# BioWorld MedTech

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Cala Health Inc.

## Cala Health scoops up $50M in series C funding

*By Liz Hollis, Staff Writer*

Burlingame, Calif.-based Cala Health Inc., which is developing wearable therapies for chronic disease, completed a $50 million series C financing. The funds are earmarked for introducing the Cala Trio for patients with essential tremor and expanding the company's therapeutic pipeline. In addition, Stacy Enxing Seng will join Cala as an independent director and board chair.

New investors include Novartis, Baird Capital, Lifesci Venture Partners and Triventures. All existing investors participated in the round, including Johnson & Johnson Innovation – JJDC Inc., Lux Capital, Lightstone Ventures, Action Potential Venture Capital, Drx Capital and Gv.

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## Auris Health's Monarch robotic system seen as highly accurate in early clinical results

*By Meg Bryant, Staff Writer*

Early first-in-human results show Auris Health Inc.'s robotic Monarch platform successfully aids in the diagnosis of peripheral pulmonary nodules using a combination of direct visualization, navigational guidance and a radial endobronchial ultrasound probe.

The multicenter, prospective, single-arm BENEFIT pilot and feasibility study is designed to demonstrate the use of the robotic endoscopic system in accessing and doing biopsies of peripheral pulmonary lesions. In initial results from 24 trial participants, the Monarch system met its primary endpoint of localizing targeted lesions confirmed via a radial endobronchial ultrasound probe in 92% of cases. The Monarch platform was used in conjunction with a navigational bronchoscopy with biopsy. Secondary endpoints, which were not analyzed in the preliminary

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## Harmonization needed, but transparency bills too sweeping, House panel told

*By Mari Serebrov, Regulatory Editor*

With seven or eight states now imposing different transparency requirements on drug companies, harmonizing those requirements under federal law is a high priority for the pharmaceutical industry, Lisa Joldersma, senior vice president for insurance and state issues at Pharmaceutical Research and Manufacturers of America, told a U.S. House subcommittee Tuesday.

But some of the bipartisan bills the Energy and

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## New DoJ memo avoids all-or-nothing cooperation credit seen in Yates memo

*By Mark McCarty, Regulatory Editor*

The history of the U.S. Department of Justice's (DoJ) approach to False Claims Act enforcement is littered with memos, but the latest memo dealing with FCA prosecutions offers partial credit for cooperation that is short of utterly exhaustive, including identification of all individuals involved in the violative behavior. This represents a departure from the so-called Yates memo, which stated that for a company to receive any

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## Longas introduces DNA sequencing technology for virtual long read capability

*By Nuala Moran, Staff Writer*

LONDON – Longas Technology Pty Ltd. has unveiled new DNA sequencing technology it claims can convert industry standard short read sequencers into virtual long read machines, increasing accuracy in resolving genomic repeats that occur in multiple locations and reducing the cost of assembling a complete genome.

The combination of novel chemistry and associated software has been tested on Illumina Inc. and BGI Group next-generation sequencers, increasing read lengths from a few hundred base pairs to 15,000 base pairs.

The technology, called Morphoseq, uses a proprietary chemical reaction to introduce

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## Study finds AI more accurate than radiologists in lung cancer detection

*By Stacy Lawrence, Staff Writer*

Artificial intelligence could offer a means to conduct large-scale cancer screening via automated image analysis that does not lead to a flood of false positives. Cancer screening guidelines for common cancers, such as breast and prostate, have been so plagued by false positives, inconclusive results and overtreatment of low-grade cancers that screening

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**BioWorld MedTech's Oncology Extra**

Regulatory Editor Mark McCarty and Senior Science Editor Anette Breindl on one of med-tech's key sectors

Read this week's edition

## Other news to note

Yarkona, Israel-based digital diabetes solution provider, **Glucome** is exploring expansion of its partnership with Germany-based **Merck KGaA**. This follows a successful joint pilot in several Vietnam hospitals, facilitated by a third party. In August 2018, Merck partnered with Glucome to assess the advantages of Glucome's digital diabetes care solution against the current standard of care in Vietnam. Glucome is now preparing to launch the digital platform commercially in Vietnam and is in the process of evaluating additional global markets for expansion.

**Lifescan Inc.**, of Milpitas, Calif., entered an exclusive agreement with Telford, Pa.-based **Sanvita Medical LLC**, to market continuous glucose monitoring (CGM) sensors. Sanvita is a subsidiary of Nova Biomedical Corp. Through this collaboration, the companies plan to launch CGM systems in North America and select countries in Europe as early as mid-next year and then expand into other markets around the world. The new CGM products will integrate with Lifescan's Onetouch Reveal digital portfolio, including the Onetouch Reveal app.

**Medacta USA** said it plans to relocate its U.S. headquarters to Franklin, Tenn. from Chicago. The company will invest $2.5 million and create more than 50 jobs in Franklin over the next five years. The company will establish its U.S. headquarters and a research and development lab in Bowers Park. A subsidiary of Switzerland-based **Medacta International**, Medacta USA specializes in the design of orthopedic products and the development of accompanying surgical techniques.

New York-based **Pavmed Inc.** reported that the first group of nine patients with carpal tunnel syndrome underwent successful Carpx procedures as part of the first-in-human (FIH) safety study Pavmed is conducting in support of its planned U.S. FDA 510(k) re-submission. The procedures were performed at St. George's Hospital in Christchurch, New Zealand, by Terrence Creagh and Howard Klein M.D. The patients were enrolled in the FIH safety study and underwent preoperative testing, including electrodiagnostic testing, according to the study protocol developed in collaboration with the FDA. The patients then underwent successful minimally invasive carpal tunnel release using the Carpx device. There were no device-related adverse events. As per the protocol, patients will undergo post-operative clinical follow-up at two weeks and 90 days, with repeat electrodiagnostic testing during the 90-day follow-up to document the protocol's safety endpoint. Another group of patients are scheduled to undergo Carpx procedures in the coming weeks. Once these procedures and 90-day follow-up are completed, Pvmed will resubmit the Carpx 510(k) application incorporating the clinical safety and effectiveness data from the study.

Minneapolis-based **Precision Therapeutics Inc.**, a company focused on applying artificial intelligence to personalized medicine and drug discovery, said its Helomics division has been selected as the preferred laboratory to provide laboratory services for the recently funded National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) grant to develop test kits, which will be branded as Accukit, for screening of microbial and viral contamination of biopharmaceuticals with its partner Wilmington, N.C.-based **Accugenomics Inc.** The Accukit development is in partnership with Accugenomics, Celgene, Merck and North Carolina State University with the goal of improving biosafety testing for biopharmaceutical products. According to the grant proposal, Helomics will collaborate with Accugenomics to develop a highly sensitive next generation sequencing-based testing platform to streamline screening of microbial and viral contamination of biopharmaceuticals. The Accukit will be able to detect 22 known adventitious viruses and bacteria at sensitivity levels required to pass strict quality control standards. The platform is also easily extendable to detect potential new contaminating agents.

