THE CANCER LETTER

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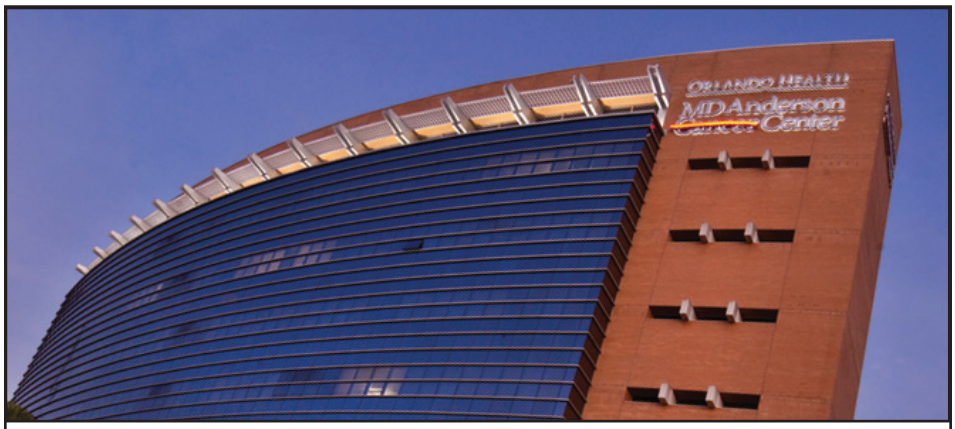

Orlando Hospital Severs MD Anderson Ties, Forming Center with University of Florida

By Paul Goldberg

On Jan. 30, somebody will have to climb to the top of Orlando Health's 10-story Charles Lewis Pavilion to cover up—or start removing—the backlit letters that, with a halo effect created by LED lights, broadcast the health system's affiliation with MD Anderson Cancer Center.

The name of the distant, venerable cancer center will vanish from Orlando's skyline. The distinctive red swoosh that symbolically negates the word "cancer" will be gone also.

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Conversation with The Cancer Letter

Orlando Health President Mark Roh: We Opted For a Florida-Centric Strategy

Orlando Health is choosing a partnership over an affiliation, said Mark Roh, president of the Florida cancer center that's ending its relationship with MD Anderson Cancer Center.

Instead, Roh's hospital is joining the University of Florida to create the UF Health Cancer Center at Orlando Health.

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In the Cancer Centers

Ludwig Donates $540 Million to Six Centers

By Conor Hale

Ludwig Cancer Research donated a total of $540 million to six of its centers, located at institutions across the country.

The Ludwig Centers at Harvard University, Johns Hopkins University, the Massachusetts Institute of Technology, Memorial Sloan-Kettering Cancer Center, Stanford University, and the University of Chicago will each receive $90 million for their endowments, which were established along with their respective centers in 2006.

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Download and Listen
To The Cancer Letter's Conversation with Mark Roh

Orlando Collaboration Didn't Fit MD Anderson's Network Model

(Continued from page 1)

Orlando Health and MD Anderson have been in a long-distance relationship for 23 years, but over the past two years, the Florida institution has been exploring other options, ultimately forming a bond with the University of Florida in Gainesville.

So, instead of re-upping its relationship with MD Anderson at the end of this month, the health system and the nearby University of Florida will start integrating their cancer programs to form the UF Health Cancer Center.

"We have different goals, different visions for our future," said Mark Roh, president of MD Anderson Cancer Center Orlando, which is about to become the UF Health Cancer Center at Orlando Health. "Their vision [is] a national campaign. [MD Anderson President Ronald] DePinho is very passionate about wanting to provide cancer care to 3 to 5 percent of new cancer patients throughout the U.S., something I can't even fathom, let alone enact."

A conversation with Roh appears on page 1 of The Cancer Letter.

Orlando Health's original deal with MD Anderson was part of an extension of the brand of the Houston-based cancer center, a deal where the hospital paid a flat fee for the use of the name.

Affiliation with the University of Florida creates a deep economic and scientific relationship.

"It's not a franchise," said Paul Okunieff, director of the UF Health Cancer Center and chair of the UF Department of Radiation Oncology. "It's a real, genuine fusion of our operations. It really is making one cancer center. It's the future. I think other people are going to need to figure this out."

Orlando Health and UF will conduct joint tumor boards, create biospecimen repositories and informatics programs. Patients—including those seeking proton beam therapy—will be referred back and forth. UF has its own proton beam center, and the Orlando Health facility is scheduled for completion in January 2015.

On the business side, the centers will join on the "top line," meaning that they will split every new dollar they earn treating cancer.

Roh declined to discuss his center's financial relationship with MD Anderson, citing confidentiality agreements.

Dan Fontaine, MD Anderson senior vice president for business affairs, said that Orlando was pursuing a regional strategy while MD Anderson is pursuing a national strategy.

"Orlando, when looking at their entire service line, made a decision from a strategy standpoint to be much more regionally focused," Fontaine said to The Cancer Letter. "We are much more nationally focused. It has been a phenomenal relationship. If it hadn't been, it wouldn't have lasted for twenty-plus years. But, as you know, in the health care world, things change."

MD Anderson Sought to Restructure Orlando Deal

When it was engineered by MD Anderson's then-President Charles "Mickey" LeMaistre and the Orlando center's president and CEO, Clarence "Buck" Brown, the collaboration was structured as a margin-sharing relationship, Fontaine said.

However, over the years, the relationship moved to a fee-for-service structure.

Fontaine said that in the final year the Orlando hospital paid MD Anderson between $2.75 million and $3 million.

"It was a contractual relationship, where there were particular clinical support services that were provided by MD Anderson in exchange for fees," Fontaine said.

"It was a simple contractual fee-for-service situation including the use of the name and the sort of things you would expect in a clinical support relationship: teleconferencing, multidisciplinary conferences between their physicians and our physicians, availability to consult with our physicians on particular patients cases."

As the deal came up for renewal, MD Anderson

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developed a different structure for its network.

