THE CANCER LETTER

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40 Years Later

Doctor and Patient Reflect on the Cure

By Matthew Bin Han Ong

On Oct. 21, 1974, John Cleland lay in a hospital bed at Indiana University Hospital.

At 23, he had just graduated from Purdue University and just married.

He was also three weeks into a fourth-line chemotherapy regimen for advanced metastatic testicular cancer. The disease had spread to his lungs.

Lawrence Einhorn, Cleland's doctor, told him that this was the end of the road.

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Conversation with The Cancer Letter

Einhorn: "I Still Harbor Hope For Similar Success Stories"

The Cancer Letter asked Lawrence Einhorn, distinguished professor of medicine and the Livestrong Foundation Professor of Oncology at the Indiana University Melvin and Bren Simon Cancer Center, to reflect on one of the most spectacular successes in the history of cancer research—his development of the curative regimen for testicular cancer.

Einhorn spoke with Matthew Ong, a reporter at The Cancer Letter.

Matthew Ong: *What was it like to meet John Cleland 40 years ago?*

Lawrence Einhorn: John himself, as a patient, looked fine, and that's one of the paradoxes with young, healthy men with testicular cancer.

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In Brief

Neel Named Director of NYU Cancer Center

BENJAMIN NEEL was named director of the **Laura and Isaac Perlmutter Cancer Center at NYU Langone Medical Center**. He will begin Jan. 1, 2015.

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How a Fourth-Line Therapy Produced a Clean X-Ray

(Continued from page 1)

"Like so many patients then and now with testicular cancer, you see these round, white, kind-of-like snowballs scattered throughout the right lung and the left lung," Einhorn, distinguished professor of medicine and the Livestrong Foundation Professor of Medicine at IU Melvin and Bren Simon Cancer Center, said to The Cancer Letter. "Certainly, without chemotherapy, John's chances of surviving more than a year was basically zero."

A conversation with Einhorn appears on p. 1.

Cleland had tried three types of chemotherapy, but the disease invariably returned.

"Back then, 40 years ago, boy, medical oncology was in its dark ages," Cleland said to The Cancer Letter. "They used some chemotherapies that today, people scratch their heads and say, 'What?' Man, I had some antique chemotherapy."

Einhorn had shown Cleland a chest film three weeks earlier, on Sept. 27, 1974. "He told me that he didn't think I was going to make it," Cleland said. "That's when he offered me cisplatin." The new platinum-based chemotherapy drug was to be combined with bleomycin and vinblastine.

On Oct. 21, Cleland was admitted with high fever—104.5—and was given another chest X-ray.

"In the afternoon, Dr. Einhorn and [his nurse] Becky Furnas Bond exited the elevator," Cleland recalled. "When they came off the elevator, I knew just from their body language that somebody had good news."

Einhorn didn't expect much from Cleland's X-ray.

"To be honest with you, most of the time, when an experimental drug is combined with other drugs, even today, in 2014, if you're using a treatment that is fourth-line therapy and you look at a chest X-ray three weeks later to see how pulmonary metastases are doing, it's going to show further progression," Einhorn said.

This image was different.

The snowballs were nowhere to be seen. Einhorn and Bond checked several times to make sure it was the right film.

"Dr. Einhorn came to my room and said, 'John, the chest X-ray is clear. I think you're gonna make it!'" Cleland said.

"Larry Einhorn saved my life. It can't get any bigger than that. So it really is my 40th anniversary just a couple of days ago, as far as I'm concerned.

"It's like I'm having a birthday."

Einhorn went on to conduct a phase III trial that, in conjunction with other surgical advancements and toxicity mitigation strategies, would lead to a 95 percent cure rate for testicular cancer patients. There are now more than 300,000 testicular cancer survivors.

Cleland's initial plan upon graduation was to work on a farm; his degree was in animal science.

Instead, he taught biology at Zionsville High School for 30 years until retiring in 2011. He and his wife had three children—a son and a pair of boy-girl twins—and is now a grandfather.

The 40th Anniversary

The IU Simon Cancer Center has raised $1 million in honor of the 40th anniversary of Einhorn's discovery.

A video the university produced for the anniversary is available here.

"When Dr. Einhorn began his work four decades ago, there was no term 'cancer survivor,'" Patrick Loehrer, director of the IU Simon Cancer Center, said in a statement. "Now, thanks to his research and leadership, 95 percent of the most common cancer in young men is curable. Today, the IU Simon Cancer Center is uniquely positioned to develop a program of significant magnitude for all cancer survivors."

The new survivorship research program will use gene sequencing technology.

Of the $1 million raised—contributions from patients and friends of Einhorn—$700,000 will be used

Cover Photo: Cleland and Einhorn, left to right, at the 40th anniversary celebration hosted by Indiana University.

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to launch the program.

According to IU, this includes a leadership gift of more than $500,000 from A. Farhad Moshiri of Monaco. Moshiri had previously created the Lawrence H. Einhorn Chair with a $2 million gift.

The Einhorn Chair will be held by the survivorship program director.

The children of Sidney and Lois Eskenazi pledged $300,000 to honor Einhorn and celebrate their parents' 60th wedding anniversary. The gift from Sandy, Dori (Meyers), and David Eskenazi and their spouses establishes the Sidney and Lois Eskenazi Fellowship in Hematology/Oncology at the IU School of Medicine.

"The significance is that what Dr. Einhorn started using resulted in a cure and not merely an extension of survival," said Peter Boyle, president of the International Prevention Research Institute, professor of global public health at Strathclyde University, and lead author of the State of Oncology 2013 report. "Oncologists now know how to cure testicular cancer, the commonest form of cancer in young men."

