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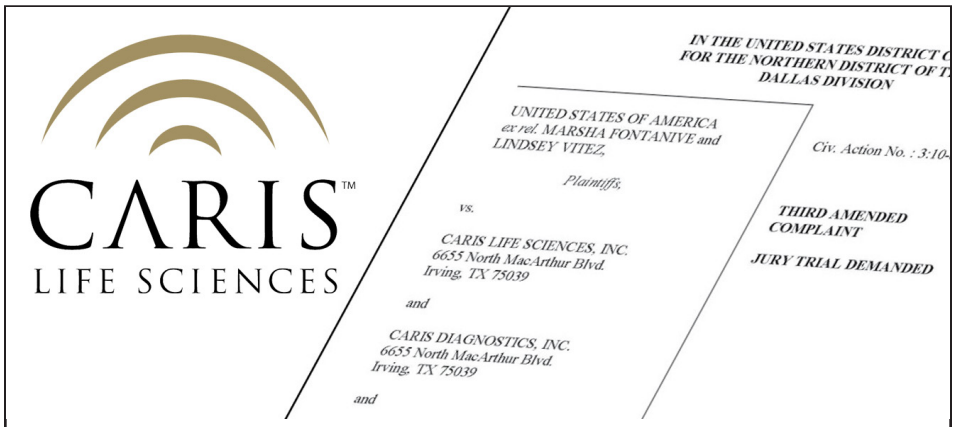

"Wild West" of Molecular Testing?
Caris Engaged in Aggressive Marketing, Improper Medicare Billing, Lawsuit Alleges

By Paul Goldberg

It's possible that molecular testing is doing a lot of good, pinpointing cancer therapies that are most likely (or least likely) to work.

It's also possible that Medicare is paying for molecular tests that are marketed aggressively despite being based on flimsy evidence.

The latter picture is painted in a suit filed by two former employees of Caris Life Sciences Inc., a company that markets the "Caris Molecular Intelligence" test, a panel of assays previously called "Target Now."

The whistleblowers 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.

(Continued to page 2)

Conversation with The Cancer Letter

Daniel Hayes Leads Tour of Caris Website

Tumor profiling information Caris Life Sciences provides in its reports isn't backed by sufficient evidence to justify some clinical decisions, said Daniel Hayes, a breast cancer expert at the University of Michigan.

(Continued to page 9)

In Brief

MD Anderson's Peter Pisters Named CEO Of University Health Network in Toronto

PETER PISTERS was appointed president and CEO of **University Health Network**, effective Jan. 1, 2015.

Pisters is vice president of MD Anderson Cancer Center's Regional Care System and a professor of surgery.

(Continued to page 17)

The Cancer Letter is taking a summer break.
The next issue will be published Sept. 5.

Caris: Whistleblower Action A "Nuisance Lawsuit"

(Continued from page 1)

The complaint alleges that Caris instructed sales representatives to market the tests to surgeons, who often make the initial clinical diagnosis of cancer. While surgeons are able to extract the tumor samples and order the test, they don't necessarily know whether an oncologist, who would be seeing the patient at a later point, would consider such tests necessary.

"Caris demanded that its sales representatives call on surgeons to obtain tissue specimens, regardless of the treatment history of the patient and regardless of whether the treating oncologist requested the test or planned to use it in determining treatment," the complaint states.

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."

This legal wrangle is unfolding against a backdrop of change in oncology:

• FDA is phasing in regulation of so-called "laboratory-developed tests," 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," a category that includes the Caris product. 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.

The stakes are as high as it gets. Molecular tests can be used to determine the care patients receive, experts say.

In general, a bad tumor marker can be as harmful as a bad drug, said Daniel Hayes, a breast cancer expert at the University of Michigan. "Unless we have a really high level of evidence, through two important and critical terms—(1) analytic validity, and (2) clinical utility—in my opinion, a marker shouldn't be used to direct care," Hayes to The Cancer Letter. An interview with Hayes appears on page 1 of this publication.

Caris officials say the whistleblower suit is symptomatic of another costly problem—litigiousness of the American health care system.

"This is a nuisance lawsuit, which is part of the problem with rising healthcare costs that ultimately hurt patients and their access to care," Caris officials said in a statement to The Cancer Letter. "This lawsuit is a whistleblower complaint filed by two disgruntled former Caris employees who left the company nearly five years ago. The trial is currently scheduled for January 2016.

"Caris Life Sciences strongly insists the allegations are meritless and the suit is frivolous, and Caris will continue to vigorously defend its position. Caris Life Sciences has been and continues to be a Medicare supplier in good standing.

"The allegations are limited to 2008 to 2011 and were investigated by the U.S. government for approximately two years. In December of 2012, the U.S. government filed a notice of non-intervention thus declining to participate in the litigation, further underscoring the baseless allegations."

JCO Made an Exception to COI Rules To Publish Von Hoff *et al.* Paper

In cases when the government declines to take over the action, whistleblowers can continue to pursue the case on its behalf.

The complaint, brought under the federal False Claims Act, has survived a motion to dismiss. If they prevail, the plaintiffs—called the relators—would be

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eligible for a portion of recovered funds.

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.

In the disclosure section of the JCO paper, Von Hoff acknowledged having played a consulting or advisory role in Caris Life Sciences and holding the company's stock.

At the same time, he checked off having been involved in providing study materials or patients, collection and assembly of data, data analysis and interpretation, and final approval of manuscript. He is identified as executive director, Caris Life Sciences Clinical Research on the company's website. Von Hoff 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.

ASCO's conflict of interest policy places limitations on principal investigators when they submit papers for publications. PIs are barred from holding "stock or equity interest in the trial sponsor" or hold a "position as officer, board of directors member, or employee of the trial sponsor."

In this case, ASCO granted an exception "to allow for the publication of this article" in JCO, said Kelly Baldwin, ASCO's program manager for science communications. Under a revision of the society's guidelines, it is allowable to grant exceptions for PIs with "widely acknowledged expertise in a particular therapeutic area and whose exclusion from other activities on behalf of the trial sponsor would represent a potential impediment to research and education efforts.

"An exception may also be appropriate if a PI is the inventor of a unique technology being evaluated in the trial."

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.

Indeed, 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).

The Whistleblowers' Allegations in a Nutshell

The whistleblower suit makes the following allegations:

• "Caris routinely waived its fee for the [technical component] of Target Now testing of Medicare beneficiaries in order to induce providers to refer patients for Target Now testing, for which Caris billed Medicare for [professional component], in violation of the [federal anti-kickback statute];

• "For a period of time, Caris billed Medicare for the [technical component] of Target Now testing that was covered under Medicare PPS payments to hospitals;

• "Caris promoted Target Now for first line pathology testing and/or in patients who had not exhausted treatment available under the standard of care, a use that is not reasonable and necessary;

• "Caris knowingly billed Medicare for Heme services that were not reasonable and necessary because the testing samples were not viable due to excessive heat exposure;

• "Caris offered kickbacks to providers in order to induce the referral of

Medicare patients for Caris's laboratory services;

• "Caris improperly unbundled consultations, global charges, and code stacks into separate, individually billable services;

• "Caris double-billed for services by improperly billing professional services as global charges and billing for services that had already been performed;

• "Caris knowingly overbilled simple procedures at a higher level of service;

• "Caris knowingly charged for both undocumented and unnecessary procedures in order to improperly obtain increased Medicare reimbursement."

Both the whistleblower complaint and the company's response are posted on The Cancer Letter website.

"As ever, Caris Life Sciences remains committed

to its core mission—provide the physicians and patients we serve with innovative, high-quality and clinically useful information to help improve patient care," the company said in a statement to The Cancer Letter.

Responding to a question about the price of the Caris tests, company officials said that prices vary. "We bill on a marker-by-marker basis, based upon the profiling panel requested by the physician and the analytical technology used," the company said in a statement. "This varies by physician and by type of cancer."

The prices aren't contained in the court filings. However, usually, panels of molecular tests are billed between $2,000 and $5,000.

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.

Administered by one of the Medicare contractors, Palmetto, MolDX would identify the tests, establish clinical expectations and set reimbursement.

The Caris test uses a combination of laboratory assays, which include:

- Immunohistochemical analysis;
- DNA microarray analysis;
- DNA sequencing/DNA mutational analysis (KRAS); and
- Fluorescent *in situ* hybridization.

The combination of tests used depends on the type of tissue collected (e.g., bone marrow or lymph nodes) and the method of specimen preservation (fresh frozen or FFPE block).

Caris: A Big Player in Profiling

According to information posted on its website, Caris has profiled the tumors of more than 60,000 cancer patients from 59 countries since 2006; ordered by 6,000 oncologists. The company says it has over 600 employees and operates four laboratories in three metropolitan areas: Dallas, Boston and Phoenix.

In all the therapeutic areas it serves—oncology, hematology, dermatology, gastroenterology and urology—Caris makes over 800,000 diagnoses annually, court documents state.

In February, former President George W. Bush was brought in as the keynote speaker at the company's annual sales meeting, where he was on-stage, speaking with Caris Life Sciences Chairman and CEO David Halbert, a long-time business associate.