These arrangements—with Banner Health in Arizona and Cooper University Health System in New Jersey—form closer alliances and have different price structures, Fontaine said. At Cooper, MD Anderson signed a letter of intent to create a $100 million Cooper-MD Anderson cancer center.

That collaboration, which will work across 1,500 miles, will involve opening a co-branded 103,000-square-foot cancer institute. MD Anderson generally views affiliations as sources of revenue (The Cancer Letter, June 21, 2013).

"As we were coming up for renewal, to take the relationship beyond January of this year, a lot of the focus was not so much on the finances but was on the fact that by this time we had established our national network strategy," Fontaine said.

"We had our relationship with Phoenix, we were going to announce our relationship with Cooper Healthcare in Southern New Jersey."

MD Anderson wanted to standardize these relationships.

"We were going to need to evolve the relationship as it existed previously into one that looked a whole lot more like our relationship with the Banner Healthcare system," Fontaine said.

The Banner and Cooper arrangement entail "a significant degree of clinical quality control, including reporting relationships between the medical leadership of the cancer program at our partner member and our clinical supervision here," Fontaine said.

"There are requirements for clinical research. There are requirements for establishing clinical trials programs. There are executive and medical leadership meetings that take place, there is training that takes place, where physicians at those programs spend time at MD Anderson in Houston, likewise some of our experts spend time at those facilities.

"So it's a much more robust standardization approach than what was conceived twenty-some odd years ago with Orlando," Fontaine said.

Fontaine didn't disclose the pricing structure, which has been treated as proprietary information.

"In the partner members that we have—without going into the actual numbers and the details—involves three components," Fontaine said. "There is reimbursement of expenses for those things that we do that are directly related to the supporting of the program in terms of physician time, business time, expertise. It's an expense reimbursement component from the partner back to us. There is also a program fee. And then there is some sort of a variable fee that is tied to expansion of participation of a larger number of patients, revenues, being treated within the program."

The Orlando affiliate would likely have had to pay a different price for the relationship with MD Anderson.

"I am sure there are differences, because when you look at the three components that we now have in our relationship—including the variable component—over time, certainly we anticipate that there may have been some differences," Fontaine said.

A National Strategy

Center	New Pts Treated	Interventional Trial Accruals *
U. of Florida	3210	178
Orlando Health	5465	128
UF Proton Therapy Institute	1484	186
Total of UF + OH + PTI	10159	492

Source: UF Shands Cancer Center

MD Anderson's network is part of a national expansion strategy, Fontaine said.

This aggressive expansion could end up placing an MD Anderson affiliate almost anywhere in the U.S., or, for that matter, worldwide.

If the Banner and Cooper affiliations are an indication, large health systems that often compete with the network of NCI-designated cancer centers would become likely clients for MD Anderson's co-branding program.

The network offers three levels of membership: certified, specialty and partner. Each of these levels offers integration with MD Anderson.

"We are a mission-driven organization," he said. "Our job is to eradicate cancer in Texas, the nation and the world. To be able to reach out further into communities.

"What we are hoping for, over the years, is that we are—particularly on the research level—are gathering information and research information than we are going to be able to reach through patients who come to Houston."

Fontaine said the goal of reaching 3 to 5 percent of newly diagnosed cancer patients sounded reasonable. Altogether, 5 percent of newly diagnosed cancer patients in the U.S. would add up to about 90,000 people.

"I don't think there is a hard, fast percentage of cancer patients," Fontaine said. "We are a methodical organization. We want to make sure that as we go into these different relationships—whether it's our certified members or partner members—that we maintain the quality, maintain the physician connection, make sure that we are really doing something for the patient that will be research-based, protocol-driven."

MD Anderson officials say that in recent years their total network activities locally, nationally and internationally contributed between $30 million and $50 million dollars in net operating margin annually. This includes the certified members, partners and care centers combined.

In his 2012 "state of the institution" speech, MD Anderson President Ronald DePinho described his plans for expanding the outreach programs:

"MD Anderson already has created some strong relationships around the country that benefit our institution, partners and most importantly, our patients. It's critical for us to extend our knowledge to other caregivers and our quality care to patients who can't come here but need our expertise. While we expand beyond Houston, we must remain committed to maintaining the quality of our clinical care enterprise. Quality of care is the cornerstone of our recognition as the world's leading cancer center. There cannot be any compromises.

"This also is recognized by the clinical division heads. A workgroup, chaired by Tom Buchholz, [former provost ad interim who has since been named executive vice president and physician-in-chief], prepared a report earlier this year that recommended a revised internal organizational structure; a proactive strategy for identifying partners; clear requirements for any named affiliation; and an academic network infrastructure to facilitate main center clinical research, serum banking and tumor banking.

"To achieve this, we're creating the MD Anderson Cancer Network. Multiple existing internal teams have been organized in a new structure to expand our clinical expertise nationally.

"They will engage community hospitals and health care systems with a goal of improving the quality of cancer care in those communities. These affiliations will be tailored to the needs of each network member, with services ranging from consulting support to specialized oncology programs to full clinical

extensions. Leaders from Clinical Operations, Clinical Business Development (formerly the Center for Global Oncology), Physicians Network and the regional care centers will work together to identify and engage new partners at every level.

"Part of the new MD Anderson Cancer Network strategy will be to seek partnerships in areas where we can positively impact how cancer care is delivered in that community. We'll look for health care partners who:

• Want to join us in our mission to eliminate cancer;

• Have leaders and professionals dedicated to elevating the care in their areas;

• Want to expand their clinical research programs;

• Have the infrastructure necessary to handle growth; and

• Importantly, are committed to MD Anderson's multidisciplinary approach to quality cancer care.

"Dr. [Thomas] Burke [until recently, executive vice president and physician-in-chief], will oversee this effort and chair a multidisciplinary steering committee that will advise on whether and at what level partnerships will be formed.

This will be an exciting and expanded effort to enhance the quality and increase access for MD Anderson's care nationwide. It also will provide the opportunity for clinical trials on a very large scale."

As of Jan. 1, Burke became the executive vice president of the MD Anderson Cancer Network.

