of care. When the new technology is cost effective to replace the old technology (either lower cost or incremental benefit or both) then have payers start to cover the testing as part of the MED-C consortium.

2) Standard of Care pathways would be defined by an independent medical oversight committee and then physicians and patients would agree to follow one of the standard of care options and/or associated clinical trials.

3) Both the labs and physicians/patients would report predefined outcomes into an open access database from which further refining of treatments would take place.

Although starting with NGS—the principles can be applied to any new testing or intervention. MED-C is pulling together all the groups that benefit from the advancing of personalized medicine to build the infrastructure that would allow a Consortium to continually update testing, treatments and outcomes to in a stepwise fashion find answers to not only oncologic diseases, but also any other disease that has a genomic, proteomic, or metabolomics association.

PG: *How would you engineer a national rollout of NGS?*

DD: First of all, I need to give a disclaimer: MED-C is not related to CMS or Palmetto in any way. It is a completely separate entity. And prior to my leaving of MolDX, I had not been involved in any substantive way in any future policies that may or may not support a concept such as MED-C or widespread rollout of NGS.

The reason I stepped down from Palmetto before any decisions or direction had been made was so I would not have any real or perceived conflicts of interest in advancing this idea. So with this said, if I was to roll out a new technology such as NGS, I would do it in the following fashion:

First—build a nonprofit consortium: pull all stakeholders together and set the focus first and foremost on what is right for the patient and what is very good science. Then, once that is established, define value for stakeholders to encourage them to help build the consortium. Then, together, build a sustainable nonprofit organization and make sure that it policies and procedures would be built in such a way that it could be reused to work on other projects. Any outcome data collected would be open for review.

Second—standardize technology: how do we know that the results that I get in Idaho are the same as they are in California as it is in New York? What would happen—and this is just the reality of oncology in the nation—if we introduced a new technology that is not defined in a certain way? It is almost certain

that the answers that would come back from that technology are going to be varied and they are going to be different based on which group runs the test. And the results of the labs cannot be aggregated together to collect outcomes.

A paper published by Boland in 2013 showed this fact—when comparing three different instruments from three different manufacturers. If you look at the most simple of mutations, namely single nucleotide polymorphisms, the concordance between the platforms was only 66 percent. And yet, if you define a false positive as a mutation only picked up by one of the three platforms, the SNP false positive rate was 20 percent. For insertions and deletions, the three-platform concordance was only 18 percent and the false positive rate was 61.6 percent.

What we would see if there was a wholesale adoption of a brand new technology like next-generation sequencing without standardization is a heterogeneous group of answers, and we wouldn't know what to do with that information. Patients with true mutations would be missed and not receive targeted drugs or be candidates for clinical trials, and others would be treated with a targeted drug that wouldn't work and may turn the medical community away from a potentially beneficial therapy. Lastly, patients that normally would have been considered for clinical trials with standardized testing may be treated with a targeted agent and no data would be collected on those patients at all to confirm or refute the benefit.

There are several groups such that are working on these standards. Until these are completed it is very difficult to know how to aggregate data from different laboratories. MED-C has formed a Laboratory Oversight Committee that is currently defining the standards that will be used for the consortium. As other groups have their standards released we will incorporate these into our testing requirements but only as long as high standards are maintained.

PG: *Is there more?*

DD: Third—develop standard of care pathways. In areas where it looks as if new technology could replace older technology, at the point the new technology becomes cost effective, testing standards can be developed and then require that patients will be treated according to standard of care pathways with inclusion of mutation driven therapies as able.

For example, let's say a patient has a certain less-common mutation, then this patient may receive first-line traditional chemotherapy, but in second-line they'll receive a targeted agent as part of an associated clinical trial or protocol. Those pathways will be centrally defined by an independent third-party broker.

And the last, fourth step—put it all together. This includes bringing physicians, patients, payers, pharma companies, laboratory, regulatory and industry together under one umbrella and assembling the components in the appropriate infrastructure and data collection methodologies and of course getting it funded so it could continue.

PG: *And this is mostly the white paper?*

DD: Yes. What isn't in the white paper is the implementation of the project. The latest white paper has been being built along with the infrastructure. On Feb. 20 we had our first MED-C joint meeting. There, we had people from the majority of the stakeholders I listed.

In the next few weeks, you will start to see announcements of more pieces that are coming together.

PG: *As far as the white paper goes, are you stopping short of clinical trials similar to ones that NCI has done?*

DD: No, because we see our project meshing beautifully with what the NCI and ASCO and Lung-MAP and others are doing by allowing more patients to have testing that will allow them to enter those clinical trials.

The truth is that in order to implement personalized medicine, it is crucial that we collect a great deal more data.

Much of that may not be available in one place. If we don't do what I'm proposing, a lot of patients will be tested and their data will never be collected. And we know, that sitting in many thousands of oncologists' offices nationwide, there are many patients who could be tested—and patients who could have their data collected using already existing infrastructure in those offices.

But unless we have the right scaffolding put in place it won't happen, and without a much larger effort of data and outcome collection we will never unlock personalized medicine.

