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CMS to Trim Spending on Diagnostic Lab Tests

By Paul Goldberg

The Centers for Medicare and Medicaid Services appear to be executing a two-step strategy to shrink the $8 billion annual price tag of clinical diagnostic laboratory tests.

• On Sept. 25, CMS released a final payment determination for the Clinical Laboratory Fee Schedule that cuts payment by over 90 percent for some tests.

One of the industry leaders, Genomic Health, saw payments for Oncotype DX breast cancer tests drop by 15 percent, and a 79 percent drop for its colon cancer test. The determination involves a set of nine codes for advanced diagnostic laboratory tests.

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Guest Editorial

Local Medicare Contractors Bring Chaos To CMS Coverage of Next Generation Tests

By Dane Dickson

Yesterday, two Medicare administrative contractors—National Government Services and Cahaba Government Benefit Administrators—released draft local coverage determinations for next generation sequencing in advanced lung cancer.

The NGS LCD covers the initial diagnosis of lung cancer and Cahaba's LCD covers patients who have been re-biopsied to test for additional mutations that may have been missed on testing of the initial biopsy by older technology.

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Drug Combination Approved in Melanoma; Dana-Farber Challenges BMS Patent Rights

By Matthew Bin Han Ong

A combination of two Bristol-Myers Squibb immuno-oncology agents—Opdivo (nivolumab) and Yervoy (ipilimumab)—received an accelerated approval for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma.

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CMS Trimming the $8 Billion Spent on Diagnostic Lab Tests

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• On the same day, the agency announced its next step in implementing the Protecting Access to Medicare Act of 2014, requiring clinical laboratories to report on private insurance payment amounts and volumes for lab tests.

These data will be used to determine Medicare's payment for lab tests beginning Jan. 1, 2017. The proposed rule is published in the Federal Register. Medicare's fee schedule for lab tests was first adopted in 1984 and has remained relatively unchanged. The new system will be updated every three years for clinical diagnostic laboratory tests and every year for ADLTs to reflect market rates paid by private payers.

The series of cuts affects an area of oncology that plays a pivotal role in genomic medicine. However, questions of the methodology for validation of these tests, their quality, the clinical significance of information they yield, and the value they provide, are largely unsettled.

Whether you come at these questions from an anti-regulatory perspective or the skeptical perspective that requires proof of value of many of these tests needs to be thoroughly validated, you would likely agree that the Oncotype DX breast cancer test, which is now at the center of this controversy, is actually quite useful.

This notion would be reinforced by publication of the TAILORx study in New England Journal of Medicine Sept. 28. The results provide support for the use of Oncotype DX to identify a low-risk subset of women that can be spared postsurgical chemotherapy.

The study, led by ECOG-ACRIN, enrolled 10,253 women, providing them various treatment options depending on their scores from the Oncotype DX 21-gene recurrence test. Women were eligible for the trial if they had been recently diagnosed with hormone receptor-positive, HER2-negative breast cancer that had not spread to the lymph nodes.

Patients were assigned to receive endocrine therapy without chemotherapy if they had a recurrence score of 0 to 10, indicating a very low risk of recurrence (on a scale of 0 to 100).

Altogether, 1,626 women (15.9 percent) who had a recurrence score of 0 to 10 were assigned to receive endocrine therapy alone without chemotherapy. At five years in this patient population, the rate of invasive disease-free survival was 93.8 percent (95% CI: 92.4-94.9), the rate of freedom from recurrence of breast cancer at a distant site was 99.3 percent (95% CI: 98.7-99.6), the rate of freedom from recurrence of breast cancer at a distant or local-regional site was 98.7 percent (95% CI: 97.9-99.2), and the rate of overall survival was 98.0 percent (95% CI: 97.1-98.6).

"TAILORx is one of the first and most important trials using a gene panel test to determine how to most effectively treat women with breast cancer," Jo Anne Zujewski, of the NCI Cancer Therapy Evaluation Program, said in a statement.

"These excellent results in the low-risk subset of women should help spare a significant number of women from being overtreated with chemotherapy. We eagerly await the results for all women in the study with the goal of only treating women for their specific type of breast cancer and sparing them the side effects of unnecessary treatments."

Cutting Payment for Oncotype DX

Genomic Health officials noted the NEJM publication in their demand that CMS return the payment rate to the $3,416 level that was set by Medicare Administrative Contractor Noridian Healthcare Solutions in 2006. The new maximum set by CMS for the test is $2,900.

"CMS can and should adopt the MAC-established rate for the Oncotype DX breast cancer test, the only test validated to predict chemotherapy benefit as evidenced by multiple studies including one of the largest-ever adjuvant breast cancer trials published today in The New England Journal of Medicine," Kim Popovits, CEO, president, and chairman of the board of Genomic Health, said in a statement. "We will begin working immediately with CMS to ensure our currently established rate extends into 2016."

The payment level for Oncotype DX was

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reconsidered by CMS after the American Medical Association gave the test a CPT code, and, following its standard procedure, CMS proceeded to set the price.

In this endeavor, the agency could adopt one of two approaches. The first, called "crosswalk," pegs payment for a test to a similar test. The second, called "gapfill," essentially sets the price.

In an advisory committee meeting Aug. 26, which is posted on YouTube, CMS officials appear to pledge to use the gapfill approach. The final determination instead uses crosswalk, pegging payment for OncotypeDX to payment for a single-gene test.

Until it received a unique CPT code from AMA, Oncotype DX fell into the catchall category of codes called "Multi-Analyte Assays with Algorithmic Analysis" (CPT codes 81500-81599). Another catchall category used to pay for genomic tests, called "Tier 2 Molecular Pathology Procedures" (CPT codes 81400-81479), is not subject to this controversy.

The Coalition for 21st Century Medicine, a Washington umbrella group, put together an analysis of cuts in the final determination. The coalition recommends that CMS continue to pay for tests in accordance with the payment levels set by MACs.

A table with the coalition's analysis of some of the cuts appears on page 4.

Insiders say they were surprised to see the reduced payments, and some said they were unable to reproduce the methodology the agency used to make the cuts.

In his blog, Bruce Quinn, a Medicare expert with FaegreBD Consulting, said CMS appears to have miscalculated the payment level for Oncotype DX, producing the median price paid by state rather than by MAC territory.