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## Cala

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In the wake of the financing, Cala Health is preparing for the limited release of the prescription Cala Trio therapy and will adopt a strategy that delivers prescription therapy with the convenience of consumer electronics by serving the patients as a direct distributor. The company has estimated that more than 7 million people in the U.S. have essential tremor.

"Cala Health is advancing neuromodulation therapy options without the need for surgery, using body-worn electronics," said Nicole Walker, general partner at Baird. Walker added that Baird is excited about investing in the field and boosting the company's growth.

### PROSPECTS for the company

Cala Health recently reported completing enrollment in what it called the largest therapeutic study ever conducted in essential tremor in the U.S., the PROspective study for SymPtomatic relief of Essential tremor with Cala Therapy (PROSPECT). The company reported late last year the start of patient enrollment in the PROSPECT study at the University of South Florida Morsani College of Medicine, Tampa, Fla., and the Keck School of Medicine of University of Southern California (NCT03597100). The multi-center study will evaluate the effectiveness of Cala Two in symptomatic relief of essential tremor. During the study, patients will wear the device on their wrists, much like a smart watch, and patterned electrical stimulation will be delivered to nerves through the skin twice daily.

Subjects will wear the device at home for three months, during which they will be asked to stimulate their dominant hand twice a day. The stimulation amplitude will be based on each subject's stimulation threshold.

Kate Rosenbluth, founder and CEO, Cala Health, told *BioWorld MedTech* that enrollment has been completed and patients had been using the treatment for three months. She added that preliminary results are expected by the end of the year.

"Yes, we plan to roll out a limited launch in target markets by [the third quarter] of this year," she said when asked if the company, per earlier predictions, was on track to launch Cala Trio in 2019. She added that the company will expand its launch next year. "At this time we are focused on the U.S. market for essential tremor," she responded when asked about other markets.

"There are several neuromodulation companies exploring technologies for implanted and noninvasive neuromodulation for a host of chronic diseases. For essential tremor, we are the only wearable neuromodulation therapy we are aware of," she concluded. Currently, the only options for these patients are pharmacotherapies or brain surgery, both of which are only partially effective.

### Origins

A few years back, Rosenbluth found a site of deep brain stimulation was accessible through the peripheral nerves in the wrist. Working with Scott Delp, the director of the Stanford Neuromuscular Biomechanics Laboratory, the two raised series A to back studies and early product development on peripheral stimulation.

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>
> Kate Rosenbluth,
> Founder and CEO, Cala Health Inc.

The company in 2016 raised funds in series B, with an eye toward clearance for a therapeutic device for essential tremor. To that end, in April 2018, the company reported that the FDA had granted its de novo request for Cala One, a neuromodulation therapy for transient relief of hand tremors in adults with essential tremor. It delivers individualized therapy that is calibrated by a physician using on-board sensors to measure the individual's tremor. Later that year, the FDA cleared Cala Health's electrode that was incorporated into Cala Trio.

In March, the company said it had licensed technology from Partners Healthcare Innovation and its affiliate, Massachusetts General Hospital (MGH) to enhance the company's noninvasive neuromodulation platform.

The technology was developed from research on transcutaneous vagus nerve stimulation and Respiratory-Gated Vagal Afferent Nerve Stimulation. Under this agreement, the MGH researchers who originally created the technology will work with Cala Health as scientific advisors.

Cala Health's is eyeing additional targets in neurology, as well as expansion into other fields including psychiatry and cardiology.

### Other players

Although Cala Health is taking a different approach for essential tremor, a number of companies have taken various paths, with a number looking at deep brain stimulation (DBS). As it looks to boost neuromodulation, for example, Abbott Laboratories offers the Infinity DBS system, which provides mild pulses of electricity to the brain to alleviate the symptoms of Parkinson's disease and essential tremor. (See *BioWorld MedTech*, May 16, 2019.)

Medtronic and Boston Scientific also have offerings. ♦

# Auris

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results include time to lesion localization, time to tissue acquisition confirmation, total procedure time, diagnostic yield and conversion to conventional bronchoscopic procedure.

## Encouraging early results

Auris expects to complete enrollment of a total 55 patients at five centers this summer. The findings, which showed no significant adverse effects from Monarch, were presented at the American Thoracic Society 2019 Conference in Dallas.

"Early results from this ongoing study have shown that the Monarch platform has the ability to successfully reach, localize and biopsy peripheral pulmonary lesions in live human subjects," said Alexander Chen, a pulmonary disease specialist and Monarch investigator in St. Louis, who presented the results. "These preliminary findings follow the successful REACH and ACCESS studies, which demonstrated that the platform improved reach beyond a conventional thin bronchoscope and can biopsy peripheral lesions with high accuracy in cadaveric lungs."

Auris Health COO Josh DeFonzo said the company was "encouraged by the initial results from the ongoing BENEFIT study, which demonstrate the potential of Monarch to help diagnose these hard-to-reach lesions."

In a separate independent feasibility study, also presented at the ATS conference, interim results showed the system successfully reached lesions that are hard to access using conventional bronchoscopic systems. That study assessed Monarch's use in 82 procedures between June and October 2018 at the University of Chicago Medical Center, University of Pittsburgh Medical Center Hamot and Fox Chase Cancer Center.

"Though the majority of these lesions were less than three centimeters in size and located in the outer third of the lung, we were able to reach them in 94% of the cases," said Kyle Hogarth, associate professor of medicine and director of bronchoscopy at the University of Chicago Medical Center.

## Benefits of the Monarch

The FDA cleared the flexible endoscopic technology in March 2018 for diagnostic and therapeutic bronchoscopic procedures using computer navigation based on 3D models of the patient's lungs. The device allows users to access hard-to-reach peripheral lesions using a controller-like interface that guides the Monarch system's robotic endoscope to the periphery of the lung.

More than 90% of people worldwide who are diagnosed with lung cancer succumb to the disease, in part because difficulty detecting cancerous lesions often delays diagnosis until it is in an advanced stage. In 2018, lung cancer was expected to kill an estimated 154,050 people in the U.S. – making it the leading cause of cancer deaths in both men and women according to the American Lung Association.

"Current bronchoscopic approaches including guided bronchoscopies may not be adequate to get a satisfactory diagnostic yield for peripheral pulmonary lesions," Eric Davidson, vice president of sales and marketing at Auris Health, told *BioWorld MedTech*. "In the paper published in the *New England Journal of Medicine*, Silvestri and colleagues reported 43% of procedures were non-diagnostic. Additionally, 36% of patients undergoing surgery for non-diagnostic bronchoscopies had benign findings. The Monarch platform has potential to address the limitations of current bronchoscopy approaches and potentially increase diagnostic yield by its ability to reach and access lesions that are located far out in the periphery, and by more accurate targeting during the biopsy."