Many payers require preauthorization and ask us to give information on patients, so if a patient agrees to a data sharing agreement then the same office staff that is working with preauthorization would, under the physician direction enter de-identified clinical data and then are allowed access to the testing as part of the protocol. Then the lab submits the biomarker data, and the clinician follows with some very simple high level data elements, like how long was the patient on a given therapy and how long the patient was alive. For most offices, that is not an onerous requirement.

We don't want to shift people away from NCI

trials, or from academic trials or pharma trials. What we want to do is get hundreds of thousands of patients that are currently not on trial in a place where we can collect data.

When we're looking at one percent mutations in lung cancer or unusual tumor types—there is not enough money in the research setting to collect the data that we need to aggregate. NCI does not have enough money. One pharma company does not have enough money to do this. What we have to do is find a way to use our existing infrastructure to collect data.

What we have to do is tie coverage of standard of care testing and treatment in a way that can also drive data collection. This would be a really good thing, not just for patients or clinicians but for everyone.

PG: *So if you build this consortium, could CMS or Palmetto drive it? Others would be involved as well, right?*

DD: The right way to form the consortium is to not have any one group own it. We have formed the Molecular Evidence Development Consortium. MED-C received its 501(c)3 public charity designation on April 2 from the IRS. We are hoping that many groups such as payers, physicians, patients, pharma, labs and industry and philanthropy will help support this effort.

We have purposefully not sought governmental funding because the need for nimbleness in getting this started and we don't want to have any potential decreases funding in other worthy groups that MED-C could potentially cause from other worthy groups. MED-C has to stand on its own. We have to make sure that it's expandable, that it's modular, and that it benefits all the stakeholders.

PG: *Would payers be paying for testing in the consortium?*

DD: Right. Payers would cover the testing and the standard regular care, for these patients that are part of this consortium, and if the drug is covered already as a standard of care the payer would pay for the drug. Drugs would be provided as part of dozens of clinical trials opened by clinicians and pharma and made available to clinics nationwide. But to be clear, the payer would be paying for testing for new technology that would replace older testing. Often the adoption of new technology can save total cost to payers. The goal is to not increase the cost for testing, but just improve it dramatically.

PG: *Would targeted drugs be provided free.*

DD: The drugs as part of the trials would be free, to those participating in those

PG: *What kind of reactions are you getting from pharma?*

DD: In February, MED-C.org was formed. And on Feb. 20 we held a "launch meeting" for MED-C. There we had high-level representation of several major pharma companies, industry leaders, laboratory groups, informatics groups, national guideline leadership, academic leaders and payers.

What was said by one participant, "someone needs to build this, and if we can't make this happen, no one else will." To answer the pharma support question, certain forward thinking early adopters are already seeing the value of having standardized testing and the ability to use that testing to collect outcomes and to place patients on affiliated clinical trials. We are hoping that every pharma company will come to support this endeavor.

Frankly, the scope of this project is such that it will need very broad support from many sources to be successful.

PG: *Could pharma provide drug for patients outside of a clinical trial?*

DD: We had an informal meeting with FDA in January, and during that time we introduced our project. We discussed general principles and reviewed this question.

It is well established that pharma can only provide drug in an off-label setting under an investigational new drug trial or in the setting where these is no other good options for treatment (where putting the patient on an investigational drug would not disturb clinical equipoise) as part of an IND-exempt trial.

One of the concerns that we all have had is "how many patients needed to be treated with a drug before we know if it works?" One of the major disadvantages of off-label drug use where there is not extensive published outcome data is the possibility of having patients receive a treatment that would be found to be ineffective if the data would have been collected.

PG: *What would it take for a lab to get paid?*

DD: This program is not meant to be exclusionary, but to provide high quality care for patients and reliable testing that helps the physicians counsel with the patients appropriately. Labs would need to demonstrate that they could meet the standardization based on high quality results, not necessarily a specific platform. The goal is for one group to be able to trust the results of another's.

Who oversees to make sure that those labs are compliant? Right now the hope is to work with groups that are already overseeing the labs such as the College of American Pathologists or others who agree with

establishing this standard.

If a lab meets that scientific standard and is certified, they can request to be included in this consortium and then get paid to run these tests by payers.

PG: *Tests that payers wouldn't otherwise pay for?*

DD: Exactly. This is where Z codes become so important.

In the PAMA legislation it talks about how there will be individual codes for every laboratory test that was run. What you're seeing is that Congress recognizes that we've got to identify these tests. Then we will be able to identify what is taking place by which labs and payment will be only to those met a certain standard to run the testing by an approved standard defined by MED-C.

PG: *So Z codes exist now and they are used by Palmetto, then the question is if and when does the MolDX program become expanded…*

DD: There's a fair amount that's still unknown. The PAMA legislation that passed last year now has to be written up in rule form and we don't know what that rule is going to look like yet.

CMS could say we're going to have four MACs that are going to run molecular policy. Many have argued that it should just be one group—because it's just too complicated to have various different groups build the infrastructure to do this right.

For example, if every MAC had to find subspecialists and pathologists that have backgrounds in clinical trials and coverage decisions to help them, I can only imagine the marked inconsistency that could take place. In addition, how would they pay for all these individuals? If CMS duplicates this work under these MACs, it just doesn't make any sense.