With FDA having played a limited role in regulating the burgeoning industry of molecular testing, there is no equivalent of labeled indications for laboratory-developed tests.

Similarly, there is no requirement to report adverse events, no penalties for marketing off-label uses, no warning letters for engaging in commercial hype, and, most importantly, no requirement to show that the tests have the potential to improve the outcomes for the patients.

Players in the field describe it as the Wild West.

Consider a recent shootout on the pages of the Boston Business Journal:

Halbert, Caris's top executive, took exception to a comment from a competitor and pulled out a proverbial six-shooter.

The Caris test is superior to that of the competitor's, he claimed in a letter to the editor and a statement issued as a company press release.

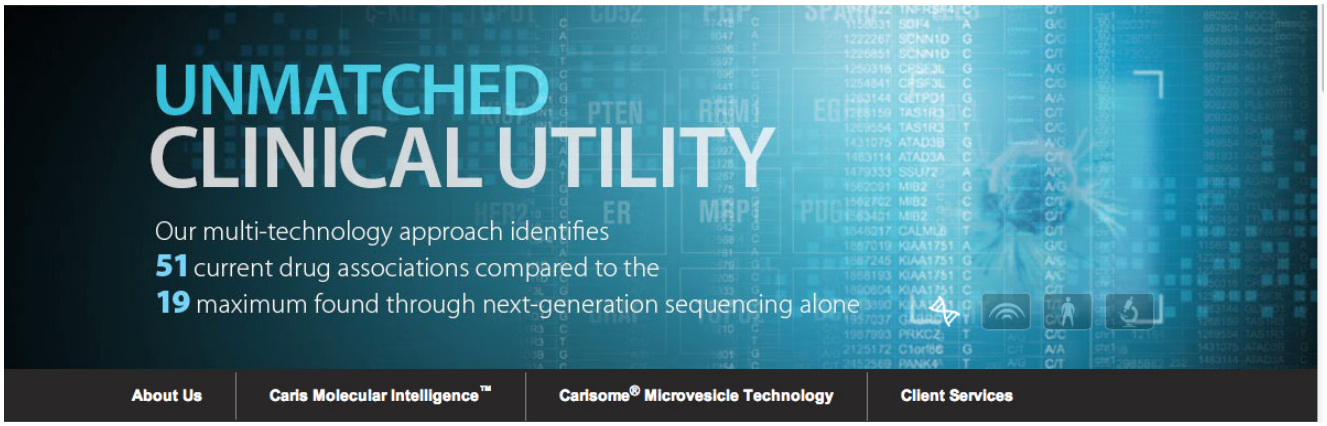
Caris is "the only profiling service offering a comprehensive analysis of all relevant drug associations currently supported by strong medical evidence," he wrote.

"[Caris Molecular Intelligence] can provide up to 51 potentially relevant FDA-approved drug associations. We are proud to offer the most clinically useful cancer-profiling service currently available to help oncologists and their patients find FDA-approved drugs that may benefit them."

This trumps the services offered by a competitor, Foundation Medicine, Halbert argued.

"By comparison, FMI's test can make no more than 19 drug associations," he wrote.

"Cancer patients who have exhausted standard of care, or who are battling particularly rare or aggressive cancers where no standard of care exists, deserve to know they have clinically useful options available to them. A DNA-only analysis, like that used by FMI, is simply not going to identify as many drug associations



Caris advertisement claims to provide more actionable information than its competitor.

to help the patient in the clinic today."

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.

An advertisement on the Caris website, too, features the metric of "drug associations," thus comparing its product with a competitor's.

In a response to questions from The Cancer Letter, Caris officials said Halbert was referring to the "biomarker panel for which evidence-based associations are defined." The company said the decisions are made by its team, which utilizes "the methodology set forth by the U.S. Preventive Services Task Force."

USPSTF is focused exclusively on preventive and screening services. The process it employs includes comprehensive review of literature—a massive undertaking performed by a contractor—and ultimately published. To evaluate a test, USPSTF convenes panels of generalists and experts in analysis of medical data. These panel members are rigorously scrubbed for conflicts of interest, and their names are publicly known.

Caris officials said their tests use three categories to clarify actionable variants:

• Variants linked to an FDA-approved drug with a specific tumor type;

• Variants linked to an FDA-approved drug approved for a different tumor type'

• Variants linked to investigational drugs in clinical trials.

Questions from The Cancer Letter and Caris's responses appear on p. 12 of this publication.

Caris Website Cites Von Hoff's JCO Paper

FDA declined to comment on the Caris statements about "drug associations." However, the agency is making plans to start reviewing laboratory-based tests and the claims they make.

"Last week, the FDA took two important steps to ensure that health care providers and patients can rely on the thousands of laboratory tests that are used every day to diagnose disease or other conditions or guide treatment," said Stephanie Yao, the agency spokesperson. "Faulty test results could lead patients to seek unnecessary treatment, or to delay and sometimes forgo treatment altogether. The success of personalized medicine—getting the right treatment to the right patient—depends on accurate and reliable diagnostic tests. Inaccurate laboratory developed tests that steer patients to the wrong treatments could jeopardize the advancement of personalized medicine altogether."

While USPSTF hasn't been a part of this controversy, one of the most authoritative documents on genomics known as the ACCE criteria, published by a taskforce of the Centers for Disease Control and Prevention and accepted as a fundamental document by CMS/MolDX uses a completely different set of metrics to determine "clinical utility." Using the ACCE criteria, very few of the associations between drugs and tumors would be considered useful for clinical application and would generally be considered experimental, insiders say.

The list of Caris's clients attached to the whistleblower suit suggests that the tests are more likely to be ordered by community doctors than academics. Academics seem to gravitate to other tests, including that of Foundation Medicine, insiders say.

Recently, Foundation for the NIH, a sponsor of the Lung-MAP trial, selected Foundation Medicine to do molecular profiling (The Cancer Letter, June

20). The trial's sponsor considered three proposals: from Foundation Medicine, Quintiles, and Personal Genome Dx.

Caris officials said they aren't involved in the NCI and FNIH trials.

"It is unclear whether the use of next-generation sequencing alone in the NCI and FNIH studies without analysis of accompanying alterations in protein expression of the drug targets can provide a suitably comprehensive profile to meaningfully guide therapy selection," company officials said in a statement.

The Caris website cites Von Hoff's 2010 JCO paper as justification for using the molecular profiling. Doroshow's critique, which points to flaws in that paper, is not noted. Also cited is a paper stemming from the BATTLE trial of personalized therapy for lung cancer (Kim, et al. Cancer Discov. 2011 Jun;1(1):44-53. Epub 2011 Jun 1).

Study author Edward Kim said the BATTLE study is a milestone in personalized medicine, but is not a justification for routine reliance on platforms of biomarker tests.

"The BATTLE study was the first step towards the development of personalized medicine for patients with lung cancer," Kim said to The Cancer Letter. "It was unique in that patients were required to have a new fresh tissue biopsy for real-time biomarker analysis. However, our biomarkers were speculated based on the best available data at the time (2005).

"We have had numerous subsequent studies that have developed marker platforms through our BATTLE discovery program, but these still need validation.

"The importance of the BATTLE study was that we were able to change the culture in approaching patients for repeat biopsies for real-time analysis of biomarkers," said Kim, chair of solid tumor oncology and investigational therapeutics and the Donald S. Kim Distinguished Chair for Cancer Research at Levine Cancer Institute of the Carolinas HealthCare System. "This has become a more acceptable clinical practice since reporting the study.

"At this time, a physician should use caution outside of a clinical trial when utilizing broad biomarker platforms in treatment decisions."

The Relators and the Stories They Tell

The suit focuses on the company's marketing and billing practices.

The relators in the suit are:

• Marsha Fontanive, former director of sales for Caris's Oncology division. Her territory included Florida, Georgia, Alabama, Michigan and Ohio. According to the complaint, she was responsible for developing marketing strategies, sales planning and sales training for Caris's oncology products in her territory. She joined the company in April 2008 and was terminated in April 2010.

• Lindsey Vitez, a former medical coding specialist. She worked out of Garland, Texas, and was tasked with coding for the Caris laboratories located in Boston, Phoenix and Irving. She joined the company in December 2008 and was forced to resign in June 2011.

The data supporting the use of Caris tests comes from Von Hoff's study in patients who had progression following at least two prior regimens for advanced disease and/or who had exhausted standard-of-care therapy.

According to court documents, North Star Advisors, a consulting firm, created a business strategy aimed at that population.

"NSA delivered their recommendation in a presentation dated Jan. 30, 2007," the complaint states. "NSA based its recommendations on its analysis of the [Von Hoff *et al*.] Bisgrove Study, Caris internal data, and physician surveys.

"NSA acknowledged the limited clinical data supporting the use of Target Now. NSA recommended that Caris position Target Now as 'an information service, and not a fully tested product.' NSA further recommended that Caris limit the marketing of Target Now for patients with common cancers who had progressive disease after two previous lines of therapy, and for rare tumors without clearly defined treatment options—those who met the eligibility criteria."