"While the median of the 21 zones is $2,900, the median of the six MACs is $3,416, which seems to be what the regulation clearly instructs," Quinn wrote in his blog.

"If my reading is correct, as shown in these screenshots, it raises a question of whether CMS can accurately and rapidly calculate the correct weighted median for over a thousand laboratory tests from millions of data points through in-house methods that won't be available to inspect on a public Excel file like this one."

The question of methodology is relevant since affected companies would likely mount aggressive opposition to the agency's move. Indeed, the final payment level for Oncotype DX was set by a judge.

"We believe that CMS went against its own precedent—and its own advisory panel—in setting 2016 rates using a 'crosswalk' pricing approach," said Bonnie Anderson, president and CEO of Veracyte. "This undermines genomic tests like the Afirma Gene Expression Classifier, which has helped spare an estimated 20,000 patients from unnecessary thyroid surgery. Moreover, it flies in the face of innovation, which is the foundation of personalized medicine."

Payment for Veracyte's gene expression analysis of 142 genes went down by a third, from $3,200 to $2,151.81.

CMS on a Find-and-Cut Mission?

Insiders say CMS doesn't really know what tests it pays for. Administrators of MACs know only that a lot of charges come through under CPT codes 81500-81599 and 81400-81479.

By requiring in the proposed rules that the purveyors of these tests submit reimbursement data from private insurers would also help the agency to identify the purveyors of tests.

As it stands, the vast majority of assays that cost thousands of dollars and are used to determine treatment for cancer patients are not reviewed by government agencies before they enter the marketplace.

Under PAMA, Medicare can defer coverage decisions to the expertise of one or more contractors to either "establish coverage policies or establish coverage policies and process claims for payment for clinical laboratory tests."

Under the act, contractor Palmetto GBA may ultimately become an authority for determining which tests are paid for system-wide, observers say. However, no decision regarding Palmetto's designation has been made.

Over the past three years, Palmetto's program, MolDX, has been working to identify tests, establish what they are able to detect, assess their usefulness, and establish coverage.

Palmetto uses unique identifiers that make it possible to identify molecular tests and their purveyors. No other Medicare contractor has an analogous program. And since Palmetto knows what it pays for, it can set policies and refine them.

Last month's cuts come on top of a move by CMS to bundle payments for clinical laboratory and standard pathology tests. The agency's objective seems to be bundle ancillary services that have a mean cost of less than $100 per service.

Coalition for 21st Century Medicine
2016 Clinical Laboratory Fee Schedule
Pricing Recommendations

Code	Descriptor	Test Name (Laboratory)	C21 Rec	CMS Prelim Det'n	Difference % Diff	%Diff
81490	Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score	Vectra® DA (Crescendo Bioscience)	$586.50	$211.44	($375.06)	-64%
81525	Oncology (colon), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence score	Oncotype DX® Colon Cancer Assay (Genomic Health)	$3104.00	$644.62	($2,459.38)	-79%
81535	Oncology (gynecologic), live tumor cell culture and chemotherapeutic response by DAPI stain and morphology, predictive algorithm reported as a drug response score; first single drug or drug combination	ChemoFX® (Helomics)	$696.92	$664.98	($31.94)	-5%
+81536	+ Each additional single drug or drug combination (List separately in addition to code for primary procedure)		+ $387.74	$35.48	($352.26)	-91%
81538	Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival	VeriStrat (Biodesix)	$2112.00	$196.64	($1,915.36)	-91%
81540	Oncology (tumor of unknown origin), mRNA, gene expression profiling by real-time RT-PCR of 92 genes (87 content and 5 housekeeping) to classify tumor into main cancer type and subtype, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a probability of a predicted main cancer type and subtype	CancerTYPE ID (bioTheranostics)	$2900.00	$1,434.54	($1,465.46)	-51%
81545	Oncology (thyroid), gene expression analysis of 142 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (eg, benign or suspicious)	Afirma® Gene Expression Classifier (Veracyte)	$3200.00	$2,151.81	($1,048.19)	-33%
81493	Coronary artery disease, mRNA, gene expression profiling by real-time RT-PCR of 23 genes, utilizing whole peripheral blood, algorithm reported as a risk score	Corus® CAD (CardioDx)	$1,050.00	$644.64	($405.36)	-39%
81595	Cardiology (heart transplant), mRNA, gene expression profiling by real-time quantitative PCR of 20 genes (11 content and 9 housekeeping), utilizing subfraction of peripheral blood, algorithm reported as a rejection risk score	AlloMap® (CareDx)	$2821.00	$644.64	($2,176.36)	-77%

Guest Editorial

The Chaos of Coverage of Next Generation Sequencing

(Continued from page 1)

These latest decisions confuse the Medicare landscape profoundly. They ignore a well formulated MolDX LCD published earlier this year that covers NGS in lifetime non-smokers who were previously tested negative for certain alterations. Rather than build upon MolDx's approach, these rogue LCDs create a cacophony.

On the surface, yesterday's decisions would seem to be a victory for patients and providers. However, on deeper examinations informed by understanding of complex technologies involved, these new LCDs are threatening to create coverage chaos.

If we are going to unlock personalized medicine, we need to move carefully forward in unison, learning from almost every patient. The haphazard patchwork of coverage that is starting to emerge, as highlighted by these draft decisions, reflects misunderstanding of technology and its clinical application, creating the potential for more harm than hope. If our national goal is to truly advance personalized care, we must begin by achieving unification of the differences among MACs.

Far from going down the path to personalized medicine, we are now in danger of spiraling down on a perilous trajectory from which there may not be an easy recovery.

Problems with the LCDs

1) Inconsistency in the Medicare Program: Arguably, the only MAC with the expertise to understand the nuances and application of molecular testing is Palmetto's MolDX program. They were the first group to introduce a NGS coverage policy in NSCLC.

That policy, although not perfect, attempted to define the parameters of a high quality NGS test. In addition, also required that data would be collected to better understand the testing and its clinical outcomes.

This precedent was a good one: standardize testing, compare to previous knowledge, and collect outcomes to advance science. But, rather than build on and improve what Palmetto had started, both NGS and Cahaba decided to go in completely different directions and not follow the thoughtful precedent of Palmetto. Because testing is paid for where the lab geographically exists and not where the patient resides, a patient could have access to each of these policies as long as there is a lab in the jurisdiction that is covered by the MAC. Rather than consistency, there is utter chaos as to how to apply this new testing.