PG: *Is there anything we haven't covered?*

DD: There are many groups that have tried building something like this. Each of them has parts of the whole. MED-C has the unique position is that it was conceived and developed by someone who was thinking about the payer's perspective and concerns. But, rather than focus only on cost or coverage, MED-C was built on the common denominator of good science and the stepwise advancement of patient care and open access in a way that would provide value to each stakeholder including the payer. MED-C provides a bridge to connect all the individual players and do it in a way that no stakeholder has a dominating voice over the others.

PG: *What are your chances of success with so many other groups involved in this space?*

DD: As I have talked to many groups, everyone has said, "someone needs to build this." I have seen too often where everyone waits for "someone" to move forward. And, often, unless there is a substantial financial motivation to do so, there is not much of an incentive.

The only way that something like this will work is if it is built by everyone and is shared by everyone. Financing for MED-C is going to be difficult.

Many groups see their own data collection efforts to be a profit center and so are very reticent to share this with anyone outside of their own network. Even nonprofit groups whose focus has been on other areas now want to get into the data marketing game and have partnered with for-profit entities to find ways of developing "joint commercialization agreements."

If we are going to unlock personalized medicine, this effort is bigger than one institution or one group of institutions. It requires everyone working together and not thinking of data as a proprietary tool for money gathering, but as vital gifts given by patients to institutions that they generally want aggregated together to cure cancer, not benefit one specific group.

Our success is not sure by any means, we have a great deal of momentum and interest, and are hitting all the right notes with all the key groups, but many groups will only support if they see the final product and so we have a little of a chicken-and-egg conundrum.

PG: *How does MED-C compare to other groups, such as ASCO CancerLinQ, or various nonprofit/commercial for-profit hybrids (Orien/M2Gen, NCCN/Flatiron, etc.)?*

DD: Let's start with ASCO CancerLinQ/Tapur Study. What ASCO is doing with CancerLinQ is wonderful. Bringing together the data from various EMRs and have it under a nonprofit umbrella with funding largely by ASCO and the Conquer Cancer Foundation hits many of the same notes as MED-C, but there are some substantial differences.

First, although MED-C starts in cancer, it is meant to develop reusable infrastructure that can be imported to other areas of medicine. Second, MED-C will require a high degree of standardization as a requirement to participation—thus making the data that MED-C does collect much more valuable to advance science.

Third, MED-C is, as its name says, a consortium of stakeholders coming together to build a very specific vehicle to advance personalized medicine. Fourth, MED-C will have relatively open access to the data for research and non-commercial use, and if donations are not sufficient, may have to require reasonable access fees (less than market value) to commercial interests. It is unclear how the CancerLinQ data will be accessed.

ASCO's Tapur study is very important, but has a few

areas that can create scientific concern. The major area is that they are not specifying any testing standard because they want to approximate real world environment.

The problem with the non-standardization of the testing is the high likelihood of false positives. With small mutation populations, it is highly likely that the number of false positives will overwhelm any true positives and as of such targeted therapy may be introduced but without any hope of working because the patient doesn't really have the mutation. This could lead to the erroneous closing of arms of the trial without knowing if it is a testing or a drug failure.

Now, the nonprofit/commercial hybrids. I recognize the need that some nonprofits have to partner with groups that are willing to build the tools and then leverage the data as payment for the tools that are developed.

MED-C does not want to see the data held commercial hostage to groups that are not contributing stakeholders to the umbrella organization. It is unlikely that the data held by one will ever be combined with the data held by another, thereby giving us a fractionated understanding of the disease. I also wonder if patients had the choice to have their data widely shared with the world to help others versus kept as a proprietary tool of the institution as a profit center (which could help the center do much good—no doubt, but also would have a private entity use as a profit tool), what would the patients choose?

PG: *Why are you trying to build this? What's in it for you?*

DD: It seems to be the right thing to do, and I was in a position where it seemed like I could do something to really advance medicine.

So far, it has been a very difficult ride, but I wake up every day thinking that we will get there and it will be worth it.

In order to build MED-C, I have given up working with MolDX, given up being the director of a cancer center, have cut my clinic schedule down substantially, stepped away from being the chair of ASCO's State Affiliate Council, all to start a nonprofit that to date has been largely funded by personal funds and donated hours by many. On the surface and a little deeper, this may be unconventional, but in the end, I hope that others will see this approach and help support and forward the Molecular Evidence Development Consortium.

If I didn't believe it would be successful, I would not have been willing to go all in.

The enthusiasm and support already seen is enough for me to know that MED-C can succeed, but it needs support from everyone.

Duke Misconduct Probe Still A Work in Progress

(Continued from page 1)

"All claims arising out of the genomics-based clinical trials for cancer treatment have been resolved and settled. The specific terms of the settlement are confidential, by mutual agreement of the parties," Duke officials said in a statement about the settlement which was first acknowledged last Friday. "There are no other pending claims or lawsuits."

Thomas Henson, an attorney for the plaintiffs, confirmed Duke's statement, offering no additional information.

The case was the subject of a report on the CBS news program 60 Minutes.