Einhorn's true gift is his ability to connect and help others, said Otis Brawley, chief medical officer for the American Cancer Society, and professor of hematology, oncology, medicine and epidemiology at Emory University.

"Otis has very few heroes, and Dr. Einhorn is one of them," Brawley said to The Cancer Letter. "The guy is without ego. He's not self-effacing, and he's not self-promoting.

"One of the things that Larry Einhorn is well known for, you can be a doc anywhere in the world, and you can find the phone in the ASCO directory, and say, 'Can I discuss a patient with you?'

"And Larry's answer is always, 'Yes.'"

Conversation with The Cancer Letter

Einhorn: We Never Say Cure After Three Weeks of Treatment

LE: Even up until the last couple weeks of life, they actually look pretty well.

But certainly, without chemotherapy, John's chances of surviving more than a year was basically zero. His chest X-ray looked much worse than he looked, as far as just looking at him walking down the street.

Like so many patients then and now with testicular cancer, you see these round, white, kind-of-like snowballs scattered throughout the right lung and the left lung.

It somewhat amazes me—you look at that chest X-ray and you think that someone can barely breathe, but again, a young, healthy person who is their 20s is very different from an elderly debilitated person in their 80s as to how they can handle the burden of disease.

MO: *What uncertainties did you face when you first put John on the combination regimen?*

LE: When you're using an experimental drug that had never been combined with other drugs and you're sort of the first person—John Cleland—to get that, A, you have no idea whether the drugs can be combined safely, B, you have no idea if it's going to help them and cause a remission, C, you have no idea how long that remission is going to last, and D, we never pronounce a cure three weeks after someone starts treatment.

MO: *How hopeful were you that your treatment would work, three weeks into administering the drugs?*

LE: To be honest with you, most of the time, when an experimental drug is combined with other drugs—and this was fourth-line therapy for John; he had failed to be cured although he responded to three previous types of chemotherapy—even today, in 2014, if you're using a treatment that is fourth-line therapy and you look at a chest X-ray three weeks later to see how pulmonary metastases are doing, it's going to show further progression.

The first level of excitement was seeing that, 'My God, something is actually helping.'

Now, in October [1974], we had no idea whether the benefit was going to last a month, six months, or, in John's case, fortunately, and for many thousands if not hundreds of thousands of patients, wind up being a curative treatment for this disease.

MO: *What was it like to see John's X-ray after that first treatment?*

LE: Well, it was equally exciting—and that's probably the wrong word—obviously, it's more exciting for the patient, but it is very exciting for an investigator to see that an experimental type of treatment in a very, very heavily pre-treated patient who really has no treatment options other than this clinical trial, actually is showing, at least on a short-term basis, that tumors that were rapidly growing in the lungs are now regressing in the lungs to where they were barely visible at the three-week level.

MO: *Would you say that your combination therapy was one of the biggest breakthroughs in treating solid tumors?*

LE: Well, actually, it's not often in solid tumors—as opposed to immunological malignancies, like leukemia and lymphoma—that you can, not just cause remissions, but also actually cure patients with the disease.

Prior to platinum, with some of these older drugs, the cure rate was 5 percent. Today, with platinum-based chemotherapy, it's gone from 5 percent to 80 percent, and that's been unprecedented—even 40 years later—to have that type of leapfrog benefit.

MO: *In retrospect, what do you know now about cancer that you didn't then?*

LE: In the 1970s, our knowledge was very rudimentary, and perhaps very naïve. And we've learned a great deal through genomic research, about the molecular basis and pathogenesis of cancer, and we're learning more and more that, instead of calling something testis cancer or lung cancer or breast cancer, or colon cancer, that we're looking at the specific mutations that drive the pathogenesis of the disease.

And instead of using chemotherapy—and again, chemotherapy with platinum is always going to be the standard for testicular cancer—but instead of just looking at chemotherapy, which is sort of non-specific, we personalize therapy, to give a drug that is specifically designed for whatever it is that's driving that particular patient's mutation.

There have been some outstanding successes like imatinib and chronic myelogenous leukemia and gastrointestinal stromal tumors, certainly Rituxan and lymphomas, and Herceptin and breast cancer. These are all known molecular-based therapies, rather than in 1970s, where we simply took a chemotherapy drug off the shelf and combined it with other chemotherapy drugs and hoped for the best.

MO: *Was that what you did with cisplatin?*

LE: Basically, then and now, when you combine drugs, you want drugs that are known to have single-agent activity, and platinum was a single agent, and in patients who have been through previous therapies was producing remissions, but no cures. Remissions were always very brief and temporary, and the toxicity was very severe with platinum.

Then you want to combine drugs that kill cancer cells by different mechanisms of action, and you want to combine drugs that have different side effects—you don't want three drugs in a combination that have the same side effect, or you won't be able to use them at full dosages.

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You want to combine drugs that play together well in the sandbox that are not just additive, but what we call 'synergistic,' so one plus one isn't just two. This was certainly true with the platinum combination chemotherapy regimens, and that philosophy for chemotherapy 40 years later is still true today.

MO: *At what point did you realize that cisplatin was this good in testicular cancer? Did you have a gut feeling before you ever gave it to patients?*

LE: I think those of us who are medical oncologists, who are involved in clinical trials, tend to be more optimistic than pessimistic. But we're also realistic. It is unusual—looking at John Cleland—even today, to have an experimental drug, or combination of drugs and ever cure anybody when it's fourth-line therapy, as opposed to first-line therapy.