Orlando Deal Two Years In the Making

University of Florida's Okunieff said the ultimate goal of the joint program with Orlando would be to pursue the NCI consortium center designation.

"It just seemed to be the right thing to do for the people of Florida," Okunieff said to The Cancer Letter. "Florida is about to be the third-most-populated state. I know that almost 17 percent of our population is over 65, and I know that we treat the third most cancers, especially in the winter.

"And we have so few academic institutions here."

Meanwhile, Okunieff said the university was "landlocked."

"We have great scientists, great doctors, but we are a certain size, and the city is a certain size, and this relationship really helps us grow," Okunieff said.

Talks between the two organizations started informally four years ago. Two years ago, these discussions became formal and systematic.

"Our doctors really, genuinely like each other," Okunieff said. "We do retreats together. We do electronic tumor boards together."

University of Florida's Paul Okunieff

The merger meant that the two organizations could share resources instead of duplicating and competing. "We each have certain facilities that the other doesn't have," Okunieff said. "We thought it wasn't wise to get into a war on buying two of them instead of one, recreating the same technology in both places.

"In Gainesville, we have direct tumor injections for bronchial tumors. They don't do that there. They do peritoneal chemotherapy there for ovarian cancer and for peritoneal tumors, which we don't do here.

"We've had joint tumor boards in leukemia for almost two years. So if a new leukemia patient presents at Orlando, which does not do bone marrow transplants, we co-design an optimal treatment plan that does not burn a bridge for a future transplant.

"And if we feel the patient should have a consult in Gainesville, it's only an hour-and-a-half drive. It's like a commute for somebody on the East Coast. MD Anderson is in Texas. It's not an easy commute.

"I don't think there is a direct flight."

Together, the two institutions treated 10,159 new patients in 2013.

The collaboration may help the University of Florida take care of patients who are currently on a waiting list for proton beam treatment. The UF center draws patients from all over the world. It has a contract to treat children from the U.K. National Health Service

as well as other European countries. Patients also come from Australia and Norway. And it is the preferred referral site for children from St. Jude Children's Research Hospital.

Altogether, 813 patients were treated last year, but the waiting list hovered around 100.

Orlando Health expects to complete its proton beam facility in early 2015.

"When the Orlando Health proton unit comes online, it will increase capacity to treat Floridians with proton therapy by 25 percent," Okunieff said. "With a waiting list for UF's proton treatment in just Jacksonville of 100 or more we feel there is need for additional capacity to serve Florida's residents.

"We anticipate that our faculty and clinical administrative expertise will be of great benefit to Orlando Health as a resource in terms of helping to define the clinical model for the most efficient and effective utilization of the facility.

"Also, since almost all our patients are on a therapeutic or registration trials this volume will allow us to understand efficacy and value (or lack of same) faster."

Similarly, the two institutions are preparing to start genotyping all patients.

"We're already genotyping a lot of people but not all," Okunieff said. "In 2012 we began an IRB protocol tissue collection initiative housed in our UF CTSI Biorepository, which is accredited by the College of American Pathologists. We are poised to begin collecting and genotyping tissue for every cancer patient we treat and both institutions are working toward that reality."

This fusion of programs and finances with the University of Florida is tighter than most similar alliances that have formed in recent years, as the boundary separating academic and community oncology continues to erode.

Transformation in the subspecialty begins at the cancer clinics. Small offices have been joining large practices, which in turn have been joining hospital-based systems. In Charlotte, NC, Carolinas HealthCare is hybridizing academic and community oncology at a health system (The Cancer Letter, Jan. 4, Jan. 11, 2013).

Last year, Memorial Sloan-Kettering Cancer Center formed an affiliation with Hartford HealthCare. The alliance, which isn't intended to generate revenues for MSKCC, is part of an effort for the cancer center to expand access to patients in order to explore targeted therapies (The Cancer Letter, Sept. 27, 2013).

Similarly, Georgetown Lombardi Comprehensive Cancer Center and Hackensack University Medical Center John Theurer Cancer Center recently announced plans to affiliate, aiming to create a single consortium.

The consortium would work across 200 miles, combining Georgetown's NCI-designation with Hackensack's expertise in hematologic malignancies. Hackensack's objectives in this collaboration include giving local residents an alternative to crossing the bridge to Manhattan to get care at an NCI-designated cancer center (The Cancer Letter, April 19, 2013).

Conversation with The Cancer Letter

Roh: "We Have Different Goals, Different Visions for our Future"

(Continued from page 1)

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

PG: *The world has changed. How has that change affected your collaboration with MD Anderson?*

MR: Well, our strategy has been to be Florida-centric. That is our focus, helping the citizens of Florida.

We know we couldn't do it alone, for sure. How can we partner with someone that we can hopefully accomplish what we set out to do? In doing that, [University of] Florida seemed like one of the options to pursue. The culture, the people—a common vision was there. In the past couple of years we've worked hard to get to this point where in many ways our work is just beginning.

Getting the documents together is one thing, but making a difference to someone sitting at home three months into their cancer is a different story.

PG: *Can you tell me anything about the financial structure of the MD Anderson deal?*

MR: Well, unfortunately, that's proprietary information. They have us sworn to secrecy, and we've actually signed documents accordingly. I'd love to tell you, but I can't.

PG: *What was the structure? When was this to be renewed?*

MR: Every 10 years.

It was due for renewal. Actually, the agreement was that it was supposed to be, a year ahead of time, a yes or no—but because of a variety of factors going on at both sides, we pushed that back to six months, and then three months, and then we started to realize that this isn't going to work.

We have different goals, different visions for our future.

PG: *What were the visions, and how were they different?*

MR: Their vision—and I'm paraphrasing; I'd recommend that you speak to them—was a national campaign. [MD Anderson President Ronald] DePinho is very passionate about wanting to provide cancer care to 3 to 5 percent of new cancer patients throughout the U.S., something I can't even fathom, let alone enact. Whereas I can understand that somewhat, but we said, 'Wait, we need to do Florida here, and do it well.'