However, the company soon "began to require its sales representatives, including Marsha Fontanive, to market and sell Target Now for use for all cancers including lung, colon, pancreatic, ovarian, gastric, liver, breast and esophageal cancers at any and all stages of disease and treatment, including but not limited to as a first-line test," the complaint states. "The sales representatives were trained to obtain orders for comprehensive testing and/or for full panels, regardless of reasonableness or medical necessity.

"Caris instructed its sales representatives to target surgeons and surgical oncologists, who typically make the initial clinical diagnosis of cancer before first line

therapeutic decisions are made. Caris demanded that its sales representatives call on surgeons to obtain tissue specimens, regardless of the treatment history of the patient and regardless of whether the treating oncologist requested the test or planned to use it in determining treatment.

"Caris's sales and marketing strategy in this regard continued during and after the employment of Ms. Fontanive. Caris set forth part of this sales and marketing strategy in its 2010 'Target Now Selling Primer,' which it distributed to its Target Now sales force in the Spring of 2010.

"Caris's goal was to convince surgeons and surgical oncologists to routinely send specimens for expensive Target Now testing to determine therapies at any and all stages of disease and treatment, including but not limited to first-line therapies. Caris did not implement protocols or take steps to ensure that Target Now was only ordered, used and paid for after a patient had progression following at least two prior regimens for advanced disease and/or had exhausted conventional, standard-of-care therapy. But Target Now testing outside the eligibility criteria is not reasonable and necessary, because there is no evidence that it leads to better outcomes than standard of care treatment options, which do not require expensive lab tests to determine.

"Caris did not implement protocols or take steps to ensure or inquire as to whether treating oncologists used Target Now to make treatment decisions. Target Now testing is not reasonable or necessary unless it is used by a physician in determining treatment.

"Matt Sargent, vice president of national accounts for the Caris Oncology Division, directed and oversaw an aggressive campaign to market Target Now testing for use in determining first-line treatment, and/or outside of the eligibility criteria set forth above. In or around January 2010, Mr. Sargent hired several sales representatives, including David Basher and Jerome Madison, who had specific expertise in gaining access to surgical operating suites for marketing to surgeons. At the Caris national sales meeting in April 2010, Mr. Sargent gave the sales force the specific directives to target 'all surgery specimens first line and above' for Target Now testing.

"Although the company's Medical Director David Loesch, M.D., objected to this sales strategy during the meeting, Mr. Sargent told the sales staff to disregard his opinion. Mr. Sargent also told the sales staff in attendance that if they did not want to sell to surgeons they could find a job elsewhere. At the April 2010 meeting, Caris changed its compensation plan to reward sales representatives for bringing in surgical samples."

"*URGENT*** Heat Issues"**

Caris started offering hematology services in January 2009.

The company had to overcome the usual challenge of keeping the samples cold during shipment. The fact that the hematology laboratory is located in Phoenix exacerbated the challenge.

"However, Caris's measures were not adequate, and when it discovered that specimens were being compromised by heat exposure, Caris continued to perform the Heme tests on the degraded samples knowing full well that the laboratory test results were compromised," the complaint states, "Caris then billed Medicare for beneficiary tests, despite the fact that the compromised test results rendered them neither reasonable nor necessary."

Here, the complaint draws on internal documents:

"On July 15, 2009, Susan Bailey, Vice President – Oncology Product Development/Management, sent an e-mail to Caris's Oncology management team and sales force. The subject line was '***URGENT*** Heat Issues.' Ms. Bailey states: 'PLEASE MAKE SURE THAT YOUR CLIENTS ARE INCLUDING A FROZEN COLD PACK WITH ALL HEME OR CTC SAMPLES. We are experiencing viability issues because of the extreme heat and clients not including a frozen cold pack or even a refrigerated cold pack.'

"Raul Braylan, M.D., Caris's clinical medical director of hematopathology, replied, 'I am not sure if the issue is that the clients are not including a frozen or refrigerated cold pack. My concern is that even the frozen packs are not surviving the high temperatures we are experiencing here and throughout the South.'

"On the following day, Dr. Braylan sent another response to Ms. Bailey's e-mail, which stated: 'We checked different samples received today (all containing cold packs) and the temperature levels are at 80F or higher. One sample from Ocala, FL came in totally ruined. I already informed Andy about this issue and also called Ocala clinic. Fortunately, it was a blood sample and not a bone marrow, so I offered to repeat the testing free if they send us an additional sample. I consider this issue a very serious one requiring an immediate correction. We are facing great difficulties in determining if the data that we obtain are the results of disease or exposure to high temperature.'

"Dr. Braylan's communication to the Ocala clinic is the only example that Ms. Fontanive is aware of where Caris notified a customer about a ruined specimen. To the best of Ms. Fontanive's knowledge, Caris did not inform any other customers that the results of their tests

were compromised due to heat exposure. Instead, Caris allowed its physician customers to base treatment decisions on unreliable data."

The Questions of Billing

The suit states that from the start of its commercial service, Caris has faced the challenge of getting Medicare reimbursement.

Under Medicare, laboratory tests performed during a patient's hospital stay are covered by "prospective payment" to hospital and cannot be billed separately. In essence, the hospital would have to get the bill for the test and wouldn't get any additional payment.

There are, however, exceptions, which include the "fourteen Day Rule," which applies when a test is ordered at least 14 days after the patient's discharge from the hospital.

Another exemption is the "Grandfather Rule," which allows independent laboratories to bill Medicare for the technical component of lab services rendered to hospital patients if the hospital "had an arrangement with an independent laboratory that was in effect as of July 22, 1999, under which a laboratory furnished the TC [technical component] of physician pathology services to fee-for-service Medicare beneficiaries who were hospital inpatients or outpatients and submitted claims for payment for the TC to a carrier."

If an independent laboratory did not have an arrangement with a covered hospital as of July 22, 1999, but seeks to bill Medicare for the technical component of pathology services provided to the covered hospital's patients under the Grandfather Rule, Medicare requires the independent laboratory to obtain and maintain documentary evidence of the hospital's covered status.

According to the complaint, this presented challenges for Caris.

The document reads:

"A fresh frozen specimen is required [by Caris] for the DNA Microarray Analysis test. Fresh frozen samples must be frozen within thirty minutes of collection and shipped to Caris on dry-ice by overnight delivery for immediate analysis—though completion of the test usually takes several days. As such, Caris's Target Now tests that utilize DNA Microarray Analysis cannot qualify under the Fourteen Day Rule because the test must be performed within days of collection, and thus cannot be ordered at least fourteen days after a patient's discharge. Due to the short time frame from collection to analysis, DNA Microarray Analysis cannot qualify for the archived specimen exception either.

"Therefore, Caris can bill Medicare for the technical component of DNA Microarray Analysis only under the Grandfather Rule."

The complaint states that the relator Fontanive first became aware of these limitations from a prospective client.

The document states:

"In the summer of 2008, Ms. Fontanive called on Susana Savino and Barbara Serra from the pathology department of Florida Hospital in Orlando, Florida to sell Caris's Target Now services. Ms. Savino and Ms. Serra expressed concerns about utilizing Target Now, because of the Fourteen Day Rule. This was the first time Ms. Fontanive had ever heard of the Fourteen Day Rule.

"In April 2009, Caris published a document entitled 'Medicare Billing for Caris Diagnostic Services.' In it, Caris acknowledged that 'in most instances' it could bill Medicare only for the professional component of its services, and it identified the three exceptions that would permit technical component billing.

"In March, April and May of 2009, Caris made a limited attempt to bill hospitals for Target Now services provided to Medicare beneficiaries that did not qualify for direct Medicare billing by Caris. Caris met much resistance from the billed hospitals, and only a handful actually paid the bills. In order not to isolate its customers, Caris chose not to attempt collection of any bill for Target Now services that a hospital chose not to pay. Ms. Fontanive is aware of only one hospital in her territory ever receiving a bill from Caris for Target Now services, which was sent to Martin Memorial Medical Center in Stuart, Florida. But Caris never attempted to collect on the bill after the hospital questioned it. Caris instead chose to pursue a new reimbursement strategy: it held the bills for the technical component of Target Now tests while it attempted to qualify these accounts under the Grandfather Exception."

The filing includes a partial list of Medicare beneficiaries who received Target Now testing in March, April, and May of 2009 for whom Caris billed Medicare for the PC but waived payment from the hospitals for the TC.

"For a period of time, Caris submitted false claims to Medicare for the technical component of Target Now tests performed on specimens collected during beneficiary hospitalizations," the complaint states. "The

claims were false because the tests were covered under the PPS payments to the hospitals, and the tests did not qualify for any exception that would allow Caris to bill Medicare for the technical component.

"Subsequently, Caris began providing hospitals with illegal remuneration by

declining to collect payment for the technical component of Target Now tests in order to induce the hospitals to continue referring patients for Target Now tests, for which Caris would then bill Medicare for the professional component.

"These claims were false because they resulted from violations of the [anti-kickback statute]."

Conversation with The Cancer Letter

Hayes: A Bad Tumor Marker Can Be as Bad as a Bad Drug

(Continued from page 1)

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, was clicking through the Caris website as he spoke with Paul Goldberg, editor and publisher of The Cancer Letter.