So the first clue that it was doing something happened three weeks later in two different aspects:

Number one, the fact that we could actually combine these drugs safely, because it's not a given that you can put platinum together with other drugs and not produce overwhelming side effects that can be tolerated.

The second clue was, instead of further progression—which is what would've happened if he wanted no therapy—he was actually in remission. And then the third clue was, the nature of testicular cancer is such that when a patient is out at one year, it's unusual for the cancer to come back.

But until someone is out at one year, and that would be not October 40 years ago, but October 39 years ago, then you have some optimism that John, as a single patient, is cured of his disease.

But then you need a larger number of patients to know that this is not just a medical curiosity for one anecdotal patient, but that actually works across a cohort of patients.

So it wasn't until we had about 20 patients out at over a year, that we really did appreciate the fact that this was not just producing several months of remission in a couple of patients, but this was actually making a major difference forward and curing the majority of patients with testicular cancer.

This was a good two years or so after John became the first patient to be cured with platinum-based chemotherapy.

MO: *Before John, did you treat other patients with this regimen?*

LE: We had one patient before him, and this is another heavily treated patient that was more critically ill than John was. John actually looked pretty healthy, and this patient died within the first three weeks.

Whether that was partly from the drugs, or more likely, mostly from the tumor, it's difficult to know. And again, when you start a new type of treatment, as I said before, there's no guarantee that you can even give drugs safely when you combine different drugs.

The nature of experimental trials is, you're not going to use them as a brand new experimental drug that's never been used before at a combination on a perfectly healthy patient who's never had any other type of treatment before, most of the time.

There are patients who have been through previous types of treatment, especially if an older treatment has some degree of efficacy.

MO: *What did you do to reduce the combined toxic effects of your regimen?*

LE: If a drug works, as a science, we learn how to mitigate the side effects. So the most horrendous side effect, initially, was the incredibly severe nausea and vomiting, so we and others have worked at developing selective drugs that don't eliminate platinum-induced nausea and vomiting, but greatly reduce the amount of nausea and vomiting that people have.

When John was getting treated, and we didn't have any of those drugs then, the average patient would have 12 emetic episodes. They would vomit 12 times on day one of a five-day course of chemotherapy.

And today the average patient on day one would get some degree of nausea, but usually will have zero episodes of vomiting. So the nausea and vomiting worked out very well.

The second thing had to do with the drug causing kidney failure, which is a more serious side effect—not as troubling to a patient as nausea and vomiting—but more serious, perhaps even fatal.

And so we quickly learned that platinum was a heavy metal like mercury and other heavy metals, and that we can prevent the kidney damage by just making sure that we give lots of intravenous fluids before we gave the platinum and after we gave the platinum.

It became a pretty simple method to reduce the nausea and vomiting and reduce the potential life-threatening kidney damage once we and others had a little bit more experience with the drug.

And then as the years went by, we learned that we can reduce the dosages of some of the drugs, shorten the duration of therapy without reducing the therapeutic results.

When John was treated, the duration of therapy was much longer than it is today, because we've done phase III clinical trials demonstrating non-inferiority with lower dosages—the platinum hasn't changed—but lower dosages of the drugs, and shorten the duration of the therapy.

MO: *Did you lead most of these studies as well?*

LE: Indeed, yes.

MO: *Is there any way to repeat your success with other cancers? What leads can oncologists and researchers follow today?*

LE: Sure. And again, 2014 is very different from 1974, and I think I still harbor hope that similar success stories with other epithelial cancers will be produced, but probably not with chemotherapy.

It will be with specific molecular targeted agents or—what's very red-hot in the last couple of years—with immune checkpoint inhibitors to stimulate the immune system and figure out what drug works best for an individual patient, and also to hopefully figure out whether it can be safely combined with other drugs and produce results.

MO: *You're saying that the future is in genomics, immunotherapy, and molecular targeted therapies.*

LE: Exactly. And there's always some role for chemotherapy, and drugs like platinum aren't going to be replaced by molecular targeted agents, but I think the new, yet-to-be-discovered drugs will probably be non-chemotherapy molecular targeted agents, and drugs that affect the immune system.

I think in the last 10 years, the advances that have been made for patients in successful treatment have been phenomenal, and there's virtually no form of cancer that we deal with in 2014 that we don't, at the very least, relieve symptoms and produce palliation and prolong survival.

Now, in 2014, we don't have an 80 percent cure rate in any disease other than testicular cancer as far as a solid tumor, but we're moving forward, and that's the main thing.

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Caris Life Sciences Lays Off Estimated 20 Percent of Staff

By Paul Goldberg

Caris Life Sciences Inc. last week reduced its workforce by 50 people—about 20 percent, sources said.

While a 50-person reduction in force is small by pharma industry standards, the development could be significant because Caris is a key player in the emerging market for molecular therapies.

Company officials characterized the layoff as an effort to manage personnel expenses.

"The company's revenue and case volume has grown by over 50 percent so far this year," Caris officials said in a statement to The Cancer Letter. "Evaluating and maintaining the appropriate staffing levels is a constant effort for the company as we keep our offering on the cutting-edge. Of course, we will continue to monitor this to ensure that we provide the highest quality and most advanced molecular profiling service available, which our customers have come to expect and which their cancer patients deserve."

The privately held company markets the Caris Molecular Intelligence assays, which are widely used by oncologists, primarily outside of academic medicine.

Caris is not involved in the NCI trials of molecularly guided therapies.