One time we tried to have a three-way, but it didn't work out.

Orlando Health Center's Mark Roh

PG: *Really?*

MR: Again, this is where the differences became so clear. We're going in completely different directions.

PG: *I understand you were discussing this with the University of Florida for a couple of years.*

MR: And we let [MD Anderson] know that.

A couple of years ago we said the discussions are continuing. We don't know where they're going to go.

We had a meeting in Canada, I remember, and we told them that. I'm not sure how they read it, but it continued.

It wasn't like it was in secret or behind closed doors. We had conference calls with Houston and Gainesville trying to say is there something here, because part of the issue that really excited all of us is that the docs in Gainesville saw the benefit of a three-way, we did, and so did the docs in Houston.

Because of clinical research, more patients, larger patient population, we all could win at this. But I guess it didn't work out that way.

PG: *Was your collaboration with MD Anderson structured in a way that included biospecimens or genomic analysis? Was there some sort of a shared enterprise there?*

MR: Well, it wasn't quite shared. I guess I can look at that and answer it in two ways. The actual clinical services agreement did not get that granular. It didn't really get that specific. It didn't prohibit it, but it did say we got to leave that up to the individual investigators in Houston and Orlando.

PG: *Was that possible for it to function? Did it function in this way?*

MR: There were challenges, let's just leave it at that.

PG: *That's what drives a lot of these collaborations now, which wasn't there 23 years ago.*

MR: You are right. Many of our faculty, like me, either trained there, or were on staff there. We have allegiances and loyalties to many of the staff there, our friends and colleagues, and we tried to make it work, but it just…

PG: *Well, genomics would probably be a big chunk of that.*

MR: Oh yeah.

PG: *And informatics, right?*

MR: All of that, exactly right.

PG: *Were you able to integrate in terms of informatics and genomics?*

MR: I can say we had discussions.

PG: *Well, that explains a lot. How would these two considerations fit into your deal with the University of Florida?*

MR: Quite a bit different.

You are sitting at the table with your colleague. It's even. We are all on equal footing.

We all share in the success; we all work towards that success. Obviously, their genomics capability I can't really compare to Houston, but it's better than ours in Orlando.

They have a lot of good people up there. And to have all of us working together, toward a common goal, to me, is extremely exciting.

This whole thing developed with just a cadre of a number of us from Orlando and Gainesville. And the only way this is going to work is the troops who take care of patients at both sites are excited and motivated.

And I generally believe that they say wow, our patients that we draw from a population of four million in central Florida. In Gainesville, I don't know if you've ever been there, there's not a population like that up there. So when they look at their potential growth opportunities, even the president of the university says "We are landlocked, we are surrounded on all sides."

There's not as much potential, with Disney, with Universal, with all that's here in central Florida, and the I-4 corridor too.

PG: *So basically what you would be doing is setting up the infrastructure for genomics. Would you basically be building from scratch? Do you have it do they have it?*

MR: Not the genomics, but active clinical research programs yes definitely.

And that's the other thing we start to look at. Each of us has our strengths and areas that we could improve on, and in many areas they complement each other. Our shortcomings are their strengths, and vice versa.

PG: *Can you tell me which ones are which?*

MR: Well, take basic science. We don't have basic science opportunities.

The genomics, they have CLIA-certified labs that do the genomic analysis at UF. They have individuals with R01s, we don't. One of the other things we are looking at is hopefully together we'll have a chance to compete for an NCI designation. Alone, neither of us have the resources to invest to get to that point. Together, we think it's realistic. Not tomorrow, but in three to five years.

PG: *How would you integrate the systems? Because I understand you're actually integrating the two cancer centers.*

MR: Yes we are.

Right now, it's called the joint oncology program. There's a governance aspect, which is the [UF] Shands [Hospital] board, the UF board, and Orlando Health, but then there's the oversight committee and the management committee.

The budgeting, the growth opportunities all the things you would do in running a business, are driven by the oversight committee basically, which consists of guys like the chancellor of health affairs, myself and some of our leadership.

PG: *Let's say a dollar comes in—is it going to be split? How will that work?*

MR: We have different programs and different volumes of patients.

What we are looking at is, we looked at every option here and it took quite a while, and we thought of the thing you just suggested and that strategy, and the deeper you got the more convoluted and difficult it became. So we came to the decision that here is our baseline business as of a certain date, and incremental profit beyond that is what we end up sharing.

So here's our baseline, here's our Orlando-Gainesville baseline, and then a year from now,

what do our finances look like? And then we divide it from there.

PG: *You divide the profit margin?*

MR: Yes.

PG: *That's fascinating. Has anyone done that this way?*

MR: Not that we are aware of. And that's exciting. A little anxiety producing, too. Because otherwise it's just talk. If you're not sharing finances, neither of you have much skin in the game.

PG: *So you are trying to make it a closer integration. You've already had enough distance with MD Anderson, now it's closer in.*

MR: Oh yeah.

PG: *But they [UF] have proton beam, you do not.*

MR: We are building one. In January 2015 it should be ready to start treating patients.

PG: *You have one as well?*

MR: It's under construction. The gantries have been delivered already, but not the actual thing.

PG: *So there will be two in Florida?*

MR: Well interestingly in Jacksonville, a private entity has a third. So there are two in Jacksonville. I can't explain that.

PG: *That would be a fascinating other conversation. But they have a transplant program, you do not.*

MR: Correct. They're strong in bone and soft tissue sarcomas from a surgical perspective. We have strong medical, but not much surgical.

So the collaboration there is good. We do intraperitoneal chemotherapy, they don't. Thoracic breast— you see there are variations here in strength and in opportunities for development.

We co-recruit—that's what we're in the process of doing in several specialties—because historically, this has not been an academic center. No one could pretend otherwise.

I look at it as a hybrid. A number of us have been in academia for a variety of reasons, we're not still in academia, but we still have that interested that passion for it. This allows us to move back in that direction without being part of a school of medicine with a dean and all the things that come with it.