2) Lack of Support for FDA: Each one of the tests covered by these policies falls under the category of laboratory-developed tests.

FDA has been worried about the lack of consistency of LDTs especially when treatment decisions are based on the results of these tests. In 2014, the FDA announced to congress its intent to strengthen its oversight of LDTs. Margret Hamburg, then commissioner of the FDA said: "Ensuring that doctors and patients have access to safe, accurate and reliable diagnostic tests to help guide treatment decisions is a priority for the FDA. Inaccurate test results could cause patients to seek unnecessary treatment or delay and sometimes forgo treatment altogether. [This] action demonstrates the agency's commitment to personalized medicine, which depends on accurate and reliable tests to get the right treatment to the right patient."

By not attempting to approach anything but the most rudimentary standards of testing these new policies continue to perpetuate the Wild West of LDTs that the FDA has wanted to see better verified to ensure patients are receiving the highest quality care.

3) Non-Standardized Testing: NGS testing requires three components: a) pre-analytical preparation, b) sequencing, and c) data interpretation using complex algorithms. Each step in the process can lead to discrepancies depending on decisions made by the lab.

Currently, there has been virtually no comparison between testing from one lab to another. Even if both labs are of high caliber, they may disagree on what is the best method to approach each area.

Published data comparing certain platforms and their associated informatics, have shown a concordance of only 80 percent for the simplest DNA alterations, and less than 20 percent for more complicated alterations. False positives (finding alterations that do not really exist but are reported as being present) on the other hand, can make up as many as 50 percent of the alterations reported. As of such, a substantial portion of patients could receive treatment that they will not respond to due to being falsely told they have an alteration of erroneous reporting. In addition, these patients could be shunted from other valuable treatments that they could have received while chasing this analytical shadow.[1–3]

4) Increased Sensitivity Does Not Necessarily Mean Improved Outcomes: NGS can pick up alterations in DNA that only exist in a very small portion of the cells (low allele frequency). Depending on the sensitivity of an assay and the heterogeneity of the tumor specimen, only a small percentage of cells may contain the maker (as low as 1 percent) and yet be

reported as being positive for an alteration that directly guides treatment.

Given the low percentage of cells, even if there is 100 percent response to the identified cells, this may leave the vast majority of the tumor untreated and the patient with a poor outcome. Yet, it is also possible that these low frequency alterations are driving the entire system. As of such, the increased sensitivity needs to be reviewed with outcomes to determine clinical benefit.

5) Limited Published Information: Most payers require that every new intervention show clinical benefit before being covered as standard of care. The NCCN recommendation for testing for these alterations is listed as "Emerging Targeted Agents." The evidence for testing for these alterations is based on case reports (vemurafanib, BRAF V600E), ASCO abstracts (dabrafenib, BRAF V600E; crizotinib, MET amplification), and small studies. There are multiple ongoing trials that are waiting for final reporting on these agents.

As of such, even with a NCCN recommendation, there is not sufficient evidence to allow wholesale application. Furthermore, the NCCN has not discussed when to place these agents in the treatment sequence. Whereas EGFR, ALK and ROS1 have published data showing benefit when targeted therapy is used first line, it is unclear where to sequence these other agents. Ongoing clinical trials or outcome registries need to be finished before we will have complete answers.

Yet these emerging markers and other rare markers need to be analyzed, and we need to collect as much information as possible. Collecting data on every patient tested, allows these emerging targets to be verified for clinical benefit. Furthermore, there is no convincing published evidence that reanalysis of a tumor specimen through further biopsies can improve outcomes, and rather than re-biopsy a patient, it may be reasonable to save the morbidity and cost by analyzing the original specimen.[4]

6) ROS1/ALK Translocations and KRAS Testing: Although there are point mutations and small insertions in these genes that may create driver mutations, the vast majority of clinically significant alterations are translocations, and although these can be identified with specialized, high quality forms of NGS currently done by a few leading commercial and academic groups, most labs feel additional testing must be done to avoid false negatives.

ROS1 and ALK are listed as genes as part of the panel and rationale to allow coverage with NGS. In many cases the most common forms of NGS will miss the translocations if additional testing with fluorescent in situ hybridization (FISH) is not performed. Furthermore, unlike colon cancer, KRAS testing is not listed in the NCCN guidelines for lung cancer as a requirement before starting a tyrosine kinase inhibitor and there is published information that KRAS mutations do not harbor the same negative impact as it does in colon cancer[5-6].

By allowing these genes to be tested by any form of NGS, many patients will be put in harm's way, either missing appropriate testing to identify therapy, or inadvertently missing treatment based on erroneous understanding of KRAS in lung cancer.

7) Coding Issues: Many payers have regulations prohibiting payment for the same service twice, therefore if a payer covers NGS under CPT 81445 (5-50 gene solid tumor based on EGFR, ROS1, ALK, MET, BRAF, KRAS), and ROS1 and ALK have to be tested by FISH to look for translocations, and KRAS is thrown out as not being clinically actionable, the NGS gene number falls to three clinically necessary genes and below the 5-50 gene level and therefore should not be billed or covered. If the NGS can adequately replace the FISH testing, then it is a reasonable advance.

8) Lack of Information Collection: By allowing patients to receive testing and treatments that compete with existing trials and not collect any outcomes on these patients, we potentially place patients in harm's way by receiving ineffective treatments or missing key toxicities that if captured could be published and lead to better understanding of disease. Off-label use of drug in oncology has been widely practiced, but only when there has been information already published. By allowing off-label use of drug when there is not a body of literature, we run the risk of hampering rather than helping advance science.

9) Expanding Panels of Unclear Merit: By allowing broad panels to be reported, it is possible that the extended information will detract from those things that are truly beneficial for a patient. For example, if an estrogen receptor was identified as a biomarker on a tumor specimen in NSCLC and tamoxifen was given as a therapy rather than standard chemotherapy, it is almost certain that the patient would have a markedly inferior outcome.