The layoff affected the evidence review, IT, and quality assurance staff as well as administrative and facilities employees, sources close to the situation said to The Cancer Letter. The company's lab staff and the sales force have been left largely unaffected.

As is always the case when pharma and biotech companies reduce staff, bitter anonymous comments appeared on the CafePharma website.

Caris assays use IHC, FISH/CISH, PCR, and next-generation sequencing. In the past, Caris declined to disclose the prices of its services (The Cancer Letter, Aug. 8).

On its website, Caris says that its assays were used in making treatment decisions for as many as 60,000 people in 59 countries since 2006.

"[Caris Molecular Intelligence] can provide up to 51 potentially relevant FDA-approved drug associations," David Halbert, Caris's top executive, wrote in a recent letter to the Boston Business Journal, claiming that it's "the only profiling service offering a comprehensive analysis of all relevant drug associations currently supported by strong medical evidence.

"By comparison, [the Foundation Medicine Inc.] test can make no more than 19 drug associations," he wrote.

The reference to "potentially relevant FDA-approved drug associations" may be confusing even to insiders. The agency approves drugs, not associations between targets and biomarkers. In some cases, FDA approves drugs and biomarker assays known as companion diagnostics, where the testing and treatment based on this testing shows a favorable outcome.

In a recent interview with The Cancer Letter, Daniel Hayes, a breast cancer expert at the University of Michigan, said Caris may have "over-interpreted the test they provide that might suggest that a drug won't work" (The Cancer Letter, Aug. 8).

Hayes and other experts say that they fear that in some cases the findings on such tests may prompt doctors to rely less on evidence-based guidelines and instead base treatment decisions on findings of molecular tests and interpretations that are far from definitive.

"On their website they say they've done 60,000 cases," Hayes, the university's Stuart B. Padnos Professor of Breast Cancer Research and a member of a recent Institute of Medicine committee that issued a report on omics, said in his recent interview with The Cancer Letter. "That's a lot of patients, and I am not sure they were treated properly, based on results that I am not sure we can trust."

There is no question that big changes are brewing in the market for molecular tests.

• FDA is phasing in regulation of so-called "laboratory-developed tests," a category that includes the Caris product, starting with assays that may lead patients to select one treatment option over others (The Cancer Letter, Aug. 1).

• Tests that provide genomic information lie at the foundation of the new generation of NCI-sponsored trials (The Cancer Letter, June 20).

• Pharma companies, as they develop drugs intended to target specific markers, have been pressing FDA to regulate laboratory-developed tests. As it stands, the many assays currently utilized in clinical practice don't have to demonstrate safety and efficacy and are largely billed in such a way that Medicare and private insurers cannot identify what is being tested and why.

• Payment policy for tests is also in flux. Medicare and private insurers have no way to distinguish the majority of genomic tests from each other and no way to decide whether these tests are medically necessary, insiders say.

A few tests—for example, Oncotype DX—have specific codes, but the majority are lumped together in two classifications: "Tier 2 Molecular Pathology Procedures" (CPT codes 81400-81479) and "Multi-

Analyte Assays with Algorithmic Analysis" (CPT codes 81500-81599).

The codes tell payers what the laboratory did, without saying what the test is for. Medicare is trying to unblind this process through a program called MolDX.

Caris is also facing a lawsuit filed by two former employees, who allege that their former employer violated the federal anti-kickback statute by routinely waiving some of its fees to induce referrals to federal healthcare programs.

The suit, filed in the U.S. District Court for the Northern District of Texas, Dallas Division, also alleges that over one very hot summer, Caris ran tests on hematology specimens that were compromised by heat. If this is correct, the results of these tests would have been uninformative and treatment choices based on such findings questionable.

Caris's court filings deny all allegations, and in a statement to The Cancer Letter, company officials described the action as a nuisance lawsuit.

Scientific justification for the use of the Caris Molecular Intelligence tests is based on a single-arm study conducted in 66 patients with solid tumors who had failed two prior therapies. The study used a novel metric: the patients' progression-free survival on therapies chosen by the test was compared to PFS reported on their previous progression.

The findings were presented by the researcher Daniel Von Hoff at the plenary session of the 2009 annual meeting of the American Association for Cancer Research and published in the Journal of Clinical Oncology the following year. "In 27 percent of patients, the molecular profiling approach resulted in a longer PFS on an MP-suggested regimen than on the regimen on which the patient had just experienced progression," the paper concluded.

Von Hoff is identified as executive director of Caris Life Sciences Clinical Research on the company's website. He is also the physician in chief and director of translational research at TGen in Phoenix, Ariz.; the chief scientific officer for US Oncology and for Scottsdale Healthcare's Clinical Research Institute; and a clinical professor of medicine at the University of Arizona.

Critiquing the Von Hoff et al. paper in a separate JCO article, James Doroshow, director of the NCI Division of Cancer Treatment and Diagnosis, wrote that the findings are inconclusive in part because it's unlikely that the patients' PFS on previous recurrence could have be measured in a uniform fashion.

A randomized study would be required to confirm the positive results, Doroshow wrote.

Doroshow's division at NCI has reorganized the institute's clinical trials infrastructure to focus on studies of interventions based on biomarker data (The Cancer Letter, June 20; June 6; May 16; May 2; April 11; April 4).

Discounts are Owed on Some Orphan Drug Uses, HRSA Says

By Paul Goldberg

The Health Resources and Services Administration last week warned pharmaceutical companies that they must continue to offer 340B Drug Pricing Program discounts on some uses of orphan drugs.

Under the Affordable Care Act, the indications covered by the orphan drug designation are exempt from 340B discounts, which can be as deep as 50 percent.