> *"Early results from this ongoing study have shown that the Monarch platform has the ability to successfully reach, localize and biopsy peripheral pulmonary lesions in live human subjects.*
>
> Alexander Chen, Pulmonary Disease Specialist and Monarch Investigator in St. Louis

The Monarch is currently being used in about 20 institutions across the U.S. in patients who are candidates for a bronchoscopic evaluation of lung lesions, Davidson said, noting the BENEFIT study is not intended to expand indications and was not part of the FDA's conditions for marketing clearance.

Next steps are to review the findings from the pilot study based on a complete dataset and evaluate the system's safety, its ability to localize peripheral lesions and successfully biopsy them, especially "eccentric lesions," and its ability to improve provider workflow, according to Davidson. "Plans are being made to initiate larger prospective studies in the near future," he said. Auris is also exploring potential opportunities to expand Monarch use down the road.

## Recent acquisition target

The Redwood City, Calif.-based company was snapped up in February by Ethicon Inc., a subsidiary of health care products behemoth Johnson & Johnson (J&J), for about $3.4 billion in cash. The deal, which was completed last month, includes additional contingent payments of up to $2.35 billion tied to specific, unnamed milestones. (See *BioWorld MedTech*, Feb. 14, 2019.) At the time, Ashley McEvoy, J&J's executive vice president and worldwide chairman for medical devices, said the acquisition furthers J&J's goal of "building a connected, data-driven digital ecosystem that pairs our market-leading surgical solutions with advanced technologies to improve the patient experience."

J&J has other robotic platform technologies in development in general surgery with Verb Surgical, through a collaboration with Alphabet's life sciences arm, Verily, and in orthopedics via the acquisition of Orthotaxy. Auris' technology is expected to complement those efforts, which aim to provide a full range of procedures from open to laparoscopic, robotic and endoluminal, J&J said.

Founded in 2012, Auris raised $733.3 million in six funding rounds prior to being acquired by J&J. The most recent, a series E round led by Partner Management Fund, netted $220 million. Other investors included Mithril Capital Management, Lux Capital, Coatue Management and Highland Capital. ♦

## Harmonization

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Commerce Subcommittee on Health is advancing to shed light on drug prices may go too far, sweeping in medical devices, discouraging samples being given to doctors and threatening the innovations being developed by startups.

At the hearing on the seven proposed bills, several lawmakers expressed concern about the Sunshine for Samples Act, H.R. 2064, which would require manufacturers of certain drugs, devices, biologics and medical supplies to report the total aggregate value and quantity of samples they give to health care providers each year. Under the bill, those payments would be publicly disclosed on the Department of Health and Human Services' (HHS) Open Payments database beginning in 2023 on an aggregate basis by product, but not by health care provider.

Doctors on the committee bristled at the implication that getting drug or device samples impacts their prescribing. "The sample issue is a red herring," Rep. Larry Bucshon (R-Ind.) said. As a cardiothoracic surgeon, Bucshon said after he prescribes something for his patients, he checks with staff to see if samples are available – it's not the other way around.

Ranking Member Michael Burgess (R-Texas), who's also a physician, said samples can be a big help for patients. They allow a doctor to begin treatment immediately while waiting for prior approval from a payer for a prescription. They can be used on a trial basis to ensure a product works for a specific patient. And they help patients with no insurance get access to the products they need.

"I fear that this policy . . . could lead to a sort of public shaming of companies that are trying to benefit patients. Should such a policy deter manufacturers from providing samples to physicians, patients will be harmed," Burgess said, as he urged his colleagues to think through the potential unintended consequences of all the transparency bills they were considering.

Madelaine Feldman, president of the Coalition of State Rheumatology Organizations and a witness at the hearing, worried that disclosure of free samples, especially of drugs with a hefty list price, would have people saying drug companies are trying to buy off doctors rather than seeing it as a generous act. Echoing Bucshon, she said samples have nothing to do with prescribing.

When asked whether he thought the bill would create a perverse incentive not to provide samples, Douglas Holtz-Eakin, president of the American Action Forum, responded, "I don't know that it would eliminate the samples, but that's a risk you don't have to take." He explained that the data on drug samples are already available and then questioned whether it would be worth it to impose reporting requirements on device samples. "It's a costly set of reporting," he said, and samples are not that typical in the device world.

Rep. Greg Walden (R-Ore.), ranking member of the full Energy and Commerce Committee, had his doubts about the benefit of the Sunshine for Samples Act. "I don't have too many people rushing me at town halls and saying, 'Please add more reporting requirements, more regulations, more rules,'" he said. "Yet we know there's a place for [transparency], but I think we need to be really judicious . . . because we don't want to create more bureaucracy, more time away from caring for patients."

### SPIKEd launch prices

Another transparency bill that raised concerns is the Stopping the Pharmaceutical Industry from Keeping Drugs Expensive (SPIKE) Act, H.R. 2069, which was introduced by Reps. Steven Horsford (D-Nev.) and Tom Reed (R-N.Y.). Besides making drug companies justify certain price increases, the bill would require justification of launch prices that are $26,000 or higher a year or per course of treatment. A summary of the manufacturer's justification, which would include total R&D expenditures and revenue and profit information, would be published on the Centers for Medicare and Medicaid Services' (CMS) website.

> *"Shouldn't we keep the focus on price increases . . . rather than launch prices of orphan drugs produced by smaller companies advancing cures?*
>
> Rep. Fred Upton (R-Mich.)

Given the tremendous cost of R&D that goes into developing new therapies that can cure rare diseases, Burgess noted that many innovative drugs are launching with a price higher than $26,000. "We must consider the potential impact that this requirement could have on the industry," he said. "The incentives for drug development in this space are working, and scaring companies away from investing in such drugs does not serve patients who might benefit from this innovation. . . . If we make it difficult, capital will go elsewhere."

Rep. Fred Upton (R-Mich.) pointed out that small startups are often the ones innovating in the rare disease space. When it comes to reporting requirements, "shouldn't we keep the focus on price increases . . . rather than launch prices of orphan drugs produced by smaller companies advancing cures?" he asked.

The focus should be on what the beneficiary pays, Holtz-Eakin said. "I do think the kind of documentation that's envisioned by the SPIKE Act is unprecedented," he added. "I've never seen it anywhere else in the economy. And for smaller manufacturers, it's going to be quite burdensome."

Questioning the value of that burden, he said, "I don't see that this produces any pressure on pricing. It's a pretty expensive piece of transparency that may or may not be effective."

Frederick Isasi, executive director of Families USA, countered the concerns about the unintended consequences of some of the transparency measures by saying it's a myth that innovation will dry up. He noted that three-fourths of the patents filed by drug companies are for products that already have been approved.

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# DoJ

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cooperation credit, the entity had to "completely disclose" any and all relevant facts regarding individuals, only after which might the company have been eligible for cooperation credit.