PAUL GOLDBERG: *Let's start with the fundamentals.*

DANIEL HAYES: I've been quoted many times as saying: a bad tumor marker is as bad as a bad drug. Unless we have a really high level of evidence, through two important and critical terms—(1) analytic validity, and (2) clinical utility—in my opinion, a marker shouldn't be used to direct care.

The best examples I can think of are ER to direct endocrine therapy and HER2 to direct anti-HER2 therapy in breast cancer. There are other cancers, like KRAS for anti-EGFR antibodies, and more recently ALK mutations for crizotinib.

The issue I have with many of these companies—and I believe Caris is one of those—is that they have over-interpreted or berry-picked positive studies from many different assays that may or may not actually be predictive for a specific drug. Or, even worse, they make assumptions based on logic that a drug ought to work or not without any evidence to back up these assumptions.

As I go through their examples on the Caris website, first I see that they don't have a breast cancer example up there, so I don't know if they're doing it for breast cancer anymore.

But when I went to the lung cancer report, their example was that paclitaxel, docetaxel and nab-paclitaxel would not work for the particular patient example who has non-small cell lung cancer. They apparently based that assumption because the patient's cancer was not making PGP, TUBB3 or TLE3. They don't really tell you the results were for that patient, as far as I can figure out.

In the forms that I've seen before, the ones for my patients (for whom another doctor has ordered the Caris assay), they actually gave the results of the assay. But I don't see the results of the assays here anywhere. For example, selected studies have, indeed, suggested that each of those markers is associated with sensitivity or resistance to the taxanes, but other studies show they are not.

They are far from having the high levels of evidence that I think anyone who has reviewed the literature carefully would suggest to support that a patient that has non-small cell lung cancer should not be treated with a taxane simply because of one of these three tests.

What would happen is that a patient with non-small cell lung cancer might not receive a drug that has been shown to be pretty effective in that disease. This is a huge concern.

Further, I have no way of figuring out how or how well the assay was performed. Analytic validity of their assays may be quite good, but I have no way of knowing. I would assume that they are. I would have no way of looking at that. So I can't comment.

But what I can say is that I think they have over-interpreted the test they provide that might suggest that a drug won't work.

One of the things that I've become fond of saying is that we often think we are using these markers to decide whom we *should* treat, but because in oncology, clinicians (and also, it has been shown in several studies, patients) would prefer overtreating with something that has a chance of working than undertreating, especially in the metastatic setting.

I just opened up the doxorubicin file in the Caris website because as I was reviewing the example on their website for lung cancer, I double clicked on the list, and it takes you to the website that has all the drugs.

In that case, the example for the lung cancer patient was paclitaxel, but further down the list they display a link to doxorubicin, so I've just opened up doxorubicin and their report suggests that doxorubicin should not work in patients who are not topoisomerase II-amplified.

That's a very good theory. It is a theory that's been

studied quite carefully, but the data are mixed and it's still controversial. Many of us do not believe that topo II should be used to decide who should and should not receive doxorubicin, and neither the ASCO nor NCCN guidelines panels have suggested it should be used to make this decision. So, if I am interpreting their website, they would suggest withholding doxorubicin from a patient with non-amplified topo II. I think this is dangerous.

PG: *This is on their current website?*

DH: I'm on their website right now. I personally have published that HER2 might be associated with relative sensitivity or resistance, and that it is possible that HER2-positive patients might be more likely to respond to doxorubicin, and HER2-negative patients might be less likely to. However, in our papers, we've been quite cautious, because these data are speculative and that's far from proven. And very far from being absolute.

I would never use HER2 as a reason to treat or withhold a patient with doxorubicin, nor would I order or use topo II, for that matter, and I don't think clinicians should order this [topo II] test.

So, in fact, I'm willing to go on record to say that, in my opinion, it's irresponsible to provide such information to doctors, because I think it's providing information for which high levels of evidence don't exist to make a clinical decision. And the issue is—and I'll say it again—that a bad tumor marker can be as bad as a bad drug, if it leads to withholding what could be a potentially effective therapy.

On their website they say they've done 60,000 cases. 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. I live in a glass house—meaning I've not only developed and studied new markers, but I've also worked hard to help develop criteria to evaluate whether they have analytical validity and clinical utility so that guidelines bodies, and clinicians and their patients, can decide if they should be used to guide therapy. I've published widely about trying to establish criteria for what I mean by high levels of evidence—and by that I mean level of evidence "1." That's what it takes to develop clinical utility. For example, Richard Simon, Soon Paik and I have proposed criteria to determine if a tumor biomarker test has level-1 evidence, and although this proposal is up for discussion, at least it's an effort to make order out of chaos.

People may throw rocks at me, but at least I can point to my efforts to clean up this mess.

PG: *So you should stay on guidelines, basically. Right?*

DH: All of us want personalized therapy. All of us want to give the right drug at the right time at the right dose, the right schedule—I'm quoting Rich Schilsky when he was ASCO president.

PG: *I hate to say this, but I think it's actually [former NCI Director] Andrew von Eschenbach. In his stump speech, he used to say that.*

DH: On the other hand, I think most clinicians and most patients would err on the side of being overtreated than undertreated, and my fear is that this assay, for example, will lead to inappropriate treatment; inappropriate management for patients with cancer, and I'm opposed to that.

PG: *It's also a question of whom do you trust. Do you trust a finding on an assay of uncertain significance or do you trust the guidelines that have been developed for a long time?*

DH: Independent of Caris, in the past, the way that we have gotten tumor biomarker tests performed and reported back to us is the pathologist gets the tissue and performs the test that we clinicians would like to have for the specific disease. They get the results back to us, and then we act accordingly. In my case [breast cancer patients], ER and HER2.

One of the things that I'm most proud of in my career is the joint ASCO-College of American Pathologists initiative to standardize the way HER2 and ER are performed and interpreted. I think those have been quite well received and have enhanced the analytic validity of those tests, which already have been proven to have high levels of evidence for clinical utility, across general pathology.

The reason I'm bringing this up is that increasingly the tissues will be sent to a third party company or lab, and that these tests would be done centrally rather than in a pathology lab. That's not there yet, that's kind of where we're going. The [Genomic Health] 21-gene recurrence score, for example, is such a test.

The issue is, should we use the estrogen receptor and the HER2 provided to us in the 21-gene recurrence score to make decisions about endocrine therapy and HER2. Right now, the published ASCO-CAP guidelines panel elected to not make that recommendation. We said that the decision should still be based on true tests for HER2, in this case IHC or an ISH test, because we had no high level of evidence data to support their use for these critical decisions.

The problem with companies that provide clinicians with these "suites" of tests is that they provide you with a lot of test information that you may not want as a clinician, and that you may not be able to

trust. And yet, they imply that because they are giving it to you, it must be right.

And, in fact, unless I'm missing something, in the website I'm looking at, they don't even provide the references that back up the statements they make, in regards to why that marker will be a marker for that drug. [In response to questions from The Cancer Letter, Caris said that relevant citations are provided in reports delivered to physicians See p. 12]

Now I've just clicked down to paclitaxel in lung cancer, which again started out with by saying that this patient shouldn't respond to paclitaxel.

And then I clicked on that, and it took me to a whole list of drugs and it was highlighting paclitaxel. And it had tumor markers, one of which was TUBB3, so I clicked on TUBB3.

And it says TUBB3, which is tubulin beta-3, is a protein that in humans is encoded by the TUBB3 gene. The link provides associated signaling pathways, associated treatments, associated tumor types—it doesn't even provide me with how the test was performed or what that patient's TUBB3 results were, nor does it provide me any set of references that say whether TUBB3 gives you an increased or decreased sensitivity to this drug, how big of a magnitude that is, and whether or not I should use that to make a decision.

All it says in the background molecular intelligence tumor report it says that paclitaxel is an agent associated with a potential lack of benefit.

PG: *As a clinician, have you ever seen the misuse of this specific test or others?*

DH: Let me just say that I'm concerned about the use of this sort of information and the way it's presented to clinicians. Many times I've used the word irresponsible in regards to patient management.

PG: *And this is not just Caris, right?*

DH: Well, in general it's not just Caris. I think anybody that's trying to sell a tumor biomarker test—whether it is a single analyte, a multiparameter signature, or a suite of tests—ought to back it up with high levels of evidence that demonstrate that use of that biomarker improves the clinical outcome.

PG: *And you're not seeing that on their website at all?*

DH: I know for a fact that the use of TUBB3 to decide whether or not paclitaxel works has been highly controversial. We do not have a level of evidence or data to support using TUBB3 to withhold paclitaxel from a patient who has non-small cell lung cancer.

PG: *Do you have other concerns? Who should be ordering such tests? Should it be oncologists? Should it be surgeons?*

DH: I will say I have concerns about any company marketing something to people who aren't the ones who end up using it.

At the University of Michigan, we work quite closely with our colleagues in surgery and pathology, and nothing gets ordered that medical oncology is going to use unless we have worked out that we want that done.

If any company came and tried to market this assay to our surgeons or pathologists, they would say, "Go talk to Dr. Hayes. If he wants it done, then we'll start ordering it." I think it is unethical to go to surgeons or pathologists to market an assay that they personally aren't going to use to make a decision. In this case, the medical oncologists are the people who are going to see and treat the patient. They may be left with information that is either wrong, or confusing, and they don't know what to do with it. That's not good for patients.