Thus, for diseases that affect fewer than 200,000 people in the U.S. and that have been recognized as orphan indications by FDA, there would be no discounts.

The logic for the exclusion is straightforward: pharma companies need to be incentivized to develop drugs for smaller populations. At FDA, these drugs are exempted from the application user fee, and when approved, they receive longer exclusivity.

HRSA's controversial stance affects the situations when drugs that have the orphan designation are used outside their orphan indications.

For example, the drug Rituxan (rituximab) would be exempt from 340B discounts when used within its orphan designations—anti-neutrophil cytoplasmic antibody-associated vasculitis, non-Hodgkin's B-cell lymphoma, and immune thrombocytopenic purpura.

However, HRSA contends that Rituxan would be subjected to discounts when prescribed for the non-orphan conditions of rheumatoid arthritis, multiple sclerosis, and autoimmune anemia.

The agency's power to issue a legislative rule on the use of orphan drugs outside their orphan designations was challenged by the pharmaceutical industry lobby and invalidates by a judge, who held that HRSA "acted beyond the bounds of its statutory authority" because Congress did "not confer any rulemaking authority upon HHS" to regulate the scope of the orphan drug exclusion. (The Cancer Letter, June 13).

So, the agency regrouped and issued a similarly phrased interpretative rule.

These two flavors of rules are very different:

• A legislative rule has the force of law; it imposes

new duties.

• An interpretive rule merely clarifies existing rules. It does not impose new duties; it explains the duties that are under existence.

But in practical terms, this is a distinction without a difference.

Sources say that more than 50 manufacturers have been contacted after HRSA's Office of Pharmacy Affairs was informed by covered entities that the 340B price was not available for products with an orphan designation.

The letter instructs them to continue to offer 340B discounts in situations where drugs that have orphan indication are used for other purposes.

Moreover, companies were warned that they would need to issue refunds to covered entities that had been charged more than the statutory ceiling price for covered outpatient drugs.

Companies were asked for a response within 30 days to notify HRSA of plans to repay affected covered entities and to offer the discounted price in the future.

"We fully support the HRSA's enforcement action against the many pharmaceutical manufacturers who are not following the government's rule on orphan drug pricing," said Ted Slafsky, president and CEO of Safety Net Hospitals for Pharmaceutical Access, a Washington, D.C., group. "The government has clearly and correctly interpreted the law as requiring them to provide discounts to rural and cancer hospitals when an orphan drug is used to treat a common condition."

Similarly, the National Rural Health Association CEO Alan Morgan that "drug companies ignoring the law should be obligated to refund rural safety-net providers."

Having derailed the HRSA's effort to make a legislative rule, pharma companies have mounted a legal challenge to the interpretative rule.

"After the Federal District Court of the District of Columbia vacated the HRSA July 23, 2013 rulemaking regarding the 340B orphan drug exemption, in July 2014, the agency issued the exact same rule, but labeled it 'interpretive,'" said Mit Spears, executive vice president and general counsel of Pharmaceutical Research and Manufacturers of America.

"While we value the hard work and efforts of all agencies, it is important federal agencies recognize and work within the bounds set by Congress. PhRMA is therefore filing suit against the U.S. Department of Health and Human Services to challenge its second attempt to issue a rule conflicting with the plain language of the statute."

PhRMA's complaint, filed on Oct. 9 and posted on The Cancer Letter website, says that "HHS's second attempted rulemaking contains the same substance as the first rule, adopts the same flawed interpretation of [orphan drug exclusion], and should similarly be invalidated as inconsistent with the statute."

In a separate development, SNHPA urged Genentech to rescind immediately its decision to sell the cancer drugs Avastin, Herceptin, and Rituxan through specialty distributors (The Cancer Letter, Oct. 3, Oct. 10).

"The change will not, to our knowledge, make patients any safer and, in fact, could cause delays in their care. It also will significantly increase safety-net hospitals' costs," SNHPA General Counsel Maureen Testoni wrote in a letter to Ian Clark, Genentech CEO of North American Operations.

Cancer Support Community Reports on Patient Experiences

Cancer Support Community released the findings report from the first year-and-a-half of the Cancer Experience Registry.

The report, titled "Elevating the Patient Voice," examined responses from 3,500 registry members (out of more than 7,000 total members), and found that more than half of patients with cancer feel unprepared to discuss treatment options with their medical team.

Findings included:

• Challenges around the cost of cancer care: about one-third of patients said they had to reduce their grocery expenses, and one-third said they depleted their savings due to cancer-related costs.

• Concerns about long-term side effects: 42 percent of patients are seriously concerned about nutrition, and about a third are seriously concerned about fatigue and exercise, or 32 and 34 percent, respectively.

• An ongoing need for social and emotional support: 37 percent of patients have serious worries about the future, and 35 percent have serious financial worries.

This research also found that patients are living with additional physical, financial and emotional concerns.

"We hear over and over that patients feel uncomfortable bringing up their issues with their doctors," said Joanne Buzaglo, vice president of research and training at CSC. "They don't want to bother them, or be seen as a 'bad patient.' We put a lot of effort into asking questions that are sensitive to

our population—and our respondents often tell us, 'no one ever asked me that before.'"

This first-of-its-kind registry aims to measure the total cancer experience, including the physical, social, emotional, spiritual and financial effects of cancer on the person diagnosed as well as his or her family.

After completing the registry profile and questionnaire, members can compare their responses with others in the community and can be connected to online educational content relevant to their concerns and interests. The registry is available to anyone who has been diagnosed with cancer at any time.