The Yates memo, named for former assistant attorney general Sally Quillian Yates, drew few cheers from life science companies for its inflexibility, and the DoJ's approach to device companies under the Yates memo had at least one device maker up in arms. Howard Root, formerly the CEO of Vascular Solutions, made the case that the terms of the Yates memo had been in force for some time prior to its unveiling in September 2015 and that the aggressiveness of federal attorneys under those practices led to an overreach of prosecutorial power in the department's prosecution of the company. (See *BioWorld MedTech*, Oct. 20, 2016.)

Hunt said in the May 7 DoJ statement that defendants in FCA cases can obtain "a more favorable resolution" to their cases by providing "meaningful assistance" to federal attorneys, starting with voluntary disclosure, still the "most valuable form of cooperation." Hunt listed the sharing of information gleaned from internal investigations and the taking of remedial actions via new or beefed-up compliance programs as additional steps that would curry favor with the department, adding that voluntary disclosure of violations unknown to the government would also be looked upon favorably.

Hunt added that federal prosecutors would take into account any corrective action undertaken unilaterally by companies that are the target of FCA prosecutions, noting that in most instances, cooperation credit would be granted via reduced damages multipliers and smaller civil penalties. The formal policy, enumerated in Title 4 of the *Justice Manual*, notes that a defendant company should disclose the identities of all individuals involved in the illicit conduct, but that the company can still qualify for partial credit short of an exhaustive list of all implicated parties, assuming the company provides some meaningful assistance to the government's investigation. However, the "truthfulness, completeness and reliability" of any such information would be factored into a calculation of cooperation credit.

Katie McDermott, a partner in the D.C. office of Morgan, Lewis & Bockius, LLP, told *BioWorld MedTech* that the unilateral disclosure of violations of which the government was unaware is "a huge piece" of the new policy. She said the federal government "has been consistent for decades of enforcement policy in encouraging voluntary disclosure," adding that the statute includes a disclosure provision. McDermott said there are instances in which a company in the life sciences finds itself in an FCA case before it has had a chance to conduct its own investigation, but that this scenario need not lead to zero cooperation credit so long as "there's demonstrable cooperation beyond the disclosure."

## Conflict with OIG

The new DoJ policy seems to conflict with the policy at the Office of Inspector General (OIG) at HHS in that the former will offer cooperation credit with a company that makes improvements in its compliance programs, a policy OIG does not hold. In theory, the difference could be messy, but McDermott said, "I think in practice it will work out in DoJ's favor." She said the effectiveness of the OIG's compliance paradigm will suffer if it holds onto that position, although OIG won't necessarily make an official acknowledgement of any such policy change. "I think they can judge these on a case-by-case basis," McDermott said, adding that the agency's approach has caused a number of companies to pass on a corporate integrity agreement (CIA) "because it doesn't make sense.

The conduct in question might be a decade in the past, and the company may have dramatically changed in its compliance practices since the investigation," McDermott said. The CIA is a tool with 20 years behind it, and she noted that corporate compliance officers were a rarity when the policy was first put into place. That is no longer the case and McDermott stated, "maybe it's time to think differently about it."

## Help with qui tam actions offered

The amended portion of the *Justice Manual* strikingly notes cooperation credit could consist of "assisting the entity or individual in resolving *qui tam* litigation," and McDermott said, "this was a very interesting part of the guidance, because DoJ historically has taken the position that it won't get involved in parallel agency reviews or *qui tam* litigation issues." She said this is "a dramatically different position" than that previously held by the department, adding that while this is "a big change from their practice and policy previously, we'll have to see what it all means moving forward."

Jason deBretteville, a shareholder at Stradling Yocca Carlson & Rauth, PC., told *BioWorld MedTech* that while the contrast of the Yates memo and this latest policy might seem to suggest DoJ policy will continue to wobble with a change in the party of the presidency, he is of the view that DoJ has a strong identity that "lessens the influence that comes with each changing administration."

However, deBretteville said the passage regarding DoJ assistance with *qui tam* actions is a head-scratcher. He said the Granston memo "is about DoJ doing its job" with regard to meritless claims, which the government should dismiss in any event. Ergo, one might have to assume the passage is in reference to meritorious claims filed against a company that is cooperating. The passage would make sense if the department is trying to craft a global resolution to the matter at hand, but deBretteville said, "I'm not sure why the government felt it needed to address a parallel *qui tam* claim," unless there was some compelling need to bring the matter to a close.

DeBretteville said the new policy does not create a new vocabulary for the defense bar in its talks with government attorneys, but it does make that vocabulary more formal. "I did appreciate the level of emphasis on remediation," he said, adding that this has been neglected in the past.

"This does seem to signal that the DoJ under the current administration is mindful of the fact that a cooperating company … is a good thing," deBretteville said. He stated that mitigating the negative impact on an enterprise can be in the interest of the U.S. as well as the enterprise, but he cautioned that life science companies must tailor their compliance programs closely to the risks associated with their business model. ♦

## Longas

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mutations into DNA molecules of half of a sample, tagging each molecule with a unique identifier. Samples are then multiplexed and amplified using standard polymerase chain reactions, before being fragmented and sequenced on a short read sequencer.

In parallel, the non-mutated half of the sample is sequenced and read as normal. The Morphoseq algorithm reconstructs long sequence reads by linking short reads with the same mutation. It then uses that as the reference to reassemble sequences in the mutation-free half of the sample.

High-throughput, low-cost sequencing, in which DNA is cut into many short lengths that are sequenced in parallel, has made sequencing routine and affordable, but said Longas co-founder and Chief Scientific Officer Aaron Darling, "that has come at the cost of read length."

The current methods for reassembling short fragments fail to resolve genomic repeats that are longer than the read length and which can occur in multiple copies throughout genomes.

"Long repeats are present at many of the most clinically informative parts of genomes, such as drug resistance genes in bacteria and the major histocompatibility locus in humans," Darling said. The ability to accurately assemble and phase those into individual chromosomes will have important clinical and epidemiological applications.

Sydney-based Longas has been working on the technology since it was spun out of the University of Technology Sydney in 2015. It is now ready for commercialization, and Darling is giving Morphoseq its first public airing in a presentation at the Sequencing, Finishing and Analysis in the Future meeting in Santa Fe, N.M., Tuesday.

Longas has hired Nick McCooke, former CEO of Solexa Ltd., the Cambridge University spinout that pioneered the next-generation sequencing technology that forms the heart of Illumina's sequencing machines. Solexa listed on Nasdaq in 2005 and was acquired by Illumina in a $660 million all-share deal in November 2006.

McCooke has been advising Longas as a nonexecutive director, based in the U.K., since 2015. He told *BioWorld MedTech* the company has come out of stealth mode now because it has good data on bacterial genomes to show the technology works.

Darling, who is professor of computational genomics and bioinformatics, worked on bacteria in the human microbiome project isolate collection, showing it is possible to generate reference quality genomes, an outcome that would have been difficult to achieve with long read sequencers because they require higher quality DNA inputs.