PG: *That's not happening often. There's a couple of places where this seems to be happening now.*

MR: What examples? I'm curious to hear.

PG: *Carolinas Healthcare would be one, where there's a new entity being built. I think possibly Memorial [Sloan-Kettering], to some extent, and its alliance with Hartford [HealthCare]. That's kind of a new hybridization. Probably Yale's hybridization with Sarah Cannon. The points are connected in different ways, but they're still the same points. Yours is different, though.*

MR: It's a variation on a theme, but it also recognition I think that the old way of doing business isn't going to cut it going forward.

PG: *You can't just slap a famous name on your building?*

MR: Exactly. And expect people to come. It's much more than that.

PG: *And they were still coming. You have a massive hospital. I guess I should ask what's the financial condition of both of the places.*

MR: I'm not going to lie, we don't have challenges. But we've had to do make some changes this year, but they're bearing fruit now. I'm being vague with you, obviously.

PG: *But you're in the black?*

MR: Yes.

PG: *And both are viable right now?*

MR: Yes.

PG: *Everybody is making changes.*

MR: You have to. We talk about UF being complementary, their systems that they have in place, their analytics exceed ours and, in fact, we are in the process of learning more about how they can help us. So instead of us reinventing the wheel, hiring people, we're using their expertise with our systems.

PG: *Will you combine the electronic medical records?*

MR: Well, we are talking about that. Unfortunately, they have Epic and we have Sunrise.

But right now we are working towards at least Orlando getting a read-only Epic. I think down the road, it makes sense you have to do that. But we are looking at a common IRB. If you want NCI designation, having two isn't going to do it. Likewise, working with pharmaceutical companies, they want fast turnaround. Having two IRBs isn't going to work.

So we've got to streamline, and be nimble and efficient. Common systems. And I have to say, on both sides, this is new. I'm not saying beyond the cancer world people are applauding. It's new and the cancer folks are really trying to push this to make sense.

It's not fiefdom here. It's what's best for the patient: how can we make this better?

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Drug Development

AVEO's Tivozanib Fails In Colorectal Cancer

AVEO Oncology said that data from a planned interim analysis of the phase II BATON (Biomarker Assessment of Tivozanib in ONcology) study in patients with colorectal cancer indicate that the study is unlikely to meet the primary endpoint in the intent-to-treat patient population.

BATON-CRC, led by Astellas, is an open-label, randomized phase II study with a primary endpoint evaluating the superiority of tivozanib in combination with modified FOLFOX6, compared to bevacizumab in combination with modified FOLFOX6 as first-line treatment in patients with advanced metastatic CRC.

A component of the BATON-CRC study is the assessment of biomarker relationships that may be predictive of response in select, pre-defined patient subpopulations.

The company said data from the planned interim analysis, including biomarker data, are being analyzed, and AVEO and Astellas are in discussions regarding next steps.

AVEO's co-founders include MD Anderson President Ronald DePinho and his wife Lynda Chin, a senior scientist at MD Anderson. In 2012, DePinho touted the company's stock in an appearance on a CNBC program for investors.

FDA has since rejected AVEO's application for the renal cell carcinoma indication, and SEC has subpoenaed the company's records.

DePinho has left the AVEO board of directors, but Chin remains on the scientific advisory board. DePinho has apologized for having offered investment advice.

Recently, Forbes columnist Matthew Herper placed AVEO on a "wall of shame" for what he described as failure to "disclose their data that made it evident what a big problem them FDA would have with them, and then walked into an FDA advisory panel completely unprepared.

In the Cancer Centers

$540 Million To Be Divided Among Six Ludwig Centers

(Continued from page 1)

The gift was made on behalf of the organization's founder, the late Daniel Ludwig, a shipping magnate, and brings the total Ludwig funding for these institutions to $900 million. The new funding was realized by the sale of New York real estate investments held by Ludwig.

"This gift provides a momentous opportunity for the entire Harvard Medical School community to glean new insights into the basic biology of cancer as well as to accelerate the translation of basic research to improve patient outcomes," said Jeffrey Flier, dean of the faculty of medicine at Harvard, in a statement.

The university plans to expand their center, using the new funds to build upon research activities, attract new biomedical and cancer researchers, and expand collaborations. The expanded center will be co-directed by Joan Brugge, the Louise Foote Pfeiffer Professor of Cell Biology and chair of the HMS Department of Cell Biology, and George Demetri, professor of medicine at HMS and the Quick Family Chair of Medical Oncology at the Dana-Farber Cancer Institute.

At MIT, Ludwig funds currently support its center and six faculty members at the David H. Koch Institute for Integrative Cancer Research, as well as training opportunities through fellowships to students and postdocs working in the field of metastasis.

"Ludwig's generosity will support our efforts to answer two critical questions: how cancer spreads in the body, and what we can do to stop it," said MIT President L. Rafael Reif.

Bert Vogelstein and Kenneth Kinzler, co-directors of the Ludwig Center at Johns Hopkins, used an initial $20 million gift to establish the center in 2006 and help build the first genomic maps of cancer.

"We've pursued some of the most important questions in cancer—not necessarily the most fundable questions," said Vogelstein, the Clayton Professor in Oncology and a Howard Hughes Medical Institute Investigator.

The center at the University of Chicago will use its grant to focus on metastasis research.

"This funding allows us to expand the center, to buy exceptional equipment and to recruit extraordinary scientists who would otherwise be impossible to get," said Geoffrey Greene, co-director of the center, the Virginia and D.K. Ludwig Professor, and chairman of

the Ben May Department for Cancer Research at the University of Chicago.

"It would not be possible to obtain this kind of funding from, say, the National Institutes of Health. Thanks to the Ludwig gift, we plan to make this center one of the best in the world."

The Ludwig Center at Memorial Sloan-Kettering has focused on immunotherapy and has generated several protocols that have progressed to phase III trials, including a trial contributing to the development of Yervoy (ipilimumab), which has extended survival in advanced melanoma.