10) Inadequate Payment to Guarantee High Quality Testing: Final fee schedules for payers are still unknown or in comment period. Although there are labs that can technically analyze a specimen for a low cost of a few hundred dollars, it is likely that the quality of this testing will be suboptimal. Unless adequate payment to ensure high quality testing, it will likely be a race to the bottom to see who can analyze specimens for the greatest margin, not highest quality.

Solutions to the Problem: Coverage with Requirement for Data Collection through a National Registry or Registries

Although there are concerns with the coverage policies presented, it is clear that NGS is a powerful tool in the war on cancer and needs to be available to patients. Some could argue that we need to hold off on coverage until the industry develops standards and outcomes, but many of the alterations that NGS can identify are rare and can be missed by old technology.

As of such, it is best to introduce high quality testing in settings where information can be collected and analyzed. This requires the use of high quality registries defined by the following characteristics:

1) Require Standardization of High Quality Testing: By making sure that the results of one lab are consistent with another, high quality standards need to be developed and verified. The College of American Pathologists and the Association of Molecular Pathologists are both working on these standards and the FDA is also developing guidance. Until these standards have been developed and vetted, interim standards must be developed and upheld by international leaders in both private and academic settings.

2) Compare Back to Companion Diagnostics Where Available: Clinical progress only advances in small steps rather than giant leaps. As of such, new standards must be compared back to the existing body of literature established by specific testing that was approved in connection with targeted therapies (companion diagnostics). In cases where there is no approved companion diagnostic, the closest standardized testing should be used for comparison. This way we can tie old and new literature together and determine if new testing improves outcomes.

3) Collect Outcomes: High-level clinical outcomes need to be collected and compared back to the new testing standard. These outcomes need to be reported relative to not only the alteration found, but also allele frequency. In this way we can determine threshold response levels that have already been established as being crucial for other disease states like Her2 and estrogen receptor testing in breast cancer. Further, collecting outcomes on each patient greatly expands the understanding of disease especially in alterations that have not been fully catalogued.

4) Attach Testing to Existing and Future Clinical Trials: By creating a high quality standard that can be reproduced, it is possible that this testing can serve as direct inclusion criteria for current and future trials. This way we can markedly increase accrual to trials, especially for new drugs and targets.

5) Aggregate All Data, Nationally and Internationally: Place all the information in a searchable centralized database that can be used to identify trends and improve treatments in an open format. Doing so, everyone can jointly learn from each other and look for new signals and associations that can be used to advance testing and treatment options. Furthermore, rare alterations can be identified and tracked and hopefully patients can be treated on small trials.

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The author is the CEO of the non-profit Molecular Evidence Development Consortium, MED-C, which was started to help address these emerging issues. Before resigning from Palmetto, he was involved in formulating that MAC's local coverage decision for next generation sequencing.

Dana-Farber Challenges BMS Drug Combination Patent Rights

(Continued from page 1)

The Oct. 1 announcement marks the first time FDA has approved a combination regimen of two immuno-oncology agents in cancer—both drugs had previously been approved as monotherapies for the same indication.

Yervoy is an anti-CTLA-4 inhibitor, while Opdivo is an anti-PD-1 drug.

BMS's exclusive patent rights to the PD-1 receptor pathway, however, are being challenged in intellectual property litigation. On the day the therapy was approved, Dana-Farber Cancer Institute announced its efforts to assert joint inventorship to five U.S. patents related to Opdivo's mechanism of action.

Dana-Farber filed a complaint in the U.S. District Court for the District of Massachusetts Sept. 25 seeking to correct the inventorship of the patents, which are directed to methods of treating cancer using a PD-1 antibody.

Officials for Bristol-Myers Squibb said they are reviewing the complaint and declined to comment.

The approval of the Opdivo-Yervoy regimen is based on data from the study CheckMate-069, which was the first to report outcomes of the regimen in previously untreated patients with unresectable or metastatic melanoma; the approval was based on the surrogate endpoints of tumor response rate and durability of response.

As an accelerated approval, continued approval for this indication is contingent upon verification and description of clinical benefit in confirmatory trials.

Patients with BRAF wild-type melanoma that received the Opdivo-Yervoy regimen demonstrated a confirmed objective response rate of 60 percent, a statistically significant increase (95% CI: 48-71; $p<0.001$) compared to 11 percent of the patients that received Yervoy alone (95% CI: 3-25). Objective response rate served as the study's primary endpoint.

Complete responses were seen in 17 percent of patients. Partial responses were seen in 43 percent of the regimen group and 11 percent of the Yervoy monotherapy group.

The Opdivo-Yervoy regimen demonstrated a 60 percent reduction in the risk of progression compared to Yervoy alone (HR=0.40; 95% CI: 0.22-0.71; $p<0.002$). Median PFS was 8.9 months with the combination (95% CI: 7.0, NA) and 4.7 months with Yervoy alone (95% CI: 2.8-5.3).

According to BMS, this trial provides clinical rationale for targeting the immune system with both agents in metastatic melanoma.

Metastatic melanoma has been a difficult disease to treat, said Jedd Wolchok, chief of Melanoma and Immunotherapeutics Service at the Department of Medicine and Ludwig Center at Memorial Sloan Kettering Cancer Center.

"Now, a new treatment option based on the combination of two valued immuno-oncology agents demonstrates significant efficacy versus ipilimumab (Yervoy) in metastatic melanoma," Wolchok said in a statement. "Today's approval represents a step forward for the melanoma community, providing hope for patients with metastatic melanoma."

The pace of change in melanoma treatment is a testament to advances in both immunotherapy and targeted therapy research, said Louise Perkins, chief scientific officer of the Melanoma Research Alliance.

"Based on the findings reported in scientific meetings and prestigious medical publications, the combination of ipilimumab and nivolumab are clearly active against melanoma," Perkins said in a statement. "We're pleased that both BMS and the FDA acted quickly so that patients will have access to the latest advances in melanoma treatment."

Dana-Farber Files Suit

BMS's exclusive right to Opdivo's primary mechanism of action, which inhibits the programmed death-1 immune checkpoint, is built on five patents.

According to the Dana-Farber complaint, the U.S. Patent Office incorrectly issued the five patents directed to the PD-1 pathway, naming Tasuku Honjo and three colleagues at Kyoto University as the sole inventors.

Three of these patents—U.S. Patents 8,728,474, 9,067,999, and 9,073,994—are subject to patent infringement proceedings filed by BMS and Ono Pharmaceutical Co. Ltd. against Merck in Delaware federal court.