In those exemplars, "it was impossible unambiguously to join together [short reads] because repeated sequences prevented standard algorithms from resolving all the contigs [contiguous regions]," McCooke said. "In each case, Morphoseq could resolve the entirety of the [chromosomal] genome."

Longas is working on generating more data to further demonstrate the utility. The company also will do a comparison of Morphoseq against other methods of labeling DNA molecules using barcodes.

McCooke said the technology has undergone what he called "semi-external" testing by researchers at the University of Technology Sydney who were not involved in its development. "We are now just at the stage of putting it in the hands of people outside the university," he said.

"There are a wide range of applications where long reads are required. Our technology means someone with an Illumina sequencer, which is the most dominant in terms of the installed base, can do long reads," said McCooke. "Currently, if they want long reads they have to go to another sort of sequencer."

As a product, Morphoseq consists of a chemistry kit for inducing mutagenesis in the sample and a cloud-based bioinformatics service to conduct the analysis.

The preferred route to commercialization is to find partners, who might be equipment manufacturers or suppliers of sequencing services.

To date, Longas has been funded by Australia's national Medical Research Commercialization Fund, with investment from the founders and directors. "We are not looking for further funding," McCooke said. "We have enough to put the partnerships into place." ♦

### Other news to note

**Sage Science Inc.**, a Beverly, Mass.-based developer of products for improving sample preparation processes in life science applications, reported the award of a $1.8 million grant from the National Human Genome Research Institute, part of the National Institutes of Health. The grant funds a two-year program to develop and commercialize a fully automated platform for the company's HLS-CATCH targeted DNA sample preparation process, which is designed to analyze genomic regions that cannot be captured with conventional tools. The HLS-CATCH method, which is currently available as a manual technique with the SageHLS system, makes it possible to analyze complex genomic phenomena such as disease-causing repeat elements or structural variations using routine sequencing technologies. With this method, researchers have already sequenced a number of important genes, including PKD1, BRCA1/2, MAPT, and MHC.

### Appointments and advancements

**Align Technology Inc.**, a dental technologies company, reported that Roger George has resigned as senior vice president, chief legal and regulatory officer, effective at the end of August. Julie Coletti, Align's vice president and associate general counsel, strategic commercial affairs, will succeed him as general counsel.

**Biosig Technologies Inc.**, a company focused on the electrophysiology market, reported that Jerome Zeldis will rejoin the company as an independent director, effective immediately. Zeldis is a former CEO of Celgene Global Health and former chief medical officer of Celgene Corp. He currently serves as CMO and president of clinical research, medical affairs drug safety, quality and regulatory at Sorrento Therapeutics Inc.

# AI

Continued from page 1

recommendations have been scaled back in recent years.

But deep learning, a subset of AI that can continue to change, adapt and improve on its own beyond any initial training, could prove better than radiologists at correctly reading and classifying medical images. The latest study to find that an AI system can best the accuracy of radiologists comes from research in which Mountain View, Calif.-based Google applied its deep learning technology to data from Northwestern Medicine.

> *"This is the conundrum about screening. If you screen too many people then you get too many false positives, and then those cause more harm.*
>
> Mozziyar Etemad, Research Assistant Professor in Biomedical Engineering, Northwestern University

They found that, specifically with an initial low-dose CT scans to detect lung cancer, the AI system improved upon both the sensitivity (true positives) and specificity (true negatives) of traditional lung cancer screening by radiologists. The study results were published in the May 20, 2019, issue of *Nature Medicine*.

### Screening realities

"This is the conundrum about screening. If you screen too many people then you get too many false positives, and then those cause more harm," study co-author Mozziyar Etemadi, a research assistant professor in biomedical engineering at Northwestern University, and a resident in anesthesiology, told *BioWorld MedTech*. "For example, prostate cancer with PSA. It turns out with most prostate cancer, even if you have it, you'll die with it. It won't be the cause of death – something else will be."

"One of the cool things with this model that Google built is that the false positives are actually really low," he continued. "So, even if the sensitivity of finding cancer isn't better – it is better, but even if it wasn't – the fact that it's not calling things cancer, when they are not, is what saves people from lung biopsies."

Lung biopsy involves inserting a large needle to extract lung tissue. Not only are there aspects that can go wrong with the procedure, but it can also be inaccurate if poorly positioned and can be prohibitive or very trying for an ill patient.

The retrospective study using Google deep learning offered a 94.4% AUC (area under the curve); this represents the degree to which it can accurately distinguish between diseased and normal tissue. This was in the 6,716 cases from the National Lung Cancer Screening Trial. It achieved a similar rate in an independent clinical validation set of 1,139 cases.

The model outperformed six radiologists. It offered an absolute reduction in false positives of 11% and an absolute reduction of 5% in false negatives vs. the radiologists when computed tomography imaging was not available. When prior computed tomography (CT) imaging was available, the results were comparable with those of the radiologists. A prior CT scan offers a point of comparison that enables radiologists to see change over time.

"Radiologists generally examine hundreds of two-dimensional images or 'slices' in a single CT scan, but this new machine learning system views the lungs in a huge, single three-dimensional image," said Etemadi. "AI in 3D can be much more sensitive in its ability to detect early lung cancer than the human eye looking at 2D images. This is technically '4D' because it is not only looking at one CT scan, but two [the current and prior scan] over time."

### AI in use

The deep learning model was developed and applied to 2,763 de-identified CT scan sets provided by Northwestern to validate accuracy. The extent to which AI-based models require training and can recognize all sorts of unusual occurrences – can limit their usefulness.

But Etemadi was profuse in his praise for Google and the lengths to which they went to ensure that the system wasn't riddled with training bias, in order to ensure its usefulness in potential real-world medical practice. A lot of work was required by the hospital itself to pull all the necessary images and information, which are taken and stored in systems designed for each individual patient but not at all for research use to examine a population.

"This area of research is incredibly important, as lung cancer has the highest rate of mortality among all cancers, and there are many challenges in the way of broad adoption of lung cancer screening," noted Shravya Shetty, the technical lead at Google. "Our work examines ways AI can be used to improve the accuracy and optimize the screening process in ways that could help with the implementation of screening programs."

Lung cancer resulted in roughly 180,000 cancer deaths in the U.S. last year. Low-dose CT as implemented according to current screening guidelines is thought to reduce mortality by 20% to 43%. The current U.S. Preventative Task Force guidelines recommend low-dose CT for adults who are 55 to 80 years old who have a 30 pack per year smoking history and currently smoke or have quit within the past 15 years.

But smoking cigarettes is becoming less common in the U.S., while the routine use of electronic cigarettes, known as vaping, is becoming more common. Vaping can be used for both nicotine and cannabis-based products. Smoking of cannabis has also become more common with legalization or decriminalization by various states. The long-term health effects of any of these practices remain relatively unknown. These changing health behaviors may force the re-evaluation of the screening guidelines and make a broader program more necessary.