It's not specific to Caris. For example, Agendia was marketing MammaPrint directly to surgeons. I was getting phone calls from medical oncologists who said that they have a 21-gene recurrence score, which they requested, but also results from MammaPrint, which the patient's surgeon ordered, and now they may have two assays that have conflicting results. What should they do?

In this specific case, I would use the 21-gene recurrence score. That's the assay that has ASCO and NCCN guideline recommendations, because we have high levels of evidence that in patients with node-negative, ER-positive, HER2-negative cancers, the Recurrence Score is a reliable estimator of risk of metastases over the ensuing 10 years, assuming adequate adjuvant endocrine therapy. Thus, one would recommend against adjuvant chemotherapy in this group if their RS is low, and for it if the RS is high. The TailoRx trial is designed to determine what to do with intermediate RS, and the RxPonder trial is likewise investigating what to do with node-positive patients. MammaPrint, in my opinion, is a very interesting assay, but does not have the high level of evidence for clinical utility that the 21-gene recurrence score has for the node-negative, ER-positive, HER2-negative patient.

Nonetheless, you put the patient in a terrible situation, because what if the 21-gene recurrence score says they have a low recurrence score and what if MammaPrint says high? Do you say, "Let's go to chemotherapy, because MammaPrint says high recurrence risk," or do you say, "Let's skip chemotherapy because of the low 21-gene recurrence score?"

That's a heck of a situation.

Caris Officials Respond to Questions from The Cancer Letter

The Cancer Letter submitted seven questions to Caris Life Sciences regarding their suite of molecular diagnostic tests, following a conversation with Daniel Hayes (See p. 1), a breast cancer expert at the University of Michigan and who served on an Institute of Medicine committee that recently issued a report on omics testing.

Questions focused on the costs of the tests, who pays for them, and how much of the information they provide is actionable.

Caris is currently involved in lawsuit brought against them by two former employees, who allege that the company violated the federal anti-kickback statute by waiving fees to induce referrals to federal healthcare programs. Caris denies the allegations, and has described the action as a "nuisance lawsuit."

1.) What is the price of the Caris panel of tests?

We bill on a marker by marker basis based upon the profiling panel requested by the physician and the analytical technology used. This varies by physician and by type of cancer. Ultimately, it is the physician(s) treating the patient that decides which test to order. In common with other companies offering molecular profiling services, the Caris Molecular Intelligence™ (CMI) service is not yet profitable but we are confident that as the value of molecular profiling gains increasing recognition in the clinical oncology community this service will become financially viable.

2.) Do all of Medicare contractors pay for CMI? If not, how many?

As outlined in #1 above, we bill on a marker by marker basis and this provides the context to which we receive reimbursement from Medicare.

3.) Do all private insurers pay? If not, how many?

Payment depends on the patient's insurance plan or policy.

4.) In a letter in the Boston Business Journal, David Halbert writes that "CMI can provide up to 51 potentially relevant FDA-approved drug associations." I have never seen this metric before. What does it measure? Who came up with it?

The 51 potentially relevant FDA-approved drug associations refers to the Caris Molecular Intelligence™ biomarker panel for which evidence-based associations are defined (see 7a below). The 51 associations also reflect the important distinction that the Caris Molecular Intelligence™ service is not limited to genomic profiling (Individual genes or next-generation sequencing (NGS) panels) offered by some companies which fail to inform physicians of important treatment options identified by non-genomic assays such as immunohistochemistry and fluorescence in situ hybridization (see figure 1). From the outset, Caris has adopted a technology-position and has constantly revised its profiling test portfolio based on multiple technologies and stringent evidence-based review of the proposed drug-target associations.

5.) Is Caris involved in any of the new-generation randomized trials sponsored by NCI and FNIH? Is there a large company-sponsored trial underway?

No. In addition, as outlined in answer #4 above it is unclear whether the use of next-generation sequencing alone in the cited NCI and FNIH studies without analysis of accompanying alterations in protein expression of the drug targets can provide a suitably comprehensive profile to meaningfully guide therapy selection.

Caris has performed over 65,000 molecular profiles to date from 59 countries and all 50 states with over 6,500 ordering physicians. We are actively involved with numerous academic projects to answer important questions in cancer treatment and biology as evidenced by the publications and presentations made by our scientific and medical team including 34 abstracts accepted at ASCO 2014. (See http://www.carislifesciences.com/asco-2014/).

6.) Is all of the information Caris tests provide actionable?

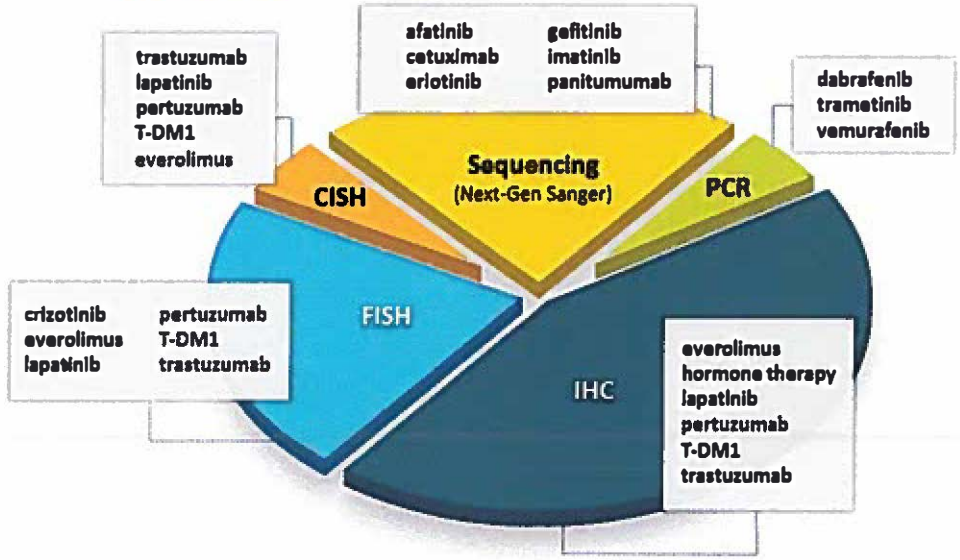
[Ninety-seven percent] of reports have drugs identified with agents with lack of clinical benefit. [Ninety-three percent] of the time they identify drugs with clinical benefit. [Ninety-six percent] of the drug-biomarker associations are actionable based on the evidentiary standards described in answer #7 below. (See figure 2.)

7.) In a sample report, the levels of evidence for specific drugs are rated on a three-level scale.
a) How and by whom was this scale put together?

In assessing scientific evidence, our team utilizes the methodology set forth by the U.S. Preventive Services Task Force Grading for scoring the evidence reviewed (see http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/

Figure 1.

The Need for Multiple Molecular Diagnostic Platforms to Maximize the Number of Actionable Drug: Target Associations to Guide Therapeutic Decisions



FISH = fluorescent in situ hybridizaiton
CISH = chromogenic in situ hybrization
IHC = immunohistochemistry

Caris Life Sciences'℠ *Caris Molecular Intelligence*™ Multi-Technology Profiling

Technologies Used:

- Next-Generation Sequencing *(NGS)* - DNA
- Fluorescence in situ Hybridization *(FISH)* - DNA
- Chromogenic in situ Hybridization *(CISH)* - DNA
- Immunohistochemistry *(IHC)* - Protein
- Sanger Sequencing - DNA
- PyroSequencing - DNA
- Fragment Analysis - DNA
- Quantitative Polymerase Chain Reaction *(qPCR - cobas®)* - DNA

51 Actionable Drug:Target Associations

abarelix	crizotinib	everolimus†	irinotecan	panitumumab†	toremifene
abiraterone	dabrafenib	exemestane	lapatinib†	pemetrexed	trametinib
afatinib	dacarbazine†	fluorouracil	letrozole	pertuzumab†	trastuzumab†
anastrozole	degarelix	flutamide	leuprolide	sunitinib	triptorelin
bicalutamide	docetaxel	fulvestrant	liposomal-doxorubicin†	tamoxifen	vandetanib
capecitabine	doxorubicin†	gefitinib†	megestrol acetate	T-DM1†	vemurafenib
carboplatin†	enzalutamide	gemcitabine	nab-paclitaxel	temozolomide†	
cetuximab†	epirubicin†	goserelin	oxaliplatin	temsirolimus†	
cisplatin†	erlotinib†	imatinib	paclitaxel	topotecan	

guide/appendix-a.html).

Level 1 evidence comprises randomized controlled trials for selected biomarker; level 2 evidence comprises non-randomized controlled trials, single arm, cohort/case-control studies; level 3 comprises analysis by expert committee of physicians and scientists reviewing scientific articles, case reports or series. Evidence is backed by review of more than 120,000 research articles related to the biomarkers in CMI by a team including both internal- and external-to-Caris specialists including oncologists, scientists, pathologists and researchers. The expert team consists of 5 PhDs, 2-3 rotating medical oncologists, 2 pathologists, and 1 medical geneticist.