"The trial is one of the two shoes I was waiting to drop," said Keith Baggerly, a biostatistician at MD Anderson Cancer Center, whose challenge of the papers published by the Duke genomics team uncovered the irregularities. "Misconduct investigation is the other."

Baggerly served as an expert witness for the plaintiffs.

"Bottom line: the settlements do not resolve Duke's responsibilities for the multiple individual and systemic failures evident in this situation," said C. K. Gunsalus, director of the National Center for Professional and Research Ethics. "Duke owes information and actions to its patients, the research community and to its medical professionals, students and faculty."

Gunsalus's guest editorial on the Duke genomics scandal appeared in the Jan. 23 issue of The Cancer Letter.

Gunsalus is also a professor emerita of the College of Business at the University of Illinois at Urbana-Champaign. She runs a consulting company and is the author of The Young Professional's Survival Guide and The College Administrator's Survival Guide.

The Cancer Letter invited Gunsalus to discuss Duke's settlement of the lawsuits. A conversation with her appears on p. 15.

The Duke misconduct investigation by the Office of Research Integrity—a unit of the Department of Health and Human Services—began in October 2010, but nothing is publicly known about its status or focus.

ORI officials declined to confirm or deny the existence of the investigation, referring all questions to Duke.

"According to ORI's usual processes defined in the Federal regulations (42 C.F.R. Part 93), an institution is responsible for handling the research

misconduct procedures and reports the findings of an investigation to ORI," said Diane Gianelli, an HHS spokesperson. "When ORI receives such reports, ORI conducts its oversight review to ensure that the investigation was conducted in a fair and timely manner with sufficient thoroughness, objectivity and competence to support the conclusions (§93.403(c)). After completing its review, ORI either closes the case without research misconduct findings or makes findings and proposes specific administrative actions."

A Duke spokeswoman said in an email that "there is nothing new to share re: misconduct investigation."

Settlement Separates Suit from Misconduct Probe

It's likely that the existence of the misconduct investigation may have pressured Duke to settle.

Observers said that the findings of the misconduct investigation had the potential to undermine Duke's position in the lawsuit.

The misconduct investigation also has the potential to deal with the broader outlines of the Duke genomics scandal—particularly the role of the deans and the clearly and demonstrably false statement that top Duke officials made to a committee of the Institute of Medicine as it investigated the matter.

Altogether, 117 patients enrolled in the three clinical studies at Duke.

Duke argued that patients who entered these clinical studies were not harmed. They were, for the most part, in late stages of disease and that the predictor models were used to assign them to existing therapies.

The plaintiffs' attorneys argued that Duke had ample opportunities to recognize that the technology tested in the three trials was fraudulent. Instead, in the spring of 2008, Duke officials silenced a whistleblower, frustrated an NCI inquiry, and, in the fall of 2009, set up a flawed internal review of the three trials.

The deans who were directly involved in silencing the whistleblower later told a committee of the Institute of Medicine that no whistleblower had come forward from Potti's lab.

The consent forms signed by the patients who enrolled in the studies extolled the potential of Duke's technology:

"This genomic predictor looks at hundreds of genes (pieces of DNA—a short form of deoxyribonucleic acid that contains information needed to construct and operate the human body) in your tumor. In initial studies, the genomic predictor seemed to determine which drug would be effective in a given patient with an accuracy of approximately 80%. The genomic predictor is still being tested in research studies and is therefore considered investigational."

The whistleblower—Bradford Perez, a third-year medical student working in Potti's lab—did more than just sound alarm.

Perez submitted a well-argued critique of flaws in the Duke genomics operation. Documents published by The Cancer Letter also show that concerns were brought to the attention of the deans in March 2008 (The Cancer Letter, Jan. 8).

Instead of a thank-you, Perez faced a full-court press led by Potti's co-author and protector Joseph Nevins and an all-star team of Duke officials, which included Deans Sally Kornbluth and Nancy Andrews.

Perez was assured that Nevins and Potti would go through their datasets to make sure that there were no "errors" present. Had this been done, fraud would have become evident more than two years earlier—in 2008 instead of 2010—and Duke's clinical trials of the predictor model would have stopped months after they began.

Disappearing the Whistleblower

As a consequence of misleading testimony by Duke officials, the Perez case is not noted in the IOM report.

According to the report, "there was discontinuity in the statistical team, which may have contributed to the research team's failure to follow proper data management practices (Kornbluth and Dzau, 2011). Junior investigators on the team either did not recognize what was wrong or did not feel comfortable expressing their concerns even though whistle-blowing systems were in place. Some members of the laboratory did ultimately come forward with concerns about the research, but only after the University began an investigation (Kornbluth, 2011)."

Elsewhere in the report, Duke officials are quoted describing the university's "just culture," which encourages anyone at any level to criticize the scientific methods of a study without fear.

The report continues:

"However, the problems with the three clinical trials were not brought to the attention of the appropriate individuals within the university leadership through any of these whistleblowing channels. According to [then] Vice Dean for Research Sally Kornbluth, a number of people came forward after the university undertook its investigation and said they 'were glad [the university was] reviewing things carefully' (Kornbluth, 2011).

"Why no one came forward earlier, or perhaps any such concern was not forwarded appropriately, is

not known, but the fact that these problems were not brought forward earlier may be an indication of the discomfort or lack of confidence that faculty and staff may have with these systems."