"At least in the U.S., smoking is on the decline. A lot of lung

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## AI

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cancer isn't caused by smoking. So, we're not screening those people," said Etemadi. "We should be, potentially. But my guess is we're not because of the invasiveness of the procedure. Basically, the risks at this point probably outweigh the benefits."

He also observed that there is a lot of visual information on a low-dose CT scan that usually remains unassessed, which an AI system could be trained to review as well. A chest CT shows the heart, blood vessels, lungs, ribs and spine, all of which could be assessed routinely by a deep learning system for signs of abnormality or disease.

The researchers are planning to start a large clinical trial to validate their work in lung cancer within the next year. Given comparable or better results than the current study, an FDA submission – either as a supplemental radiologist tool or for independent diagnosis – could follow. ♦

## Harmonization

Continued from page 5

Using hepatitis C drug Sovaldi (sofosbuvir) as an example, he reminded the subcommittee that its high launch price was set by Gilead Sciences Inc., which didn't develop the drug. Gilead bought the drug from the company that developed it.

A third bill that raised a few flags was the FAIR Drug Pricing Act, proposed by Reps. Jan Schakowsky (D-Ill.) and Francis Rooney (R-Fla.). The bill would require manufacturers to submit documentation to HHS 30 days before increasing the price of a qualifying drug. That documentation would consist of total expenditures for manufacturing the drug, the R&D expenditures for the drug, total revenue and net profit generated by the drug, and information such as CEO compensation. It also gives HHS broad authority to request other information not specified in the legislation. The bill includes a civil monetary penalty of $100,000 per day if a manufacturer fails to comply with the reporting requirements.

The FAIR Act is one step closer to government taking over the biopharma industry, Rep. Markwayne Mullin (R-Okla.) said, adding that much of the information it requires has nothing to do with the federal government. For instance, the government shouldn't have oversight of the compensation for someone who isn't a federal employee, he said.

Because of the 30-day advance notice, the FAIR Act also could lead to drug stockpiling, which would result in shortages, Joldersma said. Another unintended consequence is that it could open the door to market manipulation games.

### Unmasking the secrets

The other transparency bills the subcommittee is considering are:

• The Creating Lower Cost Alternatives for Your Prescription Drugs Act, H.R. 2757, which eliminates cost-sharing for generic drugs for low-income Medicare enrollees and caps their out-of-pocket costs for other drugs;

• The Drug Price Transparency Act, H.R. 2087, which requires all manufacturers to report average sale price (ASP) data to CMS for all drugs covered under Medicare Part B, authorizes civil money penalties against manufacturers who fail to report the data or report false data, and improves oversight related to the accuracy of the ASP data reported;

• The Public Disclosure of Drug Discounts Act, H.R. 2115, which requires pharmacy benefit managers (PBMs) to disclose the aggregate amount of rebates, discounts and price concessions that they negotiate with drug manufacturers;

• The Prescription Pricing for the People Act, H.R. 2376, which requires the FTC to conduct a study on the state of competition in the drug supply chain, focusing on whether PBMs have engaged in any anticompetitive practices.

In opening the hearing, subcommittee Chair Anna Eshoo (D-Calif.) referenced the panel's hearing last week that looked at the flow of money in the drug supply chain. "Instead of answers, we found secrets," Eshoo said. "Secret decisions about how drugs are priced. Secret deals between drug companies and the PBMs, and secret agreements between PBMs and insurers."

The seven bills the subcommittee considered this week will "unmask the secrets and ensure that low-income seniors can afford their medications," Eshoo said.

While everyone agreed that transparency is needed, the question remained: When is enough enough?

There are instances where the cost of transparency is not worth it and times when it could be harmful or damage competition, Holtz-Eakin said, adding, "I worry about transparency that generates no end result." ♦

### Appointments and advancements

**Celcuity Inc.**, a Minneapolis-based functional cellular analysis company, reported that Leo Furcht has joined its board. He is the head of the department of laboratory medicine and Pathology at the University of Minnesota and a member of the division of molecular pathology and genomics.

Anaheim, Calif.-based **Clearflow Inc.**, manufacturer of the Pleuraflow active clearance technology system for removing blood clots in the chest, appointed Michael Elniski to the position of vice president of global sales. He most recently served as franchise vice president of cardiac critical care at Merit Medical.

Diabetes data management solutions company **Glooko** reported its appointment of Mark Clements as chief medical officer. Clements, a member of Glooko's medical advisory board since 2015, comes to his senior management team from the University of Missouri-Kansas City School of Medicine, where he is an associate professor of pediatrics.

**Nevro Corp.**, a company focused on treating chronic pain, reported that its board elected President and CEO D. Keith Grossman to assume the added role of chairman of the board. Outgoing board chairman Michael DeMane will serve as lead director. The changing of the guard took effect Monday, following Nevro's annual shareholder meeting.

## Product clinical data for May 21, 2019

| Company | Product | Description | Indication | Status |
|---|---|---|---|---|
| Abbott Laboratories, of Abbott Park, Ill. | Investigational | Minimally invasive tricuspid valve repair system | Tricuspid regurgitation | Reported late-breaking data from the TRILUMINATE study; results at 30 days demonstrated that the investigational device is associated with a reduction of tricuspid regurgitation (TR) symptoms; 86.6% of patients saw a reduction in TR severity of at least one grade ($p < 0.0001$); a significantly greater proportion of patients were categorized as New York Heart Association class I or II (80.5% at 30 days vs. 25.6% at baseline), an improvement that was statistically significant; patients also experienced a mean improvement in Kansas City Cardiomyopathy Questionnaire score from 53.05 at baseline to 67.25 at 30 days, which was an increase of 14.20 points; a 5-point increase is considered clinically significant) |
| Biotronik, of Berlin | Orsiro | Drug-eluting stent (DES) | For use in percutaneous coronary intervention (PCI) procedures | Reported results from BIO-RESORT trial in which 1,506 patients with small coronary vessels were treated with the Orsiro, Resolute Integrity or Synergy DES; 3-year results show the rate of target lesion failure7 (TLF) in favor of Orsiro 7% (Orsiro vs. Resolute Integrity p= 0.08), for Resolute Integrity 10% and for Synergy 9.5% (Synergy vs. Resolute Integrity p=0.72); in terms of cardiac death and myocardial infarction, the three stents showed similar results; patients treated with Orsiro experienced significantly fewer repeat target lesion revascularizations (TLR) than those treated with the thin strut Resolute Integrity (Orsiro 2.1% vs. Resolute Integrity 5.3%, p=0.009; Synergy 4%); divergence seemed more pronounced after the first year post index procedure, when dual antiplatelet therapy was stopped; this is supported in a TLR landmark analysis between one and three year, where the TLR rate with Orsiro was 1%, with Resolute Integrity 3.7% (p=0.006) and with Synergy 2.7%; Orsiro showed a trend towards a lower rate of definite or probable stent thrombosis with a rate of 0.6% vs. 1.5% for Resolute Integrity (p=0.16) and 1.5% for Synergy; results also featured in the Journal of the American Medical Association |
| Gemelli Biotech, of Los Angeles; Medically Associated Science and Technology program at Cedars-Sinai, Los Angeles | Ibs-smart | Diagnostic blood test | Second-generation diagnostic blood test for irritable bowel syndrome (IBS) | Researchers at Cedars-Sinai validated the antibodies anti-CdtB and anti-vinculin as highly specific biomarkers measurable in blood; the second-generation blood test is >90% specific in distinguishing patients with IBS from patients with inflammatory bowel disease using each marker; when combined, the post-test probability of IBS is >98% |
| Janssen Pharmaceutical Inc., of Titusville, N.J. | Spravato (esketamine) | CIII nasal spray | Treatment-resistant depression (TRD) | The analysis showed that for people living with TRD, which is defined as having cycled through two or more oral antidepressant treatments in the same depressive episode without relief, Spravato in conjunction with an oral antidepressant is a cost-efficient alternative to an oral antidepressant plus placebo |