Three general categories are used to classify actionable variants:

1) variants linked to a FDA-approved drug within a specific tumor type;

2) variants linked to a FDA-approved drug approved for a different tumor type; and

3) variants linked to investigational drugs in clinical trials.

Research and pre-clinical publications are not used by Caris since we do not consider that such studies reach the minimum level of robust validation needed for therapy selection ranking recommendations.

b) The sample reports I see don't cite actual papers.

Reports to physicians do have citations to relevant publications based on the biomarkers expressed and can be accessed online for review.

c) Critics say that this doesn't enable sufficiently detailed discussion of complex scientific questions. How would you respond to this criticism?

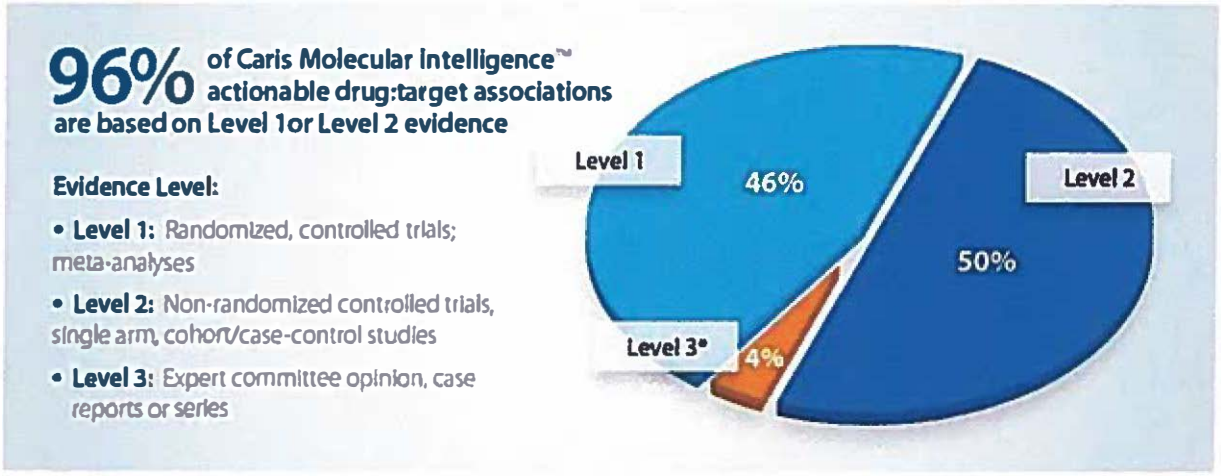
Molecular profiling of cancer via (epi)genomic, transcriptomic, proteomic and metabolic assays (panOmics) is evolving rapidly. Ambiguities exist not only with respect to the data reproducibility in many published studies but also with respect to the intrinsic biological complexity of cancer and the ubiquitous problem of analysis inter-patient and intra-patient inter-lesional heterogeneity. This problem is highlighted by the unknown role of many of the mutations in profiled genes by multiple companies using NGS and lack evidence of clinical utility as diagnostic or prognostic markers or predictors of therapeutic responsiveness. Even though the Caris Molecular Intelligence service uses NGS sequencing, we have been prudent in ensuring that only evidence-based between gene-drug associations that fulfill the criteria listed in #7a above are included in reports to physicians.

We appreciate your list of questions, all of which are pertinent to assessment of the current status of molecular profiling services in oncology and are relevant to all of the numerous companies, and academic laboratories, now offering molecular profiling services in oncology. We consider that it would be a valuable analysis to your readership if you were to pose the same seven questions to the burgeoning list of participants in this nascent field and publish a synopsis of the collective answers. In particular, a critique of why some companies and laboratories believe that use of NGS methods in isolation can provide insight into perturbations in molecular signaling pathways in which genomic alterations do not necessarily translate into altered protein expression would be a very valuable analysis (see for example the recent publication in Nature (2014) dol:10.1038/nature13438 on molecular profiling of colon cancer as but the latest example of asymmetries between genomic alterations and effects on protein expression). These complexities will require more sophisticated systems-based platforms that integrate diverse 'omics' datasets. Once again, this reinforces the long held position of Caris that in addition to rigorous standards of analytical proficiency only biomarkers for which meaningful clinical associations have been identified in peer-reviewed publications should be included in reports to requesting physicians.

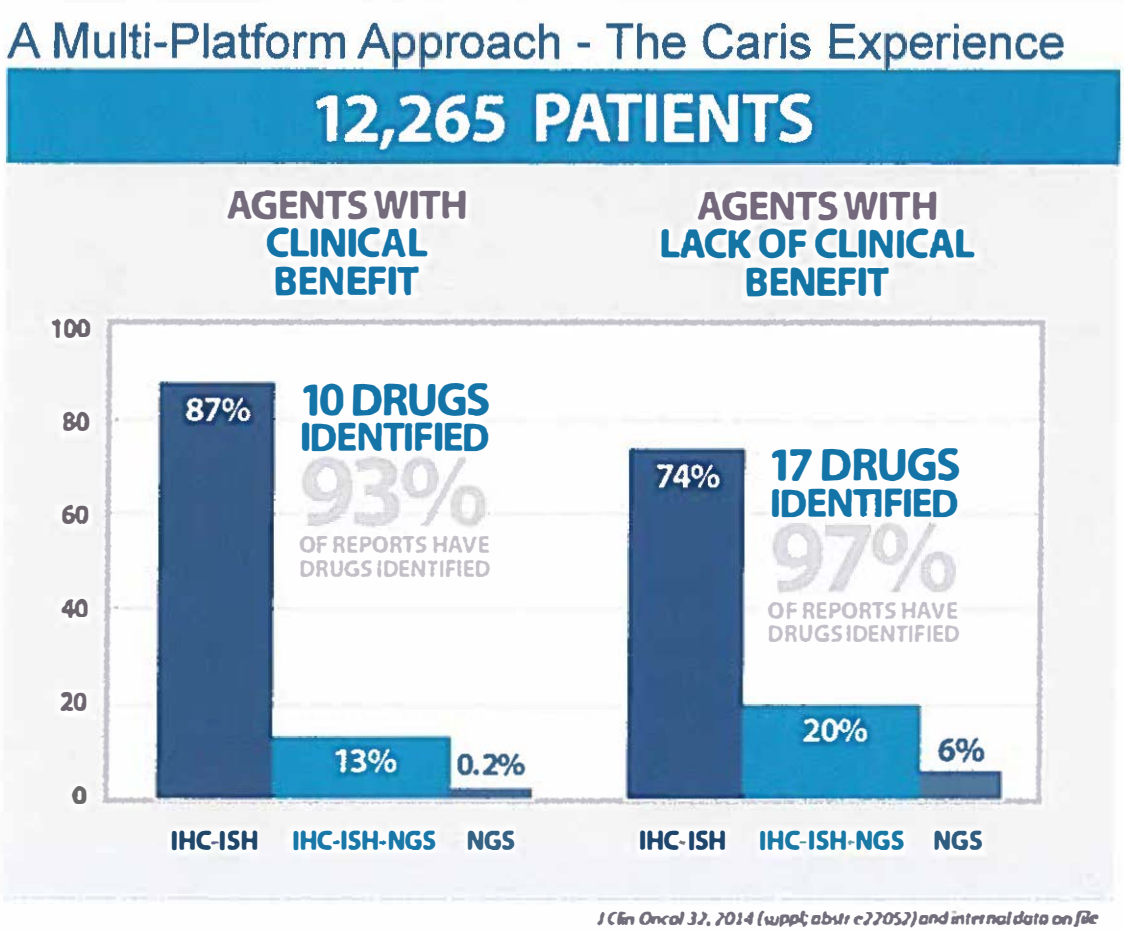
As NGS panels expand, the number of variants of unknown significance will increase and must await validation of their clinically actionable status. In addition to genomic variants of unknown significance the role of how gene-gene interactions (epistasis) in both up-stream and down-stream signaling pathways may affect response to targeted therapies is a technically complex issue that will confront companies and academic medical centers in the interpretation of both expanded NGS panels and sequencing profiles of whole genomes.

Caris combines the rigor of an academic medical institution with the innovative spirit of a technology company. We believe that innovative, high-quality testing and information can lead to more effective treatment selection and ultimately to better outcomes for patients with cancer and other complex diseases. (To view a video tour of our lab, please see http://www.carislifesciences.com/about-us).

Figure 2.



** Level 3 evidence associates ROS1 to crizotinib, which is included in the NCCN Guidelines® for the treatment of NSCLC.*



J Clin Oncol 32, 2014 (suppl; abstr e22052) and internal data on file

Community Cancer Research

NCI Launches NCORP with 53 Grants Totaling $465 Million

NCI awarded 53 five-year grants for multi-site clinical trials and care delivery research studies through the NCI Community Oncology Research Program. The program will provide $93 million each year.

The new program will have an expanded portfolio of clinical trials and other studies, including an emphasis on cancer care delivery research, which will focus on social, financing, technological and other factors that affect access to and quality of care.

NCORP replaces two previous NCI community-based clinical research programs: the NCI Community Clinical Oncology Program and the NCI Community Cancer Centers Program. NCORP will also align with the National Clinical Trials Network. Ongoing clinical trials will be incorporated into NCORP and will continue to completion, according to NCI.