The report was vetted by Duke officials, which presumably means that they reviewed it and didn't see reasons to correct it.

Both Kornbluth and Andrews have since been promoted, and Duke officials haven't apologized for their institution's testimony to IOM.

An exchange of emails, obtained by The Cancer Letter, shows that Kornbluth was aware of the Perez controversy on Oct. 5, 2010, three months before the IOM committee held its first meeting and six months before the committee first met publicly with Duke officials.

At that time, Duke's top administrators were deciding the best way to handle the Perez incident in the context of the scientific misconduct investigation. Should the Perez documents be presented to an internal Duke committee that was deciding on the scope of the misconduct investigation?

At first, Kornbluth decides that charges would be appropriate. Then she changes her mind, choosing to present the Perez materials to the standing committee, leaving it up to the group whether charges are justified.

The email is addressed to Dzau, who has since been named IOM president:

"Victor,

"My two cents: I've had a change on heart about this. I've talked to Wesley [Byerly, associate dean for research support services] at length and I think his thoughts to let the Perez stuff go in with the existing allegations (and not draft another charge) is right. I think Joe [Nevins] is going to the committee to debrief and I think the committee can then decide if they really think there is any merit in charging Joe with anything. I am feeling more and more that we may have jumped the gun with that and the answer is probably 'no.' Happy to discuss if you want. Sally."

Other Documents

In another document obtained by The Cancer Letter, Holly Dressman, a top member of the Nevins and Potti operation, expressed hope that NCI officials wouldn't request the raw data on which Potti's predictor model for ovarian cancer was based (The Cancer Letter, Jan. 16).

Had NCI's statisticians been able to get the code and the data they sought, they would have been able to perform basic forensic bioinformatics that would have enabled them to spot unsubstantiated claims, and worse.

In an email dated May 6, 2008, Holly Dressman, a co-author on the Duke group's key papers, shot an email to team captain Joseph Nevins, mentor and protector of its star scientist Anil Potti.

Dressman's email, now cited in a lawsuit against Duke, may cause a double-take:

"I am working on the [topotecan] signature in OVC and it's a big mess. NCI wants us to resubmit the revisions again and now asking for correct Topo info… and they may want the data for their stat folks to try out like what was done with plat stuff… I am beginning to wonder if the Topo signature is real. I guess for the review, I can just hope they don't ask for original data and just report what is in the NatMed paper."

Here, a government-funded researcher—who, despite losing faith in the predictor used to decide which treatment an ovarian cancer patient would receive, expresses hope that NCI would relent before getting the "original" data and would settle for data published in one of the world's premier scientific journals.

In the litigation, the plaintiffs were seeking release of thousands additional documents that Duke had previously failed to release.

A timeline of the Duke genomics scandal is available here.

Conversation with The Cancer Letter

Gunsalus: 4.5 Years is at the Extreme End of the Spectrum For a Misconduct Probe

The Cancer Letter invited C. K. Gunsalus, an expert on scientific misconduct, to discuss the settlement of the lawsuits against Duke.

Gunsalus is the director of the National Center for Professional and Research Ethics, research professor, Coordinated Science Laboratory, professor emerita, College of Business at the University of Illinois at Urbana-Champaign. She runs a consulting company and is the author of The Young Professional's Survival Guide (Harvard University Press, 2012) and The College Administrator's Survival Guide (Harvard University Press, 2006).

Her guest editorial on the Duke genomics scandal appeared in the Jan. 23 issue of The Cancer Letter.

She spoke with Paul Goldberg, editor and publisher of The Cancer Letter.

Paul Goldberg: *With the patients' case settled, is Duke out of jeopardy?*

C. K. Gunsalus: It depends on what you mean by "out of jeopardy."

Settling all current lawsuits closes one front of Duke's ongoing problems with one set of individuals.

I do not know if the settlement resolves the legal situation for all possible trial participants' families. That is, do the settlements resolve the lawsuits filed to date or all possible trial-related litigation? Are there other potential lawsuits still within a statute of limitations? If other potential lawsuits are still possible, these settlements could set a pattern for future payments.

Settling the civil lawsuits leaves open many questions about what went wrong in the conduct and oversight of the research, in the clinical trials, and in Duke's responses when problems arose. The research and trials were conducted on Duke's premises, under its auspices, and by its employees and students. Actions were taken and public statements made in the name of the institution.

Most of all, settling the lawsuit does nothing to address questions about how and why things went so tragically wrong and what institutional changes have or are being made going forward. Fundamental questions of institutional integrity are raised by the failures of their internal procedures of education, research and conflicts of interest.

Bottom line: the settlements do not resolve Duke's responsibilities for the multiple individual and systemic failures evident in this situation. Duke owes information and actions to its patients, the research community and to its medical professionals, students and faculty.

PG: *Are the deans who were involved in silencing Bradford Perez, the whistleblower, politically viable now that the court case has been settled?*

CKG: Goodness, there are a lot of assumptions embedded in that question. Let's take things one piece at a time.