Institute of Medicine Elects 2014 Class of 80 New Members

The Institute of Medicine named 70 new members and 10 foreign associates during its 44th annual meeting.

New members are elected by current active members through a selective process that recognizes individuals who have made major contributions to the advancement of the medical sciences, health care, and public health.

A diversity of talent among IOM's membership is assured by the institute's charter, which says that at least one-quarter of the membership is selected from outside the health professions, including fields such as the law, engineering, social sciences and the humanities.

The newly elected members raise IOM's total active membership to 1,798 and the number of foreign associates to 128. With an additional 86 members holding emeritus status, IOM's total membership is 2,012.

The full list is available on the IOM website. Members in the cancer research field include:

• **José Baselga**, physician-in-chief and chief medical officer of Memorial Sloan Kettering Cancer Center, and president-elect of the American Association of Cancer Research

• **Carol Bradford**, the Charles J. Krause collegiate professor and chair of the Department of Otolaryngology-Head and Neck Surgery at the University of Michigan

• **Lewis Cantley**, director of the Sandra and Edward Meyer Cancer Center at Weill Cornell Medical College/New York-Presbyterian Hospital

• **E. Antonio Chiocca**, neurosurgeon-in-chief of the Department of Neurosurgery and co-director of the Institute for the Neurosciences at Brigham and Women's/Faulkner Hospital; surgical director of the Center for Neuro-oncology at Dana-Farber Cancer Institute; and the Harvey W. Cushing professor of neurosurgery at Harvard Medical School

• **Joseph DeSimone**, chancellor's eminent professor of chemistry and William R. Kenan Jr. distinguished professor of chemistry in the Departments of Chemistry and Pharmacology at University of North Carolina and North Carolina State University, Chapel Hill

• **James Economou**, vice chancellor for research and Beaumont professor of surgery at the University of California, Los Angeles

• **Todd Golub**, a Howard Hughes Medical Institute investigator; chief scientific officer of the Broad Institute of Harvard and the Massachusetts Institute of Technology; and the Charles A. Dana investigator at Dana-Farber Cancer Institute

• **James Hill**, Anschutz Professor in the departments of pediatrics and medicine, and director of the Anschutz Health and Wellness Center at the University of Colorado

• **Paul Khavari**, professor and chairman of the Department of Dermatology at Stanford University

• **Brian Kobilka**, professor of molecular and cellular physiology at the Stanford University School of Medicine

• **Guillermina Lozano**, professor and chair of the Department of Genetics at MD Anderson Cancer Center

• **David Piwnica-Worms**, professor and chair of the Department of Cancer Systems Imaging and deputy head of the Division of Diagnostic Imaging at MD Anderson Cancer Center

• **Margaret Shipp**, chief of the Division of Hematology Neoplasia at Dana-Farber Cancer Institute

• **Dan Theodorescu**, the Paul A. Bunn cancer research chair, professor of surgery and pharmacology, and director of the University of Colorado Comprehensive Cancer Center

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Drugs and Targets

EU Approves Imbruvica In MCL, CLL Patients

The European Commission granted marketing approval for Imbruvica (ibrutinib) throughout the European Union, for relapsed or refractory mantle cell lymphoma, or chronic lymphocytic leukemia patients who have received at least one prior therapy, or in first line CLL patients in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemotherapy.

Imbruvica, a first-in-class, oral, once-daily, non-chemotherapy treatment, is being jointly developed and commercialized in the U.S. by Pharmacyclics Inc. and Janssen Biotech Inc., which will market Imbruvica in Europe.

The approval was based on data from a phase II study in MCL, the phase III RESONATE study in CLL and small lymphocytic lymphoma and the phase Ib/II study in CLL/SLL. A worldwide regulatory filing program for ibrutinib currently is underway, according to the drug's sponsor.

Imbruvica is approved in the U.S. for three indications: for the treatment of patients with MCL and CLL who have received at least one prior therapy, and for the treatment of CLL patients with deletion of the short arm of chromosome 17, including treatment-naive and previously treated del 17p CLL patients.

Pharmacyclics also entered into a master clinical drug supply agreement with Roche to evaluate the safety, tolerability and preliminary efficacy of Imbruvica in combination with Gazyva (obinutuzumab), a CD20-directed antibody that attacks targeted cells both directly and together with the body's immune system, in patients with non-Hodgkin lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma.

Initially, a phase III study will be conducted by Pharmacyclics in CLL/SLL. Plans to evaluate the combination for NHL currently are in development. Gazyva is a registered trademark of Genentech Inc.

The study of the investigational combination of Imbruvica and Gazyva through several investigator-sponsored trials also is being considered. Additional details of the agreement were not disclosed.

Janssen Research & Development also submitted a supplemental New Drug Application for Imbruvica to FDA for the treatment of patients with Waldenstrom's macroglobulinemia. If approved, this will become the fourth indication for Imbruvica, which received an FDA Breakthrough Therapy Designation for WM in February 2013.

The Centers for Medicare and Medicaid Services published two draft local coverage determinations for prostate cancer tests. The drafts were issued through Medicare contractor Palmetto GBA's MolDx Program.

One a draft LCD, for use of the Decipher Prostate Cancer Classifier test in men who have undergone radical prostatectomy, is the only genomic test for prostate cancer to receive a draft LCD for use in the post-surgery setting. The Decipher test is developed by GenomeDx Biosciences.

Under Medicare policies, a 45-day comment period will commence on Nov. 10. After comments are received and revisions, if any, are made to the draft LCD, the final LCD will be posted within the following 45 calendar days.

