MEDICAL DEVICE DAILY™

THE DAILY MEDICAL TECHNOLOGY NEWS SOURCE

WEDNESDAY, OCTOBER 5, 2016 VOLUME 20, NO. 193

MED-TECH CYBERSECURITY CONCERNS PERSIST

Insulin pump users warned of hacking risk, but probability of attack is 'extremely low'

By Amanda Pedersen, Senior Staff Writer

Johnson & Johnson's diabetes unit warned patients this week that the Animas Onetouch Ping insulin pumps may be vulnerable to a cyberattack, but the probability of one of the devices actually being hacked is "extremely low," the company said.

The pump could potentially be accessed through its unencrypted radio frequency communication system, but such an attack would require technical expertise, sophisticated equipment and proximity to the device, according to a letter the West Chester, Pa.-based Animas Corp. sent to patients on Monday. The company noted that the Onetouch Ping system is not connected to the Internet or any external network.

See Insulin Pumps, page 3

Innovation has med-tech firms and regulators in knots over cybersecurity

By Richard Smart, Staff Writer

TOKYO – Issues in cybersecurity are causing headaches for med-tech companies and the U.S. FDA, with a number of international companies directly affected. In recent months, two incidents have brought to light the complexity of the medical device market for consumers and investors alike.

See Cybersecurity, page 4

PROCURES SUPERIORITY CLAIM

FDA gives thumbs up to St. Jude Medical's Burstdr for chronic pain

By Liz Hollis, Staff Writer

St. Jude Medical Inc. has scored a win at the U.S. FDA, with the agency approving Burstdr stimulation to treat patients with chronic pain, the company said Tuesday.

With this approval, patients implanted with the company's Proclaim Elite and Prodigy MRI spinal cord stimulation (SCS) systems will have immediate

See St. Jude, page 5

REGULATORY

OIG report: Medicare spending on molecular testing down 44 percent

By Mark McCarty, Regulatory Editor

The release of the gapfilling numbers for clinical lab tests is still rankling the diagnostics and clinical lab industries, but the Office of Inspector General has released a pair of reports on the now-delayed overhaul of the Medicare clinical lab fee schedule. One of the more remarkable features of the OIG data is

See OIG, page 6

SNIFFING OUT CANCER

Owlstone advances novel breathalyzer in trials for two cancers and asthma

By John Brosky, Contributing Writer

PARIS – It will take your breath away just trying to keep up with Billy Boyle, the CEO of Cambridge, U.K.-based Owlstone Medical Ltd.

Formally launched in August 2016 as a spinout from Owlstone Ltd with $7 million in financing, the medical

See Owlstone, page 7

IN THIS ISSUE

OTHER NEWS TO NOTE

Bostwick Laboratories Inc., of Uniondale, N.Y. has entered into a marketing partnership agreement with **Genomedx Biosciences Inc.,** of San Diego, a provider of the genomic Decipher Prostate Cancer Classifier tests for men diagnosed with localized prostate cancer. Bostwick will offer Decipher Biopsy on their requisition forms, allowing for electronic ordering of the test and providing their extensive customer base the ability to easily access Decipher.

The U.S. Oncology Network said it has selected **Myriad Genetic Laboratories Inc.,** of Salt Lake City, as its preferred provider laboratory for hereditary cancer testing. As part of the collaboration, Myriad and the US Oncology Network will work together to perform hereditary cancer research through the Genetic Risk Evaluation and Testing program within The Network affiliated practices. Under this program, the two organizations will collaborate to create a database that links patient outcomes with genetic test results. Principal among the research aims of this program is to better understand the genotype-phenotype correlation, gene prevalence, and research related to improving patient counselling and access to testing.

Royal Philips N.V., of Amsterdam, the Netherlands, said it has incorporated its Volcano catheter-based imaging and measurement solutions for minimally invasive diagnostics and treatment of cardiovascular and other disease, into its portfolio of interventional cardiology solutions in Canada.

Trovagene Inc., of San Diego, a developer of circulating tumor DNA said it has been selected by the Pancreatic Cancer Action Network as the liquid biopsy provider to participate in Precision Promise,a precision medicine trial designed to transform outcomes for patients with pancreatic cancer.

APPOINTMENTS AND ADVANCEMENTS

Dune Medical Devices Ltd., of Paoli, Pa., appointed Lori Chmura to be its CEO, replacing the company's founder Dan Hashimshony. Chmura joined Dune in January to lead the company's U.S. commercial activities. Previously she worked at Medtronic, Covidien, and Johnson & Johnson. Hashimshony said he will continue to work with the company to expand its radio frequency spectroscopy technology to applications beyond breast cancer surgery.