The NCORP awards will support seven research bases functioning as hubs for the network. The bases will design and conduct trials, and provide overall administration and data management. The remaining awards will support 34 community sites in accruing trial participants, and performing quality of life studies and care delivery research. The awards will also fund 12 additional minority or underserved community sites, which will focus on patient populations consisting of at least 30 percent racial or ethnic minorities or rural residents.

This is a decline in the number of locations funded by CCOP, which supported 11 research bases, 47 community sites, and 16 minority-based sites. The NCCCP network contained 21 community hospital-based cancer centers.

NCORP-funded sites include:

Research Bases:

- Alliance
- Children's Oncology Group
- ECOG-ACRIN
- NRG Oncology
- SWOG
- University of Rochester
- Wake Forest University

Community NCORP Sites:

- Aurora Health Care
- Bay Area Tumor Institute
- Beaumont NCORP, including Beaumont Royal Oak and Beaumont-Troy
- Cancer Research Consortium of West Michigan
- Cancer Research for the Ozarks
- Cancer Research of Kansas
- Carle Cancer Center
- Catholic Health Initiative Institute for Research Oncology Research Alliance
- Colorado Cancer Research Program
- Columbus, Ohio, including Riverside Methodist Hospital, Mt. Carmel Health Care System and Adena Medical Center
- Dayton, Ohio, including Good Samaritan Hospital, Blanchard Hospital, Kettering Medical Center
- Delaware/Christiana Care
- Essentia Health
- Florida Pediatric NCORP
- Geisinger Cancer Institute
- Georgia NCORP, including St. Joseph's Candler Hospital/Lewis Cancer and Research Pavilion and Northside Hospital Cancer Institute
- Heartland Cancer Research
- Iowa-Wide Oncology Research Coalition
- Kaiser Permanente NCORP, including Kaiser Permanente Northern California, Kaiser Permanente Northwest and Kaiser Permanente Southern California
- Kansas City NCORP, including Research Medical Center and St. Luke's Hospital-Kansas City
- Main Line Health
- Metro-Minnesota NCORP, including New Ulm Medical Center, North Memorial Medical Center and Rice Memorial Hospital
- Michigan Cancer Research Consortium
- Montana Cancer Consortium
- NCORP of the Carolinas, including the Greenville Health System
- Nemours NCORP, including Nemours Alfred I. duPont Hospital for Children, Nemours Children's Hospital and Nemours-Jacksonville
- Nevada Cancer Research Foundation
- North Shore-LIJ Health System
- Northwest NCORP, including Virginia Mason Medical Center, MultiCare Health System and Fairbanks Memorial
- Ochsner Medical Center
- Pacific Cancer Research Consortium
- Sanford NCORP of the North Central Plains
- Southeast Cancer Consortium-Upstate, including Spartanburg Regional Hospital/Gibbs Cancer Center and Novant Health Forsyth Medical Center
- Wisconsin NCORP, including Gunderson Health System, St. Vincent Regional Cancer Center and the Marshfield Clinic

Minority/Underserved NCORP Sites:

• Baptist Health System/Mid South, including Baptist Cancer Center

• Columbia University Medical Center

• Georgia Regents University and Georgia Southern University

• Gulf South, including Louisiana State University Health Science Center New Orleans and Shreveport and Mary Bird Perkins Cancer Center

• The Queen's Medical Center, Hawaii

• Medical University of South Carolina, including Hilton Head Breast Health Center and the Ralph H. Johnson VA Medical Center

• Montefiore Medical Center

• New Mexico, including University of New Mexico Cancer Center, Presbyterian Health Care Services and Lovelace Women's Hospital

• San Jorge Children's Hospital, Puerto Rico

• South Texas Pediatric, including University of Texas Health Science Center at San Antonio, Methodist Children's Hospital and Driscoll Children's Hospital

• Stroger Hospital of Cook County

• VCU Massey Cancer Center, including Community Memorial Healthcenter and Hem-Oncology Associates of Fredericksburg

In Brief

Pisters Appointed President And CEO of University Health

(Continued from page 1)

He previously served as medical director of the regional cancer centers, clinical consultant for the Center for Global Oncology (now known as MD Anderson Cancer Network), and section chief for sarcoma surgery with a specialty focus in the management of sarcoma and gastrointestinal cancer patients.

The University of Toronto-affiliated University Health Network includes Toronto General and Toronto Western Hospitals, Princess Margaret Cancer Centre, and Toronto Rehabilitation Institute. It has the largest hospital-based research program in Canada.

MD ANDERSON CANCER CENTER announced a partnership with **Hospital Israelita Albert Einstein** in Brazil.

The 489-bed private hospital located in São Paulo will be the first clinical extension of MD Anderson in Latin America and the first international member of MD Anderson Cancer Network.

As an associate member of the network, the hospital will be operationally and clinically integrated with MD Anderson. Services will include medical, radiation and surgical oncology, as well as pathology, laboratory, diagnostic imaging and other supportive clinical services.

MD Anderson will provide HIAE with clinical care oversight, order sets, and treatment algorithms. The clinical integration will also include planning and clinical program support, faculty and staff education and training, quality measurement and reporting tools, access to clinical trials and research collaborations.

HIAE physicians will consult directly with MD Anderson faculty through tumor boards and visits and deliver care based on the same protocols and practice standards provided at MD Anderson.

HIAE became MD Anderson's first formal sister institution in 2002, a relationship that included a number of academic exchanges. HIAE opened a new Oncology and Hematology Center last December, modeled after MD Anderson's facilities. The four-story structure features 23 exam rooms, 28 infusion rooms, areas for meditation and yoga therapy and gardens designed to offer comfort to patients and their families. HIAE was the first hospital outside the U.S. to be accredited by the Joint Commission International in 1999.

RICHARD WAHL was named the Elizabeth E. Mallinckrodt Professor and head of radiology at **Washington University School of Medicine in St. Louis**. He also will serve as director of the Mallinckrodt Institute of Radiology. He will begin in October.

Wahl comes from Johns Hopkins University, where he is the Henry N. Wagner Jr., MD, Professor and director of the Division of Nuclear Medicine. He is also vice chair for technology and new business development in the Russell H. Morgan Department of Radiology and Radiological Sciences, and a professor of oncology.

He will succeed R. Gilbert Jost, who was head of Mallinckrodt for 15 years. Jost helped establish the Center for Clinical Imaging Research.

Wahl was among the first to use the radioimmunotherapy approach in non-Hodgkin's lymphoma. He has also been a leader in using positron emission tomography to diagnose a broad array of human cancers and other diseases. He is a fellow in the American College of Radiology, and holds 18 radiology patents.

Wahl graduated from Washington University School of Medicine and served his residency there, and then returned for training in diagnostic radiology and nuclear medicine.

DAVID ESPEY stepped down as acting director of the **CDC Division of Cancer Prevention and Control**, a position he has held since Feb. 3.

Epsey helped guide the DCPC-coordinated surgeon general's Call to Action on Preventing Skin Cancer (The Cancer Letter, Aug. 1); and the American Journal of Public Health Special Supplement.

He also received the 2014 Health Equity Achievement Award from the CDC's National Center for Chronic Disease Prevention and Health Promotion, for his work in addressing the public health issues among American Indian and Alaska Native populations.

Espey will return to his position as a CDC assignee in Albuquerque, N.M., where he collaborates with the Indian Health Service to improve the quality of cancer surveillance data in support of cancer control programs.

Pamela Protzel Berman will serve as acting director during the final stages of the search for a permanent director. Berman has been DCPC's deputy director since October 2009. She joined CDC in 1991 in what was then the Division of Injury Prevention.

MICHAEL BOOKMAN will join Arizona Oncology, a practice in The US Oncology Network, and will serve as medical director of the **US Oncology Research Gynecology Research Program**, effective Oct. 6.

Bookman is currently a professor of medicine at the University of Arizona. He previously spent 21 years at Fox Chase Cancer Center, most recently as vice president for ambulatory care and clinical research.

Bookman continues to serve as chair of the Ovarian Committee for the Gynecologic Oncology Group, which has been integrated with NRG Oncology under the NCI National Clinical Trials Network. He also serves as director of educational resources for the International Gynecologic Cancer Society.

RICHARD DAVID was named a clinical professor of urology, voluntary, at the David Geffen School of Medicine at the **University of California, Los Angeles**.

David is chief medical officer of Skyline Urology and has served on the UCLA clinical faculty for 24 years. His specialties include prostate cancer and other urologic cancers, as well as men's sexual health, bladder dysfunction, pelvic floor issues and testosterone replacement therapy.

JENNIFER ZEITZER was named deputy director of the Office of Public Affairs of the Federation of American Societies for Experimental Biology.

Zeitzer previously served as director of the FASEB Office of Legislative Relations.

JEFFREY ALBERS was named CEO of **Blueprint Medicines**.

Albers joins Blueprint from Algeta ASA, where he served on the executive management team as U.S. president prior to acquisition by Bayer. He succeeds Alexis Borisy, co-founder and interim CEO of Blueprint and Partner at Third Rock Ventures, who will remain an active member of the company's board of directors.