The Dana-Farber legal action seeks to add one of its scientists, Gordon Freeman, and another researcher, Clive Wood, as co-inventors on the patents. Wood worked at Genetics Institute in the 1990s and 2000s.

The patents were issued as recently as July 2015 to Ono and Honjo, who then licensed their rights exclusively to BMS.

Dana-Farber declined to comment on BMS's Opdivo.

Anti-PD-1 therapies work by blocking the PD-1/PD-L1 pathway, the centerpiece of a mechanism that

cancer cells use to escape attack by a patient's T cells, thereby freeing the immune system to launch a more effective response against the disease.

Dana-Farber's complaint alleges that Freeman, Wood, and Honjo collaboratively conducted the research leading to this treatment strategy.

Dana-Farber is taking this step "to confirm its ability to grant non-exclusive licenses to a wider range of companies in order to enable a faster pace of research and drug development, which will, we hope, provide greater benefit to more patients sooner," said Chief Scientific Officer Barrett Rollins in a statement.

Dana-Farber said it has non-exclusively licensed cancer immunotherapy-related patents on inventions made by Freeman, an immunologist at the institute, to nearly a dozen companies over the past decade.

In 2014, the Cancer Research Institute, an organization that funds immunotherapy research, named Honjo and Freeman among four winners of its William B. Coley Award "for their collective contributions to the discovery of the PD-1 receptor pathway."

The next step in the legal process is for BMS to file responses to the complaint later this fall, after which the court will set a schedule to resolve the question of inventorship for each of the patents.

BMS and Ono have pending lawsuits against Merck for patent infringement relating to Merck's PD-1 antibody product Keytruda.

"In these lawsuits, Bristol-Myers Squibb and Ono assert that Merck infringes or will infringe our patents," BMS said in a statement to The Cancer Letter. "The purpose of these lawsuits is to seek compensation from Merck for its infringement of our intellectual property rights and to protect our immuno-oncology business. These lawsuits do not seek to interfere with patient access to Merck's product.

"As a leader in cancer treatment and a pioneer in the area of immuno-oncology, we are excited by the progress that we and others have been making in this field—progress that holds the real potential of longer, better lives for the patients we serve. In fact, we believe that access to immuno-oncology medicines is absolutely critical to the health outcomes of many cancer patients and is the key to their long-term survival.

"At the same time, our pioneering efforts in the immuno-oncology field must be protected. To this end, BMS and Ono have established intellectual property rights protecting our immuno-oncology assets, including Opdivo (nivolumab).

"This protection has, in turn, allowed us to develop a deep and broad portfolio of innovative medicines. And it is in this spirit that we are defending our intellectual property rights against infringement."

On Oct. 2, FDA granted accelerated approval to Keytruda in metastatic non-small cell lung cancer.

Capitol Hill

Congress Averts Shutdown, Funds NIH Through December

Congress passed a continuing resolution Sept. 30—averting a shutdown—that will fund the federal government at current levels through Dec. 11.

Funding for both NIH and NCI dipped slightly as part of a 0.21 percent cut to all non-defense discretionary agencies.

President Barack Obama is expected to sign the measure, which passed seven hours before fiscal 2015 ended.

"We have made tremendous progress in our understanding and treatment of cancer over the last four decades," said Richard Schilsky, chief medical officer of the American Society for Clinical Oncology. "Progress that will result in the number of people living with cancer expected to increase from 1.66 million to 2.14 million over the next 15 years.

"But our nation's investment in cancer research has remained stagnant since 2003, not even keeping pace with biomedical inflation. We cannot afford to continue on this path, as it will surely result in missed or delayed opportunities to continue to accelerate progress against cancer."

USPSTF Speaks on its Role In the Affordable Care Act

The U.S. Preventive Services Task Force published a viewpoint in the Journal of the American Medical Association to clarify how their recommendations are linked to the Affordable Care Act coverage mandate—and how they believe clinicians, payers, and the public should interpret their recommendations.

The viewpoint, titled "Evidence-Based Clinical Prevention in the Era of the Patient Protection and Affordable Care Act: The Role of the US Preventive Services Task Force," describes how some have misinterpreted task force grades of C or I as recommendations against screening or even against coverage.

"This is not the intent of the task force," the article reads.

"A C grade is still a positive recommendation that recognizes small net benefit, and the task force recommends that clinicians offer C-rated services to patients after considering the presence of patient risk factors, patient preferences, local disease prevalence, and availability of services."

"Similarly, an I grade, a declaration of insufficient evidence, is not a recommendation against coverage but rather a call for more research."

Other highlights of the article include: that payers currently have the latitude to cover preventive services using well-established procedures to assess coverage policy, and lawmakers also have the power to require coverage of selected non-A and non-B graded services; and the linkage between task force recommendations and the ACA coverage mandate sets a minimum standard for coverage of preventive services.

The task force maintains that "the science on effectiveness—although foundational—is only one factor that needs to be considered in developing coverage policy."

On the subject of mammography screening for younger women, one of USPSTF's most controversial recommendations, the editorial states:

"The USPSTF found that screening mammography is beneficial for women between the ages of 40 and 49 years.

"The incremental benefit of starting before age 50 years is small, and the false-positives and unnecessary biopsies were significant. A woman who understands the harms but values any chance of reducing her risk of dying of breast cancer, no matter how small, should be able to make an informed decision to begin screening before age 50 years. The task force supports that individual decision, but understands that in the absence of coverage, fewer women will make that choice.

"However, the USPSTF cannot reinterpret the science and exaggerate the net benefit simply to ensure coverage. Payers, however, have the option of providing coverage (as many do). Lawmakers have the option of requiring coverage for mammography (as they have done in the past)."

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Funding Opportunity

Pershing Square Sohn Cancer Research Alliance Prize For Young Investigators

The Pershing Square Sohn Cancer Research Alliance is taking applications for its Prize for Young Investigators in Cancer Research.

The prize of $200,000 per year for up to three years is awarded annually to at least five New York City-based scientists, enabling them to continue to pursue research at a stage when traditional funding is lacking. Each prize winner is also given a mentor in the pharmaceutical industry and the opportunity to present his or her work to scientific and business audiences.