Ludwig research funding has also supported the center's Immune Monitoring Core Facility, where researchers observe immunologic therapies in patients enrolled in clinical trials at Memorial Sloan-Kettering and international collaborating sites.

Stanford plans to continue funding the school's research on cancer stem cells, where Ludwig has funded the work of 10 to15 laboratories, and has helped support an international collaboration with the Oxford University, which will conduct CD47 trials in patients with leukemia and solid tumors.

John Hennessy, president of Stanford, said the university has assembled a dream team of researchers, and that "the gift is a tremendous vote of confidence in the work they and their colleagues at other Ludwig Centers are doing."

Cancer Detection

Task Force Issues Guideline On LDCT Lung Screening

By Matthew Bin Han Ong

The U.S. Preventive Services Task Force released its final recommendation statement on screening for lung cancer with low-dose computed tomography.

Annual LDCT screening can reduce lung cancer mortality of high-risk persons aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke, or have quit within the past 15 years, the 16-member task force determined.

The Dec. 31 recommendation retains its "B" grade, which is likely to alter the practice of medicine, boosting the utilization of CT screening and follow-up procedures. The grade was based primarily on the NCI-sponsored National Lung Screening Trial (The Cancer Letter, Aug. 2, 2013).

There are no significant differences between the final recommendation and the July 30, 2013 draft recommendation. The statement is published online in Annals of Internal Medicine, as well as on the task force's website.

"Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery," the recommendation states. "The incidence of lung cancer increases with age and occurs most commonly in persons aged 55 years or older. Increasing age and cumulative exposure to tobacco smoke are the two most common risk factors for lung cancer."

LDCT has greater sensitivity for detecting early-stage cancer, and early-stage non-small cell lung cancer has a better prognosis and can be treated with surgical resection.

The task force said it found adequate evidence that annual screening for lung cancer with LDCT in a defined population of high-risk persons can prevent a substantial number of lung cancer-related deaths. Annual LDCT screening may not be useful for patients with life-limiting comorbid conditions or poor functional status who may not be candidates for surgery.

"Direct evidence from a large, well-conducted, randomized, controlled trial provides moderate certainty of the benefit of lung cancer screening with LDCT in this population," the recommendation said. "The magnitude of benefit to the person depends on that person's risk for lung cancer because those who are at highest risk are most likely to benefit.

The longer and the more a person smokes, the greater their risk is for developing lung cancer, Michael LeFevre, co-vice chair of the task force, said in a statement.

"When clinicians are determining who would most benefit from screening, they need to look at a person's age, overall health, how much the person has smoked, and whether the person is still smoking or how many years it has been since the person quit," LeFevre said.

The task force recommends extending the enrollment age of the NLST, which formed the foundation for the task force's recommendation, through age 80 years. The NLST, the largest randomized, controlled trial to date, with more than 50,000 patients, enrolled participants aged 55-74 years at the time of randomization.

NLST showed a reduction in lung cancer mortality of 16 percent and a reduction in all-cause mortality of 6.7 percent. Annual screening with LDCT provides the greatest benefit in decreasing lung cancer mortality compared with biennial or triennial screening.

Screening Scenarios From Cancer Intervention and Surveillance Modeling Network Models

Screening Scenario†				Benefit		Harm‡			CT Screens per Lung Cancer Death Averted, *n*
Minimum Pack-Years at Screening, *n*	Minimum Age at Which to Begin Screening, *y*	Time Since Last Cigarette, *y*	Population Ever Screened, *%*	Lung Cancer Deaths Averted, *%*	Lung Cancer Deaths Averted, *n*	Total CT Screens,*n*	Radiation-Induced Lung Cancer Deaths, *n*	Overdiagnosis §	
40	60	25	13	11	410	171,924	17	11.2	437
40	55	25	13.9	12.3	458	221,606	21	11.1	506
30	60	25	18.8	13.3	495	253,095	21	11.9	534
30	**55**	**15**	**19.3**	**14**	**521**	**286,813**	**24**	**9.9**	**577**
20	60	25	24.8	15.4	573	327,024	25	9.8	597
30	55	25	20.4	15.8	588	342,880	25	10	609
20	55	25	27.4	17.9	664	455,381	31	10.4	719
10	55	25	36	19.4	721	561,744	35	9.5	819

Note: The bolded row highlights the screening scenario with a reasonable balance of benefits and harms and that is recommended by the USPSTF.

* All scenarios model the results of following a cohort of 100,000 persons from age 45 to 90 years or until death from any cause, with a varying number of smokers and former smokers screened on the basis of smoking history, age, and years since stopping smoking.

† For all scenarios, screening is continued through age 80 years.

‡Number of CT screenings is a measure of harm because it relates to the number of patients who will have risk for overdiagnosis and potential consequences from false-positive results.

§ Percentage of screen-detected cancer that is overdiagnosis; that is, cancer that would not have been diagnosed in the patient's lifetime without screening.

Source: USPSTF

Based on current evidence, the task force said the balance of benefits and harms of screening may be unfavorable in lower-risk patients—persons who are at higher risk because of smoking history or other risk factors are more likely to benefit.

"Lung screening has substantial harms, most notably the risk for false-positive results and incidental findings that lead to a cascade of testing and treatment that may result in more harms, including the anxiety of living with a lesion that may be cancer," the recommendation said. "Overdiagnosis of lung cancer and the risks of radiation are real harms, although their magnitude is uncertain. The decision to begin screening should be the result of a thorough discussion of the possible benefits, limitations, and known and uncertain harms."

Detterbeck & Unger: Practical Aspects

The USPSTF report doesn't address many practical aspects of implementing lung cancer screening, wrote Frank Detterbeck, professor of surgery and surgical director of thoracic oncology at Yale University School of Medicine, and Michael Unger, a pulmonologist at Fox Chase Cancer Center, in an editorial published Dec. 31 in the Annals of Internal Medicine.

"Disproportionate screening attracts individuals who have great anxiety about developing lung cancer even though their risk is actually not so high," Detterbeck and Unger wrote. "These people need reassurance, with discussion of their risk for lung cancer and the issues associated with screening as they apply to them.