MolDX, developed in 2011, facilitates the clinical review, coverage and payment policies for molecular diagnostic tests. The MolDX Program is a contractor to Noridian, a national contractor that administers Medicare benefits for Jurisdiction E, where GenomeDx is located.

According to GenomeDx, Decipher predicts the aggressiveness of a patient's disease based on genomic information that is distinct from that provided by PSA and other clinical risk factors. Clinical studies have demonstrated that Decipher can accurately predict aggressive disease and help physicians make more informed treatment decisions for men with prostate cancer. Decipher was developed in partnership with the Mayo Clinic.

Palmetto also issued a draft local coverage determination for Prolaris, a prostate cancer test developed by Myriad Genetics Inc.

The determination is posted to the Medicare Coverage Database on the Centers for Medicare & Medicaid Services website, and establishes the coverage policy for Medicare beneficiaries. The current language in the Prolaris draft LCD provides reimbursement coverage for the approximately 50 percent of prostate cancer patients defined as low and very low risk.

Priority Health announced it plans to cover the FoundationOne and FoundationOne Heme genomic profiles for patients with cancer developed by Foundation Medicine Inc.

FoundationOne interrogates the entire coding region in 315 genes and select introns in 28 genes commonly altered in solid tumors, according to Foundation Medicine. FoundationOne Heme analyzes

DNA in 405 genes and RNA in 265 genes that are most commonly altered in hematologic malignancies, sarcomas and select pediatric cancers.

Celgene Corporation and Sutro Biopharma will collaborate on developing multispecific antibodies and antibody drug conjugates.

This agreement follows a previous December 2012 collaboration, and focuses on the immuno-oncology space, including established targets such as PD-1 and PD-L1, and novel targets using Sutro's cell-free biologics development platforms, Xpress CF and Xpress CF+.

Celgene will have the exclusive option to acquire Sutro, including rights to all Sutro-owned programs at that time, on pre-specified terms: Sutro will receive upfront payments totaling $95 million, which includes an equity investment. Sutro may also receive up to an additional $90 million during the initial research term, including payments for manufacturing-related and productivity milestones.

Sutro will be responsible for discovery and early pre-clinical development of all collaboration multispecific antibodies and ADCs, as well as the manufacturing of pre-clinical product candidates. Celgene may assume responsibility for global development and commercialization and will have worldwide rights to all collaboration products, with the exception of certain collaboration products for which Sutro retains U.S. development and commercialization rights, in the event Celgene does not exercise its option to acquire Sutro.

In Brief

Neel Named Director of NYU's Perlmutter Cancer Center

(Continued from page 1)

Neel will oversee translational programs in immunotherapy, cancer genetics/targeted therapies and epigenetics, imaging, community outreach and supportive oncology. He will also be responsible for all programs throughout NYU Langone's network of cancer-related clinical care.

Neel most recently served as director of the Ontario Cancer Institute at Princess Margaret Cancer Center. He also served as professor of medical biophysics at the University of Toronto, and holds a Tier 1 Canada Research Chair in signal transduction and disease. His research has focused on cell signaling in cancer and developmental disease, functional genomics of breast cancer and ovarian cancer tumor initiating cells.

He was appointed assistant professor of medicine at Harvard Medical School in 1988, and began his own independent research laboratory in the Molecular Medicine Unit at Beth Israel Hospital, now known as Beth Israel Deaconess Medical Center. He also served as the director of the Cancer Biology Program from 1994-2007 and as deputy director for basic research in the Hematology Division at BIDMC from 2003-2007. In 2006, he was appointed to the William B. Castle Chair of Medicine at Harvard Medical School.

He is also an elected member of the Board of Directors for the American Association for Cancer Research, and previously served as the program chair for the annual meeting of the AACR.

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BRAD POLLOCK was named chair of the Department of Public Health Sciences at the **UC Davis School of Medicine**.

Pollock came to UC Davis from the University of Texas Health Science Center at San Antonio, where he was the founding chair of the Department of Epidemiology and Biostatistics in the School of Medicine.

He is the principal investigator of a $19 million NCI grant to engage community physicians in expanding participation in cancer clinical trials as well as research on cancer control and cancer care delivery. The grant includes a focus on underserved populations, including Latinos, adolescents and young adults. While his research focuses on pediatric oncology, Pollock also has extensive experience in multi-institutional studies on adult cancer, HIV, diabetes and obesity.

He also co-chairs the Clinical Trials Task Force for the Patient-Centered Outcomes Research Institute's PCORnet national network, and he previously chaired the Biostatistics, Epidemiology, Research Design Key Function Committee of the national Clinical Translational Science Award Program.

RICHARD ZELLARS was named professor and chair of radiation oncology at the **Indiana University School of Medicine**, pending approval by the IU trustees. He will begin his new duties in January.

Zellars is a breast cancer research and associate professor of radiation oncology at The Johns Hopkins University, and is assistant director of clinical trial accrual at the Sidney Kimmel Comprehensive Cancer Center. He previously held faculty positions at the University of Texas Health Science Center at San Antonio and Georgetown University.

Zellars' research focuses on the safety and efficacy of radiation for the treatment of breast cancer. He also does research into health care disparities in African-American women who typically have more severe radiation toxicities. He also founded the Cancer in the Under-Privileged, Indigent or Disadvantaged Summer Fellowship, which exposes first-year medical students who have a demonstrated interest in serving disadvantaged populations to the specialty of oncology.