In May 2015, PSSCRA awarded the prize to six winners: Timothy Chan, of Memorial Sloan Kettering Cancer Center; Arvin Dar, of the Icahn School of Medicine at Mount Sinai; Evripidis Gavathiotis, of Albert Einstein College of Medicine; Moritz Kircher, of MSKCC; Christine Mayr, of MSKCC; and Sohail Tavazoie, of The Rockefeller University.

In order to apply, applicants must have between two and eight years of experience running their own laboratories and must have a Ph.D., M.D., or M.D.-Ph.D. or equivalent. The deadline to submit a letter of intent is Nov. 9.

More details on the application process, including full eligibility criteria, are available on their website.

In Brief

O'Reilly to Step Down as Chair Of Pediatrics at MSKCC

RICHARD O'REILLY will step down as chair of pediatrics at **Memorial Sloan Kettering Cancer Center**, after nearly 30 years. He will serve as chair until a successor is found, according to Physician-in-Chief Jose Baselga.

O'Reilly's retirement was announced in an email from Baselga to MSK community members.

The email follows:

I am writing today to share the news that Richard J. O'Reilly will be stepping down as Chair of Pediatrics, after nearly 30 years in this role. He will continue to serve as Chair until a successor is in place and, fortunately for us, will remain a vital member of the MSK faculty and our scientific community.

A world-renowned immunologist and physician, Dr. O'Reilly has pioneered the development and clinical application of cellular therapies to treat lethal diseases of immunity and hematopoiesis. His visionary leadership and scientific achievements have created and fostered significant improvements in outcomes for patients with cancers of the blood and marrow, and both genetic and acquired disorders of the immune system.

In 1973, Dr. O'Reilly established the bone marrow transplant program at MSK for both adults and children, one of the first transplant centers in the United States, and was the first to conduct a successful marrow transplant from an unrelated, compatible donor, an approach now used successfully on well over 2,500 cancer patients annually. The transplant method of T-cell depletion, which he co-developed, transformed the field, eliminating the "boy in the bubble," when children born without an immune system required highly sterile environments in which to live, and achieving cures in more than 70 percent of these babies. He was a principle founder of the National Marrow Donor Program, a nationwide system for identifying unrelated marrow donors that now includes more than 23 million volunteer donors and extends transplants to more than 7,000 patients yearly who lack a matched familial donor. Most recently, his work has demonstrated the potential of adoptive immunotherapy after marrow grafts, with life-saving results.

As Chair of Pediatrics, Dr. O'Reilly created one of the world's largest programs in pediatric oncology. His unwavering commitment to excellence has led to countless advances in cancer treatments and improved outcomes for children and young adults, focusing on both curative approaches as well as minimizing long-term effects. He has built a cadre of outstanding, recognized physicians and scientists in these fields and fostered a new generation of leaders worldwide. His dedication to improving both the lives and experiences of our youngest patients is unwavering.

Along the way, Dr. O'Reilly has authored or co-authored more than 300 articles, papers or research studies. His colleagues have recognized the value of his work by bestowing on him the Pediatric Oncology Award from the American Society of Clinical Oncology in 2005, the Lifetime Achievement Award from the American Society for Blood and Marrow Transplantation, The Timothy Gee Humanity in Medicine Award from the Lauri Strauss Leukemia Foundation and Boerhaave Medal for Achievements in Hematology from Leiden University in the Netherlands, to name a few.

Needless to say, identifying a successor is no easy feat. I have asked Charles Sawyers to lead the search

committee to find the next Chair of Pediatrics. We will share additional information as it becomes available.

In the meantime, we will find many opportunities to recognize Dr. O'Reilly's unmatched career, extraordinary contributions and significant achievements in both the field of bone marrow transplantation and as our distinguished Chair of Pediatrics.

JAMES WADE was named deputy director for quality and network development at the **Inova Dwight and Martha Schar Cancer Institute**.

Wade has held faculty positions at Johns Hopkins University, University of Maryland, University of Washington, Fred Hutchinson Cancer Center and Medical College of Wisconsin prior to his most recent position as chairman at Geisinger Cancer Institute.

The institute will serve as a cornerstone of the Inova Center for Personalized Health, announced earlier this year.

LORENZ STUDER, director of the Center for Stem Cell Biology at Memorial Sloan Kettering Cancer Center, was named a fellow by the **MacArthur Foundation**.

Studer is a stem cell biologist researching large-scale generation of dopaminergic neurons for transplantation, which could provide treatment for Parkinson's disease and other neurodegenerative diseases.

Studer devised novel protocols for the transition of human pluripotent stem cells into neural and neural crest tissues and for the production of functional, stable dopaminergic neurons in large quantities.

In long-term studies, Studer demonstrated that the cells produced by his method are able to integrate into the brain, function effectively as the substantia nigra neurons that die in Parkinson's disease, and do not proliferate. When transplanted into animal models, Parkinsonian symptoms significantly improved, giving hope for this replacement therapy as a treatment for Parkinson's disease in humans.

Studer held several research positions at both the University of Bern and the National Institute of Neurological Disorders and Stroke within the NIH before joining the Memorial Sloan-Kettering Cancer Center, where he is currently founding director of the Center for Stem Cell Biology and a member of the Developmental Biology Program.

The full list of MacArthur Fellows is available here. https://www.macfound.org/fellows/class/2015/

THREE INVESTIGATORS were named recipients of the 2015 **Paul Marks Prize for Cancer Research** by Memorial Sloan Kettering Cancer Center. The award recognizes investigators age 45 or younger for their efforts in advancing cancer research.

The winners are **Bradley Bernstein**, of Massachusetts General Hospital; **Howard Chang**, of Stanford University; and **Daniel Durocher**, of the Lunenfeld-Tanenbaum Research Institute. Each will receive an award of $50,000 and speak about his research at a scientific symposium on December 3. The award was named for Paul Marks, president emeritus of MSK.

Bernstein is a professor of pathology at Massachusetts General Hospital and Harvard Medical School and an Institute Member of the Broad Institute of MIT and Harvard. His research is focused on epigenetics. Specifically, his lab studies how the protein scaffold called chromatin packages long strands of DNA in the nucleus of each cell, and how this packaging influences both normal development and cancer.