**Notes**

For more information about individual companies and/or products, see Cortellis.

## Appointments and advancements

Medical technology company **Rewalk Robotics Ltd.** appointed Chunlin (Allen) Han to the board of directors, replacing Ning Cong, who stepped down from the board on May 14. Han is an executive director of Liquid Harmony Ltd. and head of investment and financing for Realcan Pharmaceutical Group Co. Ltd. Han's board role was effective May 15, pursuant to an investment agreement with Timwell Corp. Ltd., the U.S. and Israeli-based company said.

U.K.-based **Scapa Group plc**, a diversified health care and industrial company, reported that Heejae Chae is stepping down as its group chief executive and member of the board. The company said that a search for Chae's successor is underway and that he will remain with Scapa to ensure a smooth transition.

U.K.-based **Tissue Regenix Group plc**, a regenerative medical devices company, reported that Steve Couldwell will resume full-time duties as CEO in June, following what Chairman John Samuel called a "necessary absence." During this period, Gareth Jones assumed the role of COO.

## Product regulatory actions for May 21, 2019

| Company | Product | Description | Indication | Status |
|---|---|---|---|---|
| Hemovent GmbH, of Aachen, Germany " | Mobybox | Extracorporeal life support | Support or replace heart and lung function in the event of cardiac and/or respiratory failure | Obtained CE mark |
| Kurin Inc., of San Diego | Kurin | Blood culture collection tests | Blood culture diversion | Obtained CE mark |

**Notes**

For more information about individual companies and/or products, see Cortellis.

### Regulatory front

Stephen Ferguson, board chairman of the **Cook Group Inc.**, said the FDA's question-and-answer guidance for risk-based monitoring of clinical studies should more consistently use the term "study" or "trial," and suggested the agency consider whether references to international standards would be more helpful for sponsors attempting to determine their compliance. Ferguson said the FDA should use the term "possible critical risks" in lieu of language referring to "important" risks, and recommended the agency add a clinical site's experience with clinical trials when determining the frequency with which a study site should be subject to monitoring activities. Also in the context of study site monitoring frequency, Ferguson said the agency seemed to suggest a monitoring plan for each study site that takes part in a study, but that a monitoring plan might account for both the nature of the study and the study site. The Cook Group is the parent company of Cook Medical Inc., of Bloomington, Ind.

The U.S. **FDA** updated its advisory to health care providers for the Impella RP ventricular assist device by **Abiomed Inc.**, of Danvers, Mass., stating that the benefits of the device are still assumed to outweigh the risks for on-label device use. The agency said an ongoing postmarket study, which was the subject of the Feb. 4, 2019, initial advisory, suggested a lower survival rate for patients who would not have qualified for the premarket clinical study, adding that the survival rate for those in the PAS who would have met the enrollment criteria for the pre-approval study enjoyed a 64.3% (nine of 14) survival rate while the survival rate otherwise in the PAS was 10.7% (3 of 28 patients). The FDA further advised clinicians that patients in the pre-approval study had experienced no in-hospital cardiac arrest or treatment with an intra-aortic balloon pump.

### Daily M&A

Garland, Texas-based **Galt Medical Corp.,** a vascular and interventional medical devices company, acquired Arrotek Medical Ltd., a developer of minimally invasive devices for catheter-based, interventional uses located in Sligo, Ireland. The merger opens Arrotek to new market segments in North America, Europe and elsewhere.

**Varian Medical Systems Inc.**, of Palo Alto, Calif., has agreed to acquire Pittsburgh-based **Cancer Treatment Services International** (CTSI) for $283 million. Privately held, CTSI operates the American Oncology Institute in Hyderabad and 10 multidisciplinary – radiation, medical and surgical oncology – cancer centers across the Indian subcontinent as well as a U.S.-based Oncology Solutions division that provides cancer care professional services to health care providers worldwide. Varian will finance the acquisition with a combination of borrowings under its credit facility and cash on hand. The transaction is anticipated to close in approximately two weeks, subject to the satisfaction of customary closing conditions.

# Oncology Extra

## Keeping you up to date on recent developments in oncology

*By Mark McCarty, Regulatory Editor, and Anette Breindl, Senior Science Editor*

### Platinum-based nanocomplex offers dual cancer therapy

Precise delivery of cancer therapies continues to be a focus of research, and scientists in China have responded to the need for a better oncological mouse trap with a bifunctional platinum nanocomplex (PtNC) that is light-activated and produces "dually cooperative cancer therapy through spatiotemporally selective thermo-chemotherapy." This device makes use of a polycarboxylic nanogel as the nanoreactor template to synthesize the PtNCs consisting of a zero-valent platinum core and a bivalent platinum shell that features tunable ratios of core to shell. The exposure to light prompts a hyperthermic reaction based on photothermal conversion from the platinum core, but the light also prompts a release of chemotherapeutic platinum from the shell via a hyperthermia-triggered destabilization of metal-metal interaction. The net effect is to produce a spatiotemporally selective synergistic thermo-chemotherapeutic injury of tumor cells, but the PtNCs also demonstrate enhanced tumor accumulation by means of a hyperthermia-triggered hydrophilicity-hydrophobicity transition. The authors stated that their design of spatiotemporally activatable nanoparticles "provides an insightful tool for precise cancer therapy." They present their findings in the May 14, 2019, online issue of *ACS Nano* under the title, "Spatiotemporally Light-Activatable Platinum Nanocomplexes for Selective and Cooperative Cancer Therapy."