"This substantial population exists despite being outside the focus of the USPSTF report (that is, those appropriate for screening). These people have reasons for their concerns; turning them away because they do not meet the criteria does not provide them the reassurance they seek.

"They usually respond well to an educated discussion if screening and their risk for lung cancer, but this requires specialized knowledge and time. However, chest CT—which is notorious for false-positive findings—is not a simple way to provide reassurance to anxious, lower-risk individuals."

Also, effective implementation of lung cancer screening hinges on reaching high-risk individuals—studies show that higher-risk smokers are less interested in being screened despite recognizing that they are at risk, according to Detterbeck and Unger.

"Another issue, as seen in studies of adherence to colon cancer screening, is whether we can achieve adequate adherence and follow-up in persons who are at highest risk for lung cancer," Detterbeck and Unger wrote. "It is unlikely that sporadic CT screening will achieve results identical to those seen in the NLST (where adherence was 95 percent)."

The task force advocates for screening in organized programs, Detterbeck and Unger argues—not simply a scan, but a structured screening process.

"Is the health care system willing to support what the USPSTF is recommending?" they asked. "Are we willing to provide the resources to make the process of patient selection and counseling achievable and to make contribution to a registry and tracking of quality metrics actually happen?

"To paraphrase Winston Churchill, 'This is not the end. It is not even the beginning of the end. But it

is perhaps, the end of the beginning [of screening for lung cancer].'"

Bach: Reliance on Modeling "Dismaying"

The task force relies heavily on disease state models to extrapolate beyond the empirical data, wrote Peter Bach, a pulmonologist and health systems researcher at Memorial Sloan-Kettering Cancer Center, in a separate editorial published Dec. 31 in the Annals of Internal Medicine.

"On the basis of models, the task force chose to lengthen the duration of screening to a maximum of 26 years and increase the upper age of eligibility for screening to 80 years, even though NLST participants were screened for only 3 years and were ineligible to enroll if they were older than 74 years (only 8.8% of participants were aged 70 years or older at enrollment)," Bach wrote. "This may be appropriate, but here, too, the grading of this extrapolation should match the low level of evidence supporting it.

"The American College of Chest Physicians grades extrapolations outside of studied populations as a 'C.' Most hierarchies of evidence would place modeling studies, even those with great rigor, in the category of expert opinion, the lowest level of evidence."

Lung cancer is a poorly understood and highly heterogeneous condition, Bach wrote.

"In this specific case, I found the task force's reliance on the modeling dismaying, particularly now that their 'B' rating will be converted into insurance mandates," Bach wrote. "Even the highly accomplished CISNET researchers who generated the models do not seem to have been able to generate models of lung cancer that parallel its natural history or simulate the empirical pattern of benefit seen from computed tomography screening in the NLST.

"Seeing this, the task force might have stopped short of relying on these models for extrapolation well beyond the empirical data. In addition, they might have considered how little is known about the net benefit of screening annually over many years.

"The task force seems to have looked for findings where there was 'consensus' between the models as a way of overcoming the heterogeneity between them. However, because they are starkly different on so many fronts, looking only for the overlap is reminiscent of the Texas sharpshooter and the fallacy that accompanies him.

"The sharpshooter shoots first at the barn and then draws the target around the greatest cluster of hits."

Cancer Statistics

ACS: Decline in Death Rates Saved Over 1.3 Million Lives

By Conor Hale

Declines in death rates over past two decades have added up to a 20 percent drop in the overall risk of dying from cancer, according to the American Cancer Society's annual statistics report.

The report, Cancer Statistics 2014, finds progress has been most rapid for middle-aged black men, with death rates declining by approximately 50 percent. Despite this, black men continue to have the highest cancer incidence and death rates among all ethnicities in the U.S.

The report is a compilation of recent data on cancer incidence, mortality, and survival based on incidence data from NCI and the Centers for Disease Control and Prevention, and mortality data from the National Center for Health Statistics. The data are disseminated in two reports: Cancer Statistics, published in CA: A Cancer Journal for Clinicians, and its companion article, Cancer Facts & Figures.

The 20 percent decline translated to the avoidance of approximately 1,340,400 cancer deaths, or 952,700 among men and 387,700 among women, between 1991 and 2010. In 2014, the report estimates there will be 1,665,540 new cancer cases and 585,720 cancer deaths in the U.S.

Among men, prostate, lung, and colon cancer will account for about half of all newly diagnosed cancers, with prostate cancer alone accounting for about one in four cases. Among women, the three most common cancers in 2014 will be breast, lung, and colon, which together will account for half of all cases. Breast cancer alone is expected to account for 29 percent of all new cancers among women.

Lung, colon, prostate, and breast cancers continue to be the most common causes of cancer death, accounting for almost half of the total cancer deaths among men and women. Just over one in four cancer deaths is due to lung cancer.

Between 2006 and 2010, cancer incidence rates declined slightly in men, by 0.6 percent a year, and were stable in women. At the same time, cancer death rates decreased by 1.8 percent a year in men and 1.4 percent a year in women.

The magnitude of the decline in cancer death rates from 1991 to 2010 varies substantially by age, race, and sex, ranging from no decline among white women aged 80 years and older, to a 55 percent decline

among black men aged 40 years to 49 years. Notably, black men experienced the largest drop within every 10-year age group.

"The halving of the risk of cancer death among middle aged black men in just two decades is extraordinary, but it is immediately tempered by the knowledge that death rates are still higher among black men than white men for nearly every major cancer and for all cancers combined," said John Seffrin, CEO of the American Cancer Society.

In Brief

Duke's Gary Lyman to Co-Direct Fred Hutch Outcomes Research

GARY LYMAN was named co-director of **The Hutchinson Institute for Cancer Outcomes Research**, based at the Fred Hutchinson Cancer Research Center. He will co-lead with **Scott Ramsey**, a member of the Cancer Prevention Program in the Public Health Sciences Division at Fred Hutch.