Chang is a professor of dermatology at Stanford University and a faculty member of its cancer biology PhD and epithelial biology programs. He is also director of the Center for Personal Dynamic Regulomes at Stanford.

His lab studies how cells know where they're located in the body and how that effects metastasis. In his recent work, Chang discovered that long noncoding RNAs helps cells sense where they are. One of the first lncRNAs he discovered is called HOTAIR, which he found could be used to predict whether breast cancer will spread.

Durocher is assistant director of the Lunenfeld-Tanenbaum Research Institute, part of the Sinai Health System in Toronto and a professor of molecular genetics at the University of Toronto.

He is being recognized for his research on how cells maintain the integrity of their genomes, and especially how they deal with a particular type of damage called the DNA double-strand break, which can be caused by phenomena like ionizing radiation and exposure to certain chemicals, but they can also occur when cells undergo regular division. Much of his recent research has focused on how the BRCA1 protein helps cells respond to DNA damage.

SANTOSH KESARI joined the **Providence Saint John's Health Center** and its John Wayne

Cancer Institute.

Kesari will serve as director of neuro-oncology, professor of neuro-sciences and chairman of the Department of Translational Neuro-Oncology and Neuro-therapeutics.

His research focuses on immunotherapy, molecular genetics, drug development for cancer stem cells and development of biomarker-based clinical trials for cancers.

Before joining Providence Saint John's, Kesari was professor of neurosciences at the University of California, San Diego, School of Medicine, and director of neuro-oncology at Moores UC San Diego Cancer Center.

KIRAN TURAGA was named the Sharon K. Wadina Endowed Professor in Sarcoma Research at the **Medical College of Wisconsin**.

Turaga serves as associate professor of surgery and director of Froedtert & the Medical College of Wisconsin's Regional Cancer Therapy Program.

The professorship is named for Sharon "Sherry" Wadina, who was diagnosed with sarcoma of the inferior vena cava and referred to the Froedtert & MCW Clinical Cancer Center. Wadina supported research in soft tissue sarcoma and formed the endowed chair position, one of the few in the U.S. that focuses on sarcoma research.

Turaga joined MCW in July 2010, and serves as a section editor for the Annals of Surgical Oncology. He also serves on the Mesothelioma Research Foundation's scientific advisory board.

JAN SCHLÜCHTER was named chief commercial officer of **Myriad Genetics GmbH**, effective Oct. 15.

Myriad Genetics GmbH is the Zurich-based international subsidiary of Myriad Genetics Inc. and oversees the international operations outside the U.S. He will focus on commercializing the company's portfolio of hereditary cancer tests, companion diagnostics and test kits.

Most recently, Schlüchter served as global head of key account management at the Novartis headquarters in Basel, Switzerland. Previously, he held general management roles in Greece and Germany.

A STAND UP TO CANCER CANADA DREAM TEAM researching new approaches to treating triple-negative breast cancer and other aggressive types of breast cancer has been formed following a $9 million investment from a coalition of funders.

The Dream Team reflects a collaboration of Stand Up To Cancer Canada, the Canadian Breast Cancer Foundation, with support from CIBC and the Ontario Institute for Cancer Research. The American Association for Cancer Research International - Canada, is SU2C Canada's scientific partner.

Tak Mak, director of the Campbell Family Institute for Breast Cancer Research at Princess Margaret Cancer Centre in Toronto, is leader of the Dream Team.

The Dream Team co-leader is **Samuel Aparicio**, the Nan and Lorraine Robertson chair in breast cancer research at the University of British Columbia in Vancouver and head of the Department of Breast and Molecular Oncology at the BC Cancer Agency.

The SU2C Canada-CBCF Breast Cancer Dream Team is the first to be announced since SU2C Canada was launched in 2014. The team is funded over a period of four years for $6 million provided by SU2C and by CBCF, with support from CIBC, and $3 million from OICR. The team will conduct clinical trials in six provinces, with those in Ontario funded by the OICR commitment.

The principal investigators of the Dream Team include **Morag Park**, director of the Rosalind and Morris Goodman Cancer Research Centre at McGill University; **Kathleen Pritchard**, senior scientist at Sunnybrook Research Institute at the University of Toronto; and **Karen Gelmon**, professor of medicine at the University of British Columbia in Vancouver.

Serving as patient advocates are **Randy Mellon** of Toronto, breast cancer survivor; **Zuri Scrivens** of Langley, British Columbia, breast cancer survivor; and **Wendie den Brok**, advanced TNBC survivor and medical oncologist in training at the BC Cancer Agency in Vancouver. Den Brok will also serve as an investigator on the scientific team.

THE CENTER TO ADVANCE PALLIATIVE CARE and **National Palliative Care Research Center** published a state-by-state report card evaluating access to palliative care.

The report, "America's Care of Serious Illness: 2015 State-by-State Report Card on Access to Palliative Care in Our Nation's Hospitals," was published in the Journal of Palliative Medicine, describes how millions of Americans living in the south of the United States, as well as in Alaska, Kansas, New Mexico and Wyoming, still have inadequate access to palliative care teams.

https://reportcard.capc.org/

The report's key findings include that only 23 percent of for-profit hospitals have palliative care, and that not-for-profit hospitals are seven-times more likely to have a palliative care team than for-profits; 90 percent of hospitals with 300 beds or more have palliative care teams, as well as 96 percent of teaching hospitals; and that 17 states received a grade of A (up from 3 in the 2008 report and 7 in the 2011 report): Connecticut, Maryland, Massachusetts, Minnesota, Montana, Nebraska, Nevada, New Hampshire, New Jersey, Ohio, Oregon, Rhode Island, South Dakota, Utah, Vermont, Washington and Wisconsin.

In Brief

Accelerated Approval Granted To Keytruda in NSCLC

FDA granted accelerated approval for Keytruda (pembrolizumab) to treat patients with advanced non-small cell lung cancer whose disease has progressed after other treatments and with tumors that express the protein PD-L1.

Keytruda is approved for use with a companion diagnostic, the PD-L1 IHC 22C3 pharmDx test, the first test designed to detect PD-L1 expression in non-small cell lung tumors.

In 2014, Keytruda was approved to treat patients with advanced melanoma following treatment with immunotherapy ipilimumab. Another drug, Opdivo (nivolumab), manufactured by Bristol-Meyers Squibb, also targets the PD-1/PD-L1 pathway and was approved to treat squamous non-small cell lung cancer (a certain kind of NSCLC) in 2015.