Before Algeta, Albers spent seven years at Genzyme, where he served as vice president of the U.S. hematology & oncology business unit.

THE CONQUER CANCER FOUNDATION of the American Society of Clinical Oncology named **Raj Mantena** and **Aaron Sasson** to its board of directors.

Mantena has founded and co-founded several oncology companies, including ICORE Healthcare. In April, he donated $1 million to the foundation's CancerLinQ program. In September 2013, Mantena matched all individual donations to the foundation dollar-for-dollar.

Sasson is chairman and co-founder of Lanetix, which provides cloud-based computing services for the logistics and transportation industry. He is also chairman and co-founder of GT Nexus, a company focused on global supply chain management.

The foundation also reappointed the following board members for another term: W. Charles Penley as chair; Martin Murphy as chair emeritus; Thomas Roberts, Jr. as incoming 2015 secretary; and members Michael Gordon and Robert Mayer.

THE DR. SUSAN LOVE RESEARCH FOUNDATION received a nearly $1 million grant from the NIH to continue development of a portable self-reading ultrasound for breast screening.

The two-year UH2 Phase I exploratory cooperative agreement will support work on a device that can be used by local health aides to triage palpable breast lumps, enabling them to distinguish between those which are benign and those which should be biopsied.

The goal is to develop a low-cost ultrasound device by employing imaging enhancing algorithms and computer-aided detection and diagnosis. The device will

not require highly trained professional staff for operation, making it accessible to a broader range of health care facilities in lower- and middle-income countries.

A clinical validation trial will be performed at county hospitals in Southern California to determine the sensitivity and specificity of the ultrasound device. NIH will then assess the feasibility for transitioning the project to a UH3 Phase II grant, which would include a clinical trial in Jalisco, Mexico, to validate effectiveness, acceptability, and feasibility of the technology in a developing country.

Development and clinical validations will be performed in collaboration between surgeon Susan Love, of UCLA; breast imaging radiologist Wendie Berg, of the University of Pittsburgh School of Medicine; and Christine Podilchuk and Richard Mammone of ClearView Diagnostics. Mammone, a professor of electrical and computer engineering at Rutgers University, invented the scanner technology and founded ClearView.

MASSACHUSETTS GENERAL HOSPITAL received the **American Hospital Association's** inaugural Equity of Care Award for its efforts to reduce health care disparities and promote diversity within the organization's leadership and staff. The award was presented July 21 at the Health Forum-AHA Leadership Summit in San Diego.

In 2011, the AHA joined four national health care organizations to issue a call to action to eliminate health care disparities by focusing on increasing the collection of race, ethnicity and language preference data; increasing cultural competency training; and increasing diversity in governance and leadership.

MGH established a system-wide Committee on Racial and Ethnic Disparities in 2003 to focus internal attention on the challenge of disparities, improve the collection of race/ethnicity data, and implement quality improvement programs to reduce disparities. The Disparities Solutions Center was established in 2005 in response to national and local calls to address disparities in healthcare.

THE ASSOCIATION OF COMMUNITY CANCER CENTERS launched an online oncology drug database with information on drug coding, billing and reimbursement.

The database includes information on both provider-administered Medicare Part B drugs and prescribed Part D drugs commonly used in treating cancer patients in the ambulatory setting, as well as supportive care products.

Each drug listing will contain billing (HCPCS, NDC) and diagnosis (ICD-9) codes, FDA-approved indications, and manufacturer information, including contact information for the medical affairs department and reimbursement specialists.

BRISTOL-MYERS SQUIBB formed an agreement with **Leica Biosystems** to develop companion diagnostic tests.

The fully automated, tissue-based companion diagnostic tests will be developed on the Leica BOND system. They will be paired with targeted therapeutics produced by Bristol-Myers Squibb. Other terms of the agreement were not disclosed.

ASTRAZENECA and **Qiagen** agreed to collaborate on the development of a liquid biopsy-based companion diagnostic to be paired with Iressa, AstraZeneca's targeted therapy for non-small cell lung cancer.

The project builds on a master framework agreement signed by both companies in 2013, and aims to develop and market a novel Qiagen companion diagnostic that analyzes plasma samples to assess EGFR mutation status in NSCLC patients. The assay will be designed to guide the treatment of NSCLC patients with Astra Zeneca's oral monotherapy when tumor tissue is not available.

Iressa (gefitinib) is an epidermal growth factor receptor-tyrosine kinase inhibitor. The two companies plan to develop a test that detects 21 EGFR mutations to identify patients most likely to benefit from the therapy, adapting Qiagen technologies from the therascreen EGFR RGQ PCR Kit.

The new test kit is planned to run on Qiagen's Rotor-Gene Q system, a member of the QIAsymphony family of automated instruments.

OPTIM ONCOLOGY and **Urology Centers of Oklahoma**, divisions of Oklahoma Multispecialty Group, have joined **The US Oncology Network**.

Optim Oncology and Urology Centers of Oklahoma are made up of 20 physicians, including 13 urologists, one uropathologist, three radiation oncologists and three medical oncologists. They practice from 14 primary locations plus five satellite offices located throughout Oklahoma. The practice offers integrated medical and radiation oncology services.

Urology Centers of Oklahoma has treated more prostate cancer cases than any other provider in Oklahoma, with more than 1,000 cases since 2007.

Physicians at both Optim and Urology Centers of Oklahoma can now offer patients clinical trials through

US Oncology Research. They will also have access to US Oncology's drug distribution center.

FDA and the European Medicines Agency both granted orphan drug designations to **ABT-414**, an investigational anti-epidermal growth factor receptor antibody drug conjugate developed by **AbbVie**. The compound is being evaluated for safety and efficacy in patients with glioblastoma multiforme.

Results from the phase I clinical program evaluating ABT-414 in combination with temozolomide in patients with recurrent or unresectable glioblastoma multiforme were presented at the annual meeting of the American Society of Clinical Oncology earlier this year. AbbVie will continue to develop the compound in phase II glioblastoma multiforme trials, according to Gary Gordon, vice president of oncology clinical development at AbbVie.

ABT-414 is also in clinical trials for the treatment of patients with squamous cell tumors.

Obituary

Emmanuel Farber, Experimental Pathologist, Dies at Age 95

Emmanuel Farber, a pathologist who made contributions to the understanding of chemical carcinogenesis, died Sunday, Aug. 3.

Farber's studies in experimental pathology demonstrated that chemical carcinogens are capable of binding to nucleic acids, in turn generating specific DNA adducts. This led to the observation that chemical carcinogenesis is a sequential process, and he proved this theory by showing that cancer could be induced through a series of step-by-step chemical treatments in the liver, according to an obituary published by the American Association for Cancer Research.

Farber served on the surgeon general's first Advisory Committee on Smoking and Health from 1961 to 1964. The committee was responsible for issuing the 1964 Surgeon General's Report on the dangers of smoking and tobacco-related disease.

Farber was born in Toronto Oct. 19, 1918. He received his medical degree from the University of Toronto in 1942. After completing his residency training in pathology at the Hamilton General Hospital, he served in the Royal Canadian Army Medical Corps, and later obtained a doctorate in biochemistry from the University of California, Berkeley.

He was later named professor and chairman of pathology and professor of biochemistry at the University of Pittsburgh School of Medicine and at the Fels Research Institute of Temple University, where he was professor of pathology and biochemistry and director of the institute.

In 1975, Farber returned to Toronto to serve as professor and chairman of the Department of Pathology and professor in the Department of Biochemistry at the University of Toronto. At his death, he held the title of chairman emeritus and professor in the Department of Pathology.

Farber was an active member of the AACR, and served as vice president and president between 1971 and 1973. He was a member of the board of directors and served as associate editor of Cancer Research; and was elected as an inaugural fellow of the AACR Academy in 2013.

Farber was also a member of the Pennsylvania (East) State Legislative Committee, and the Molecular Epidemiology Working Group and served on the Panel on Medical Sciences of the U.S.-Japan Cooperative Science Program, National Advisory Cancer Council of the U.S. Public Health Service, Lung Cancer Task Force, Committee on Food Safety and Food Safety Policy of the National Academy of Sciences, Chairman of the Pathology B Study section of NIH, Committee on Pathology, Division of Medical Sciences of the National Academy of Sciences and National Research Council, the Histochemical Society, and the American Society of Experimental Pathology.

He was a member of the editorial boards of American Journal of Pathology; Laboratory Investigation; Journal of Histochemistry and Cytochemistry; Oncology News; Teratogenesis, Carcinogenesis, and Mutagenesis; International Journal of Cancer; Chemical Biological Interactions; Liver; and Hepatology.

Over the course of his career, Farber received the Parke-Davis Award in Experimental Pathology, the Samuel R. Noble Foundation Award, the Rous-Whipple Award of the American Association of Pathologists, and the G.H.A. Clowes Memorial Award of the AACR.

In 1984, he was made a fellow of the Royal Society of Canada. In 1985, Farber was elected as the honorary member of the Society of Toxicologic Pathologists, the highest honor the society bestows. He was also vice president and president of the American Society of Experimental Pathology and president of Histochemical Society.

Farber is survived by daughter Naomi Farber, son-in-law Steven Grosby, and grandson Samuel Grosby.