The facts available say that Brad Perez, one of the lowest-power, most vulnerable people involved, acted heroically by raising his concerns in an entirely professional manner—and then acted on his values and convictions at great cost to himself by repeating a year of his education and withdrawing his name from prestigious publications that would have advanced his career.

So far, the available record doesn't show much that reflects well on those with whom he interacted at the university. There are serious open questions about what originally happened; about who knew what, and when; and why the institutional response appears to have failed at so many junctures. An objective and thorough investigation is required. That kind of investigation should be sought and welcomed by those who were working within the system to do the right thing.

Without a thorough and well-documented investigation that is made public, stains will mark the reputation of many people, including some who might have acted honorably at the time. Absent this investigation, their names cannot be cleared nor can those who either made mistakes or bad judgments—or potentially worse—be held accountable nor remedial steps taken.

PG: *What do you read into the fact that a misconduct investigation is still ongoing after 4.5 years?*

CKG: Thorough, well-documented investigations into complex topics do take a long time. While the federal regulations anticipate four months, extensions are not uncommon.

A complex review conducted by a committee of experts can be hard to complete quickly for a number of reasons, not least the sheer scheduling complexity of assembling a group of competent experts at the same time and place repeatedly.

Still, 4.5 years is at the extreme end of the spectrum, especially at an institution as well-resourced and sophisticated as Duke.

One complicating factor in this situation is that it appears that there are multiple organizations to which Duke is accountable: the funders of the research, the journals, the National Cancer Institute, the funders of the clinical trials, the human subjects protection agency, etc.

There may be multiple regulations that govern the process—and the terms under which corporate entities funded, provided agents and data analysis may add further complications.

I hope that there are people external to the university centrally involved in the investigation to address questions always present about conflicts of interest. I hope that those involved are well-supported in terms of investigatory expertise by individuals well-versed in prevailing standards of best practice—and in the requirements of relevant federal and funder rules and regulations. A report coming after this much time, looking into matters as serious as those present here, should be held to a very high standard of scrutiny.

PG: *Was it a good idea for Duke deans to deceive the IOM Omics committee about reports of troubles in*

the Potti lab? (They said there weren't any.)

CKG: From a distance, it's hard to understand the statements attributed to Duke's representatives in the final Omics report.

The impression given is that many of them used finely parsed language to make statements that might have been literally accurate without being fully forthcoming. Multiple statements, with the benefit of hindsight, appear very carefully crafted. For example, the Omics report says:

"…numerous missed signals that there were problems with the research (Califf, 2011b)…Junior investigators on the team either did not recognize what was wrong or did not feel comfortable expressing their concerns even though whistle-blowing systems were in place. Some members of the laboratory did ultimately come forward with concerns about the research, but only after the University began an investigation (Kornbluth, 2011)." (Omics report, p. 116).

"At the time of the three clinical trials, Duke University used both anonymous and non-anonymous reporting systems. It also had a compliance hotline through which individuals could report breaches of the rules and regulations governing clinical research (Califf, 2011). However, the problems with the three clinical trials were not brought to the attention of the appropriate individuals within the university leadership through any of these whistleblowing channels." (Omics report, p. 257).

As The Cancer Letter has reported, as early as 2008, Duke was holding information from a highly credible source from within the laboratory raising serious issues about the integrity of research on which the clinical trials were based.

Were these the "missed signals" to which the first quote refers? Did they not report them because these concerns were raised within the graduate medical education system and not through a formal whistleblowing system?

Reading carefully, all of the public comments by Duke seem to focus on improving their "whistleblowing channels." Why was a document labeled "Research Concerns" raising clear issues relating to research integrity apparently not considered relevant either within Duke or as worthy of reporting to the omics committee?

"As reported by Robert Califf in August 2011, Duke eventually surveyed 162 investigators involved in 40 papers coauthored by Potti, half of whom were by then at other institutions. Two-thirds of these papers, he testified, will be partially or fully retracted, with others pending evaluation. **Yet in no instance did anyone make any inquiries or call for retractions until contacted by Duke**. This experience suggests the need for coauthors to have more shared responsibility for the integrity of the published research." (Omics report, p. 268, emphasis added).

It seems a bit convenient to state that none of the co-authors raised any concerns when, in 2008, a co-author removed his name from papers because of concerns about the integrity of research.

In research organizations, concerns about research integrity arise through any number of channels: questions to officials, in informal conversations, in the form of disputes, and also as formal allegations. In 1998, I wrote:

"…a university wishing to assure that it responds well and appropriately to whistleblowers may get good results by focusing upon its overall ethical environment, by providing guidance to faculty and staff for handling complaints and working to resolve the problems that will inevitably arise…. Why does an effective response start so early? Because every whistleblowing case starts with an individual seeking advice or help with some kind of problem. The spectrum of unhappy people who seek recourse from institutional officials (a broad category in itself) spans those who enter with vague descriptions of their unhappiness to those who enter with a long list of specific complaints. At that stage, only rarely does that person see him- or herself as a whistleblower, or express a wish to file charges or allegations…" (Gunsalus, How to Prevent the Need for Whistleblowing: Practical Advice for University Administrators (1998) Science and Engineering Ethics)

PG: *What does this say about Duke's ability to investigate itself? Given what we now know about the Perez case and the Holly Dressman email (in which she expresses hope that NCI wouldn't get the underlying data for the ovarian cancer predictor), is it appropriate to let Duke investigate itself?*

CKG*:* No institution with thousands of employees is monolithic. Large institutions are complicated entities that are never static. There is tremendous turnover in personnel.