The effectiveness of Keytruda for this use was demonstrated in a subgroup of 61 patients enrolled within a larger multicenter, open-label, multi-part study.

The subgroup consisted of patients with advanced NSCLC that progressed following platinum-based chemotherapy or, if appropriate, targeted therapy for certain genetic mutations (ALK or EGFR). This subgroup also had PD-L1 positive tumors based on the results of the 22C3 pharmDx diagnostic test.

Study participants received 10 mg/kg of Keytruda every two or three weeks. The major outcome measure was overall response rate: tumors shrank in 41 percent of patients treated with Keytruda and the effect lasted between 2.1 and 9.1 months.

FDA had previously granted Keytruda breakthrough therapy designation for this indication. The drug also received priority review status. Approved under the agency's accelerated approval program, an improvement in survival or disease-related symptoms in patients being treated with Keytruda has not yet been established.

Keytruda is marketed by Merck & Co., and the PD-L1 IHC 22C3 pharmDx diagnostic test is marketed by Dako North America Inc.

The European Medicines Agency Committee for Medicinal Products for Human Use delivered two positive opinions, recommending marketing authorization for Kyprolis and Blincyto.

Kyprolis (carfilzomib) received a recommendation for a combination with lenalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

Blincyto (blinatumomab) was recommended a conditional marketing authorization for the treatment of adults with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukemia.

"The results of the ASPIRE study demonstrate that Kyprolis extended the time patients live without their disease progressing. Additionally, there is a critical need for new therapies for patients with relapsed or refractory B-cell precursor ALL," said Sean Harper, executive vice president of Research and Development at Amgen.

Kyprolis is a proteasome inhibitor for use in the treatment of patients with relapsed multiple myeloma. Blincyto is the first clinical validation of the bispecific T cell engager immunotherapy platform.

The CHMP positive opinions will now be reviewed by the European Commission, and if granted, the two products will have marketing authorization in the 28 member countries of the European Union (EU), as well as Iceland, Lichtenstein and Norway.

Kyprolis was granted orphan drug designation by the EMA in 2008, and in February, its marketing authorization application was granted accelerated assessment by the EMA. Kyprolis (carfilzomib) for Injection was approved as a monotherapy in the U.S. in July 2012, and in combination with lenalidomide and dexamethasone in July 2015.

Kyprolis is a product of Onyx Pharmaceuticals Inc. Onyx Pharmaceuticals is a subsidiary of Amgen and holds development and commercialization rights to Kyprolis globally, excluding Japan.

Blincyto is a bispecific CD19-directed CD3 T cell engager antibody construct that binds specifically to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T cells.

Blincyto was granted breakthrough therapy and priority review designations by FDA, and received accelerated approval in the U.S. for the treatment of Ph- relapsed or refractory B-cell precursor ALL.

FDA granted Priority Review for defibrotide for the treatment of patients with hepatic veno-occlusive disease, also known as sinusoidal obstruction syndrome, with evidence of multi-organ dysfunction following hematopoietic stem-cell transplantation.

FDA review of the new drug application is expected to be completed by March 31, 2016.

The application, submitted by Jazz Pharmaceuticals plc, includes safety and efficacy data from three clinical studies of defibrotide for the treatment of hepatic VOD with MOD following HSCT, as well as a retrospective review of registry data from the Center for International Blood and Marrow Transplant Research. The safety database includes over 900 patients exposed to defibrotide in the clinical development program for the treatment of hepatic VOD.

Defibrotide was granted Orphan Drug Designation by the FDA in May 2003 and has Fast Track designation. Defibrotide is being made available as an investigational new drug free of charge through an expanded access Treatment Protocol that is currently enrolling patients diagnosed with VOD in the U.S. In Europe, defibrotide is marketed under the name Defitelio.

Aspen Park Pharmaceuticals Inc. acquired worldwide rights to APP-111, first-in-class oral, antitubulin targeting agent for the potential treatment for the form of castration resistant prostate cancer, from The Ohio State University, through the Ohio State Innovation Foundation.

APP-111 is used to target cancer that does not respond or becomes resistant to currently available androgen receptor antagonists and testosterone-reducing agents.

"It has now become clear that there is significant cross-resistance that occurs between androgen receptor antagonists (enzalutamide) and testosterone reducing agents (abiraterone) in men with metastatic castration resistant prostate cancer. So after a patient fails one of these drugs, a new drug with a different mechanism of action is required," said Mario Eisenberger, the R Dale Hughes Professor of Oncology and Professor of Urology, at The Johns Hopkins Hospital. "Cytotoxic agents that target tubulin remain the most effective agents against advanced prostate cancer, but currently they can only be administered IV and have significant side effects like neurotoxiticity and myelosuppression. An orally available agent, like APP-111, that targets tubulin would be expected to have activity against prostate cancer and would be an important addition to the armamentarium for treatment of castration resistant prostate cancer."

This small molecule drug binds to microtubules and prevents polymerization which has been shown to not only block cell division and induce cell death, but also disrupts androgen receptor signaling required for tumor growth, according to Aspen Park, which expects APP-111 to be in phase Ia/Ib clinical studies in late 2016.

UbiVac formed a collaboration with Janssen Biotech Inc. one of the Janssen Pharmaceutical Companies of Johnson & Johnson, to develop new preclinical and clinical versions of UbiVac's proprietary DRibble immunotherapy for use in preclinical studies of oral cancer.

The Johnson & Johnson Innovation Center in California facilitated the research agreement on behalf of the Janssen Disease Interception Accelerator.

UbiVac will receive an upfront payment, plus additional financial commitments, contingent upon reaching certain pre-determined research, development and manufacturing milestones. In addition to funding the research, Janssen has an option for further development and licensing of the new DRibble immunotherapy.

City of Hope and Sorrento Therapeutics Inc. formed a company, LA Cell Inc., to focus on the development of cell-penetrating antibody therapies. LA Cell has exclusively licensed technology developed at City of Hope that enables modified monoclonal antibodies to penetrate into cells and target disease-causing molecules.

The deal totals over $170 million and includes an equity provision as well as upfront and milestone payments to City of Hope.