DAVID MAURO was named as executive vice president and chief medical officer of **Advaxis Inc.**

Mauro will oversee the company's clinical immuno-oncology programs. He most recently served as executive director and section head of Oncology Clinical Development at Merck & Co., where he was involved in oversight and implementation of multiple programs within the oncology portfolio, including its recently approved PD-1 inhibitor, Keytruda (pembrolizumab).

Prior to joining Merck, Mauro was director at Bristol-Myers Squibb, where his responsibilities included Erbitux (cetuximab) and Oncology Early Development.

During his career, Mauro has participated in multiple FDA submissions and approvals, including three successful new drug applications for Erbitux, Sprycel (dasatinib) and Sylatron (peginterferon alfa-2b), and two PMA filings for EGFR PharmDx and KRAS Companion Diagnostics.

JAMES TULSKY received the Pathfinder in Palliative Care Award from the **American Cancer Society**.

Tulsky is chief of Duke Palliative Care and professor of medicine and nursing at Duke University.

Presented at the Kathleen Foley Palliative Care Research Retreat, the award recognizes innovation and ingenuity in contributing to the advancement of the palliative care field. Tulsky received the award for his work on oncologist-patient communication; being an advocate for palliative and supportive care research; and his mentorship of faculty in palliative care research.

In the 1990s, Tulsky was the first to examine how residents and faculty talk to patients about resuscitative choices. His landmark study identified major deficiencies in communication and he became a leader in developing interventions to improve clinician communication skills. This led to the development of an NCI-funded online intervention which improved the oncologist's ability to identify and respond to empathic opportunities and improved trust between clinician and patient.

He was also a member of the Institute of Medicine committee that recently authored the study on "Dying in America," which recommended major changes to care for seriously ill patients.

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MARY KOZIK was named senior director of development at **Winship Cancer Institute of Emory University**.

Kozik is the former chief of institutional advancement for The Preservation Society of Newport County in Newport, R.I. She was responsible for raising over $21 million since 2012. Previously, she served as the vice president for institutional advancement and chief development officer at Fox Chase Cancer Center. She has also held positions at the Lifespan Health System and The Leukemia and Lymphoma Society.

Kozik will succeed Vicki Riedel, who will oversee principal gifts for the Woodruff Health Sciences Center of Emory University. She will lead a team that was responsible for raising more than $11 million in private donations in the 2014 fiscal year.

NORTHWESTERN MUTUAL, through its foundation, will fund four young investigator grants for childhood cancer research. The awards support **Alex's Lemonade Stand Foundation's young investigator program**.

The addition of these four research projects results in eight total funded research projects this year, an $800,000 commitment. Each researcher receives a total grant of $100,000 over two-years. Four of the recipients received their initial funding last year.

The eight grant recipients are: **Charalambos Kaittanis**, of Memorial Sloan Kettering Cancer Center, for studying the effects of radiation therapy; **Laura Schuettpelz**, of Washington University at St. Louis, for harvesting bone marrow; **Shizhen Zhu**, of the Mayo Clinic, for neuroblastoma development; **Cigall Kadoch**, of Dana Farber Institute, for sarcoma tumor research; **Jeffrey Huo**, of The Johns Hopkins University School of Medicine, for studying the epigenetic origins of the retinoblastoma tumor-initiating cell; **Carl Koschmann**, of University of Michigan, for therapy for pediatric glioblastoma; **Katherine Tarlock**, of Fred Hutchinson Cancer Research Center, for therapeutic strategies for leukemia; and **Mireya Velasquez**, of Baylor College of Medicine, for research for leukemia and lymphoma.

THE ASSOCIATION OF COMMUNITY CANCER CENTERS received a charitable contribution from **Bristol-Myers Squibb** to develop a comprehensive program in immuno-oncology for community-based providers.

The contribution will enable ACCC to establish **the Institute for Clinical Immuno-Oncology** to educate providers about its implementation and delivery in the community setting.

The initial phase of the program will involve the establishment of the project infrastructure, including staffing, project planning, and marketing, and identification of potential partner organizations. An advisory committee comprised of ACCC members and other IO leaders will be created to oversee the planning and development of ICLIO.

Early phases of the program will include the identification and engagement of clinician scholars and thought leaders, an educational needs assessment of the ACCC membership, a one-day national conference, a monthly series of online courses and newsletters for clinicians and fellows, and multiple scientific and policy publications highlighting the project findings and outcomes.

A STAND UP TO CANCER inaugural Dream Team launched in 2009 to focus on epigenetic therapy will continue with a commitment of $7.5 million from **the Van Andel Research Institute**.

Peter Jones, the institute's research director and chief scientific officer, and Stephen Baylin, deputy director of the Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins University, will serve as leaders of the Dream Team.

The VARI-SU2C Epigenetics Dream Team will include top scientists from four other leading institutions: Charles Rudin, of Memorial Sloan Kettering Cancer Center; Jean-Pierre Issa, and Patricia Kropf, of Temple University and Fox Chase Cancer Center; Kirsten Grønbæk, of the University of Copenhagen; and Anthony El-Khoueiry, of the University of Southern California Norris Comprehensive Cancer Center.

"We are extremely excited to build on the foundations already laid by the Epigenetics Dream Team by moving promising therapies into clinical trials," Jones said.

The original Dream Team, with Baylin as leader and Jones as co-leader, has received nearly $11 million in funding from SU2C, a program of the Entertainment Industry Foundation.

The team's work has involved clinical trials investigating the response of patients with lung cancer to epigenetic therapy alone, or as a way to sensitize patients to subsequent chemotherapy. VARI's support over three years will allow the team to move forward with more extensive clinical trials in other cancer types.