The statements in the omics report attributed to high-ranking Duke personnel indicate that, at the time those statements were made, something was seriously amiss in internal communication at Duke.

Whether it has improved significantly since that time is hard to gauge from a distance. I'd like to think that a reputable research institution could learn from its mistakes—and those of its peers—and do a sterling job

of an internal investigation, and do so credibly. After all, no one has more at stake than those who have tied their professional reputations to the institution's integrity.

It would be helpful for both Duke and the wide array of individuals associated with responding to the problems in the Nevins/Potti group and trials if someone with both authority and full information could explain how the current investigation will have better access to internal events and processes and won't go so far afield from facts—or else explain why the impression presented by the documents that came out through discovery are leading us to draw inaccurate conclusions.

PG: *Given this extraordinary period of time, 4.5 years, is it possible that ORI is stepping in? Should someone—ORI or Duke—address the matter of effort to deceive the IOM committee?*

CKG: There is actually no one better situated to conduct a thorough, complete, exhaustive investigation than Duke itself if certain conditions are met:

• The investigative body is constituted in a way that maximizes the likelihood of a credible outcome, including individuals outside the reporting chain and professional sub-communities of those involved in the events being investigated.

• At least one individual outside the institution is involved in the investigative process and drawing conclusions who has full and total access to all evidence, all witnesses, and a strong voice in the report.

• Expertise is available to support the process in areas including legal and investigative needs.

In Brief

Theodorescu and Lerner Named Editors-in-Chief of Bladder Cancer

DAN THEODORESCU and **SETH LERNER** were named editors-in-chief of the new journal **Bladder Cancer**.

Theodorescu is director of the University of Colorado Cancer Center and is a professor of urology and pharmacology at the University of Colorado School of Medicine.

Lerner is the Beth and Dave Swalm Chair in Urologic Oncology and is director of the Multidisciplinary Bladder Cancer Program at Baylor College of Medicine.

The multi-disciplinary journal will specialize in all things related to the disease, including understanding of the epidemiology/etiology, genetics, molecular correlates, pathogenesis, pharmacology, ethics, patient advocacy and survivorship, diagnosis and treatment of tumors of the bladder and upper urinary tract.

"I've been studying bladder cancer for 20 years and it's gratifying to be part of this journal from its inception," says Theodorescu. "We want Bladder Cancer to provide a clearing house for information about breakthroughs in basic science, translational research and patient care."

Theodorescu manages an active translational molecular biology lab focused on the mechanisms leading to bladder cancer growth and metastasis. He also has been involved in the discovery, development and testing of COXEN (CO-eXpression ExtrapolatioN), a precision medicine strategy to predict which tumors will be sensitive to which drugs based on genetic analysis of tumor samples.

He also led the team that in 2014 described the first drug against Ral, an oncogene that contributes to several cancer types including bladder, pancreas, lung, colon and prostate.

Lerner is author of more than 160 peer-reviewed articles, and co-editor of Textbook of Bladder Cancer. His research interests include use of selective estrogen receptor modulators for treatment of bladder cancer, gene therapy, targeted molecular therapeutics, and outcomes of radical cystectomy and pelvic lymphadenectomy.

He is working on the ongoing SWOG-NCI phase III trial comparing extended vs. standard pelvic lymphadenectomy at time of radical cystectomy for muscle invasive bladder cancer. Lerner also serves as chair of the Local Bladder Cancer committee of SWOG, co-chair of the NCI's Bladder Cancer Task Force and the Analysis Working Group of The Cancer Genome Atlas Project for muscle invasive bladder cancer.

UW HEALTH and **ProHealth Care** signed an agreement to co-manage ProHealth Care's new cancer center in Pewaukee, Wis. In addition, several **Aurora Health Care** cancer specialists will deliver care at the center.

The center is nearing completion, and plans to open Aug. 10. The 116,000-square-foot facility will offer infusion therapy, radiation therapy, imaging services, cancer rehabilitation and other services.

UW Health will provide medical direction for the treatment of all cancer patients at the location. The three systems intend to collaborate in medical oncology, surgical oncology, radiation oncology,

ancillary services and imaging. Multi-disciplinary case conferences will address cancer patients' needs and reduce variation in care.

Aurora Health Care, ProHealth Care and UW Health all belong to the statewide AboutHealth network, announced in August 2014.

THE GEORGE WASHINGTON UNIVERSITY Cancer Institute developed free online training that covers the fundamentals of oncology patient navigation in the U.S. The program was funded by the Centers for Disease Control and Prevention.

"Patient navigation addresses barriers to care, ultimately improving health outcomes," said Mandi Pratt-Chapman, director of the GW Cancer Institute. "Training for patient navigation is usually in-person, expensive, and not necessarily evidence-based. Our training is accessible to anyone who is or wants to be a patient navigator and goes a long way in establishing standards of practice for the field."