Lyman served as professor of medicine and as a senior fellow at the Duke Center for Clinical Health Policy Research and Director of the Comparative Effectiveness and Outcomes Research Program in Oncology at the Duke Cancer Institute since 2007.

He will hold appointments within the Cancer Prevention Program, the Division of Medical Oncology at the University of Washington School of Medicine, and affiliate appointments within the Department of Health Services at the UW School of Public Health and in the UW School of Pharmacy. He will also practice as a medical oncologist in the Breast Cancer Program at Seattle Cancer Care Alliance.

Lyman is co-leading the development of comprehensive breast cancer and survivorship guidelines at the American Society of Clinical Oncology. He has served on numerous ASCO committees, and currently serves on the board of directors. He is also active with the American Society of Hematology and several other professional clinical and cancer research organizations.

GARY SCHWARTZ was named chief of the Division of Hematology/Oncology at **NewYork-Presbyterian/Columbia University Medical Center**. He will also serve as associate director for research of the Herbert Irving Comprehensive Cancer Center.

Previously, Schwartz was chief of the melanoma and sarcoma service at Memorial Sloan-Kettering Cancer Center, where he also directed the Laboratory of New Drug Development. He will continue his research on melanoma, sarcoma, and cancers of the gastrointestinal tract.

Gary Lyman *Source: FHCRC*

Schwartz has worked on a number of NIH review committees and has served on the editorial boards of various scientific journals, including the Journal of Clinical Oncology and Clinical Cancer Research, of which he is currently an associate editor. He is currently the co-chair of the experimental therapeutics committee of the Alliance for Clinical Trials in Oncology.

RICHARD GANNOTTA was named president of **Northwestern Memorial Hospital** and senior vice president of Northwestern Memorial HealthCare, effective Feb. 10.

Gannotta is currently president of Duke Raleigh Hospital, one of three hospitals in the Duke University Health System. He joined Duke Raleigh as chief operating officer in 2006, before becoming president last year. Gannotta is also a nurse practitioner, and is faculty for the Duke Nursing and Health Leadership Program.

At Duke, he worked on clinical alignment, program development, and physician recruitment to expand the hospital's primary and specialty care practices. The hospital attained Nurse Magnet Status, a designation of only 5 percent of the nation's hospitals.

HAROLD VARMUS, director of the NCI and co-recipient of a Nobel Prize for research into the genetic basis of cancer, received the **Medal of Honour** from the **International Agency for Research on**

Cancer in France.

Varmus also presented the 21st Roger Sohier Lecture at the IARC. The title of his talk was "Promoting the discovery and application of knowledge about cancer."

FDA News

FDA Grants Accelerated Approval To Mekinist-Tafinlar Combination

FDA granted accelerated approval for Mekinist (trametinib) in combination with Tafinlar (dabrafenib) for unresectable melanoma or metastatic melanoma with BRAF V600E or V600K mutations.

The approval was based on the demonstration of response rate and median duration of response in a phase I/II study, and is dependent on the results of an ongoing phase III trial (MEK115306 or Combi-D). The combination was reviewed under a Priority Review designation.

Improvement in disease-related symptoms or overall survival has not been demonstrated for Mekinist in combination with Tafinlar. The BRAF mutations must be detected by an FDA-approved test. Tafinlar is not indicated for treatment of patients with wild-type BRAF melanoma.

In the phase II portion of the open-label study, the main efficacy endpoint of overall response was 76 percent for patients treated with the combination (n=54; 95% CI, 62, 87), and 54 percent for patients treated with single-agent Tafinlar (n=54; 95% CI, 40, 67).

The median duration of response was 10.5 months for patients treated with the combination (95% CI, 7, 15), and 5.6 months for patients treated with single-agent Tafinlar (95% CI, 5, 7). When enrolling patients, no more than one prior chemotherapy regimen and/or interleukin-2 was permitted. Patients with prior exposure to BRAF inhibitors or MEK inhibitors were ineligible.

Mekinist and Tafinlar are both sponsored by GlaxoSmithKline.

The European Commission has amended the product information of Erbitux (cetuximab), updating the indication to include RAS wild-type metastatic colorectal cancer.

The approval follows the positive opinion from the Committee for Medicinal Products for Human Use issued in November 2013, and is based on the totality of data emerging on the role of mCRC RAS tumor status in the benefit-risk profile of the drug. The approval primarily refers to new biomarker data from the OPUS (OxaliPlatin and cetUximab in firSt-line treatment of mCRC) study.

In recent analyses of studies evaluating monoclonal anti-epidermal growth factor receptor antibodies, such as Erbitux, tumor samples of patients with KRAS wild-type tumor status (exon 2) were assessed for additional RAS mutations (defined as mutations in exons 3 or 4 of KRAS and/or exons 2, 3 or 4 of NRAS). The results from these studies suggest that patients with RAS wild-type tumors may benefit from treatment with Erbitux, while patients with RAS mutant tumors may not.

In the updated product information, Erbitux will now be indicated for the treatment of patients with EGFR-expressing, RAS wild-type mCRC in combination with irinotecan-based chemotherapy, in first-line in combination with FOLFOX, or as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.

Erbitux is sponsored by Merck Serono, the biopharmaceutical division of Merck.

FDA and the European Medicines Agency launched a joint initiative to share information on inspections of bioequivalence studies submitted in support of generic drug approvals. This collaboration provides a mechanism to conduct joint facility inspections for generic drug applications submitted to both agencies.

France, Germany, Italy, the Netherlands, and the United Kingdom are also taking part in this initiative.

A key objective of the initiative is to streamline information sharing on inspections of bioequivalence studies conducted and planned for generic drug applications. Inspectional information will be shared for clinical facilities, analytical facilities, or both.

Information will be shared about negative inspection outcomes that reveal system problems at a facility, joint inspections will be conducted at facilities all over the world, and training opportunities will be provided. This initiative will use confidentiality arrangements established among the European Commission, the EMA, interested EU member states, and the FDA.

The agreement includes an 18-month pilot phase and follows the 2009 EMA-FDA Good Clinical Practices Initiative.

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