### Boosting PTEN foils Myc

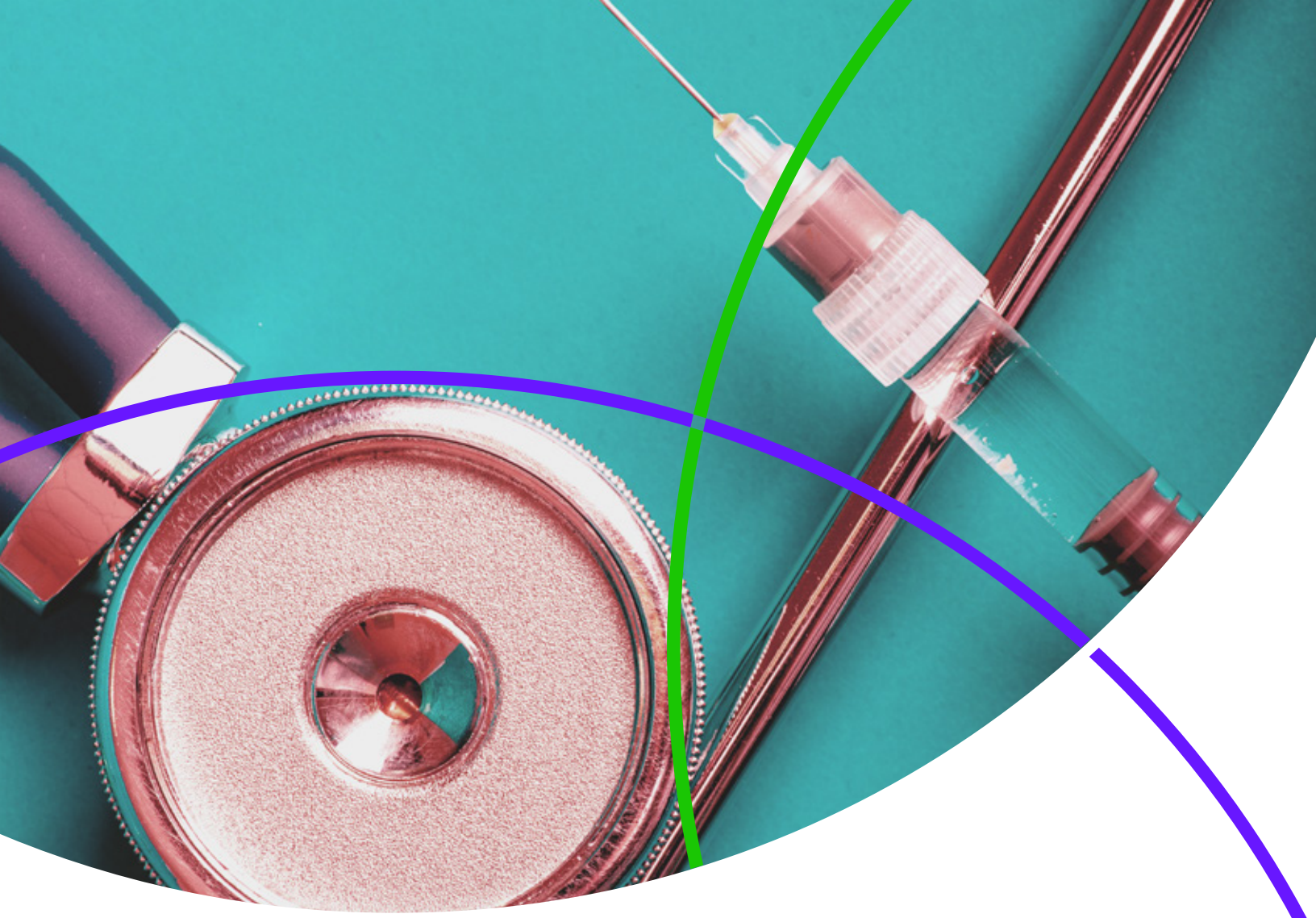
Scientists at Beth Israel Deaconess Medical Center have found a way to reactivate the tumor suppressor PTEN by inhibiting the ubiquitin ligase WWP1. Because pharmacological inhibition is easier than activation, therapeutic strategies in cancer have overall been a good deal more successful at inhibiting oncogenes than at reactivating tumor suppressors. PTEN is a tumor suppressor that is frequently dysfunctional across a wide swath of tumor types. However, having no working PTEN at all triggers senescence, and so tumor cells with dysfunctional PTEN still have one working copy of the gene. The authors boosted the working copy by inhibiting WWP1, an enzyme that normally tags PTEN for destruction. "Either genetic ablation or pharmacological inhibition of WWP1 triggered PTEN reactivation and unleashed tumor suppressive activity," the authors wrote. "WWP1 appears to be a direct MYC (MYC proto-oncogene) target gene and was critical for MYC-driven tumorigenesis. We identified indole-3-carbinol, a compound found in cruciferous vegetables, as a natural and potent WWP1 inhibitor. Thus, our findings unravel a potential therapeutic strategy for cancer prevention and treatment through PTEN reactivation." They reported their results in the May 17, 2019, issue of *Science*.

### Exact Sciences, Mayo to debut pancreatic cancer test

**Exact Sciences Inc.**, of San Diego said its long-standing collaboration with the Mayo Clinic has led to development of a test for the most common forms of pancreatic cancer, a test that offers 92% sensitivity and the same level of specificity. Researchers are presenting the findings at the 2019 edition of Digestive Disease Week, where they will describe the outcomes of a 340-sample, case-control study that tested a panel of methylated DNA markers in plasma in combination with cancer antigen 19-9 (CA 19-9), already a known marker of pancreatic cancer. The data suggest a cross-validated sensitivity of 79% in stage 1 pancreatic cancer, and cross-validated sensitivity of 99% in stage 4 pancreatic ductal adenocarcinoma (PDAC). The combination of genetic markers and CA 19-9 was significantly better than CA 19-9 alone, which to some extent is due to the fact that CA 19-9 is not highly reliable for early detection, and in some instances is normal in advanced cases of the disease. The researchers used a small number of archived blood samples in the training set for this approach, which could lead to a higher estimate of both sensitivity and specificity than the test will offer in real-world usage. However, Exact said a prospective validation study is already underway at one of the Mayo Clinics. The collaboration between Exact Sciences and Mayo is focused on identifying markers for 15 of the deadliest cancers, the company said, noting that there will be a poster at DDW demonstrating research conducted on esophageal cancer as well.

### Screening more often recommended in the morning

A fresh cup of coffee does wonders for many things in life, and recent research suggests it works well for prompting physicians to recommend their patients go in for cancer screening. The study in question, conducted at the Perelman School of Medicine at the University of Pennsylvania, suggests that physicians may grow weary of urging their patients to submit for screening procedures as the day grinds on, as demonstrated by the fact that 64% of patients eligible for breast cancer screening heard about it from their doctor in the morning, a rate that fell to 48% by the end of the day. The same dynamic was seen in colorectal cancer screening, given that 37% of eligible patients were urged to take care of the procedure at 8 a.m., while only 23% of patients heard the same message later in the day. This study drew on the records of more than 50,000 patients seen in 33 primary care practices in Pennsylvania and New Jersey from late 2014 to mid-2016, but the appointments were all either first-time visits or return checkups. The findings are reported in the May 10, 2019, issue of *JAMA Network Open*.



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