"This training will allow cancer centers and their institutions to keep pace with new patient navigation standards, raise the caliber of their patient navigation program, and protect themselves from potential legal liability," said Pratt-Chapman. "This training ensures that non-clinically licensed oncology patient navigators have a solid foundation."

The GW Cancer Institute patient navigation training covers topics such as: medical terminology and cancer basics; health care payment financing; the role of the patient navigator in the collaborative health care team; communicating in a culturally sensitive way with diverse patients; ethics, patient rights, and advocacy.

NIH raised nearly $700,000 at a gala for its nonprofit, **The Children's Inn**, which provides residences for children that are undergoing treatment at NIH, and their families.

The event, "An Evening for Hope," gathered 780 donors and spotlighted the past 25 years of pediatric medical research.

"The outpouring of support surpassed our expectations," said Robert Guerra, event chairman. "The money raised enables children to participate in groundbreaking medical research that may help them and those like them overcome these life-threatening illnesses someday."

"We are so grateful to our donors," said Jennie Lucca, CEO of The Children's Inn. "There has never been a more exciting and important time for The Inn to help children who can benefit from the rapid advancements in medical research."

The Children's Inn thanked its event sponsors, including: HP, Lockheed Martin, Booz Allen Hamilton, Deloitte, SRA EagleBank, Microsoft, Sapient, Northrop Grumman, PricewaterhouseCoopers, Westat, NETE, Maximus, GDIT, NCC, ICF International, Rob and Ruth Guerra, and ASM Research.

PROTON PARTNERS INTERNATIONAL LIMITED, which is planning to build three proton beam therapy cancer treatment centers in the U.K., announced the appointment of global partners to provide clinical equipment and technology solutions to the company.

Proton Partners is to open treatment centers in Cardiff, London and Northumbria by 2017. The first, in Cardiff, will be operational next year.

Ion Beam Applications was selected by Proton Partners to install its single-room proton therapy system, Proteus ONE, in each of the three centers.

Philips was appointed to deliver software and technology tools including Philips' Pinnacle Treatment Planning workflow environment. Philips will also provide large-bore CT scanners at each center and a PET CT in the Cardiff center.

MOFFITT CANCER CENTER and **Aetna** launched an oncology medical home model.

The model is part of a strategic direction to transition from fee-for-service medicine to value-based payment. In value-based models, doctors and hospitals are paid for helping keep people healthy and for improving the health of those who have chronic conditions in an evidence-based, cost-effective way.

According to Moffitt and Aetna, the oncology medical home program will include: evidence-based, personalized medical care utilizing Moffitt's Clinical Pathways; Coordinated and integrated care across the Aetna system; the use of clinical decision support tools; open scheduling and expanded hours.

THE SWEDISH CANCER INSTITUTE in Seattle adopted **Syapse Precision Medicine Platform software** for its personalized medicine program.

The program, launched in April 2014. "SCI plans to enroll 9,000 patients in the program during its first three years, and the Syapse platform will be instrumental in advancing this work," said Thomas Brown, executive director of the institute.

The Syapse platform uses large-scale genomic and clinical data to support prevention, diagnosis, treatment and survivorship. This platform integrates with SCI's enterprise electronic medical record and allows the treatment team to mine patient data and research results to identify which treatments work best for tumors with particular gene alterations. The platform will include the profiles of thousands of individual tumors.

Drugs and Targets

FDA Grants Breakthrough Designation to Venetoclax

Venetoclax was granted Breakthrough Therapy Designation by the FDA for the treatment of chronic lymphocytic leukemia in previously treated patients with the 17p deletion genetic mutation.

Venetoclax is sponsored by AbbVie, and is being developed in partnership with Genentech and Roche.

Venetoclax is an investigational oral B-cell lymphoma-2 inhibitor being evaluated for the treatment of patients with various cancer types. The BCL-2 protein prevents apoptosis of some cells, including lymphocytes, and can be expressed in some cancer types. Venetoclax is currently being evaluated in phase II and phase III clinical trials for the treatment of CLL, along with studies in several other cancers.

DanDrit Biotech USA Inc. signed a collaboration agreement with GISCAD Foundation, an Italian group focused on cancers of the digestive tract.

The collaboration includes VIVA, a phase III adjuvant trial of DanDrit's vaccine in patients with no evidence of disease stage IV colorectal cancer.

The primary aim of the trial is to evaluate the ability of MelCancerVac to prevent a relapse in CRC patients rendered disease free after completion of standard treatment according to local practices.

Member companies of the Pharmaceutical Research and Manufacturers of America invested an estimated $51.2 billion last year in the research and development of new innovative treatments and cures. The figure represents the majority of all biopharmaceutical R&D spending, both public and private, in the U.S.

A recent survey of PhRMA member companies was highlighted in its 2015 Biopharmaceutical Research Industry Profile. According to PhRMA, member companies invested nearly 24 percent of domestic sales into R&D in 2014.

Last year, 51 new medicines were approved by FDA. Forty-one of those approvals were by the Center for Drug Evaluation and Research and ten were approved by the Center for Biologics Evaluation and Research. Among the CDER approvals, 41 percent were identified as first-in-class treatments and more than 20 percent were personalized medicines, according to PhRMA.