MEDICAL DEVICE DAILY

Medical Device Daily™ (ISSN# 1541-0617) is published every business day by Thomson Reuters, 115 Perimeter Center Place, Suite 1100, Atlanta, GA 30346 U.S.A. Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. All Rights Reserved. No part of this publication may be reproduced without the written consent of Thomson Reuters (GST Registration Number R128870672).

CONTACT US

medicaldevicedaily.newsdesk@medicaldevicedaily.com

Donald R. Johnston, (770) 810 3118 // Holland Johnson, (770) 810-3122 // Amanda Pedersen, (912) 660-2282 // Omar Ford, (770) 810-3125 // Mark McCarty, (703) 361-2519 // Penney Holland (770) 810-3047 // Lynn Yoffee, (770) 810-3123

OUR NEWSROOM

Lynn Yoffee (News Director), Holland Johnson (Executive Editor), Mark McCarty (Regulatory Editor), Omar Ford, Liz Hollis, Amanda Pedersen & Varun Saxena (Staff Writers) Europe // John Brosky (Staff Writer), Asia//Pearl Liu, Haky Moon, Alfred Romann, Cornelia Zou (Staff Writers), Latin America// Sergio Held// Israel //Joseph Straus

PRACTICAL INFORMATION

For Sales Inquiries: http://ip-science.interest.thomsonreuters.com/Bioworld_Sales_Inquiry. NORTH AMERICA, Tel: (855) 260-5607. Outside of the U.S. and Canada, Tel. +44.203.684.1797. For Customer Service Inquiries, NORTH AMERICA, Tel: (800) 336-4474. Outside of the U.S. and Canada, Tel. +44-203-684-1796. Or email bioworld.support@thomsonreuters.com. Copyright ©Thomson Reuters. Reproduction is strictly prohibited. Visit our website at www.medicaldevicedaily.com.

For ad rates and information, please contact Chris Venezia toll free at (855) 260-5607; outside the U.S. and Canada, call (646) 522-6243 or by email at christopher.venezia@thomsonreuters.com.

For photocopy rights or reprints, please contact Chris Venezia toll free at (855) 260-5607; outside the U.S. and Canada, call (646) 522-6243 or by email at christopher.venezia@thomsonreuters.com.

Send all press releases and related information to medicaldevicedaily.newsdesk@medicaldevicedaily.com.

BUSINESS OFFICE

Donald R. Johnston (Senior Director, Current Awareness), Penney Holland (Web Production Manager)

Insulin Pumps

Continued from page 1

Patients do have the option of turning the pump's radio frequency feature off to prevent unauthorized access, Animas said, but that would also block communication between the pump and meter and blood glucose readings would need to be entered manually on the pump.

Another option would be to program the pump to limit the amount of bolus insulin that can be delivered, using one of several customizable settings, such as the maximum bolus amount setting, the two-hour amount, and the total daily dose setting. If a hacker attempted to exceed or override these settings, Animas said, the attack would trigger a pump alarm and prevent bolus insulin delivery.

The company also recommended patients use the system's vibrating alert feature so that if a bolus dose of insulin is initiated remotely they would have the option of canceling the delivery.

Both of these safety measures – the bolus delivery alert and the customizable limits – can only be enabled on the pump itself, Animas said, and cannot be altered by the meter remotely. The system is also designed to record any insulin delivery and its source (pump or meter remote) for the patient to review.

Animas assured patients in the letter that it has worked with regulatory authorities and security experts to address the issue and that the Onetouch Ping system continues to be safe and effective for managing diabetes. Still, the warning comes at a time when the device industry is particularly vulnerable to cybersecurity concerns.

Last month St. Jude Medical Inc. filed a lawsuit against short-selling firm Muddy Waters Capital LLC, Medsec Holdings Ltd., and their affiliates over a report claiming St. Jude's implantable heart devices were vulnerable to cyberattack. The St. Paul, Minn.-based company said it filed the suit to hold the firms and individuals accountable for their "false and misleading tactics," and to "set the record straight" about the security of St. Jude devices. Shortly after the claims were made, the company's stock (NYSE; STJ), which had been trading around $82 a share before the Muddy Waters report, dropped about 5 percent. The stock has fluctuated between $79.55 and $80.71 over the past month, and closed Tuesday at $79.82. (See *Medical Device Daily*, Aug. 30 and Sept. 8, 2016.)

Johnson & Johnson's stock (NYSE; JNJ) held steady Tuesday after news of the Animas letter, closing at $118.82, a 0.01 percent increase over the day's opening.

PAST PROBLEMS ABOUND

Cybersecurity issues are not new to the device industry, but it has been a growing concern over the past couple of years. In 2015 the FDA made an unprecedented move by telling hospitals not to use the Symbiq infusion pump from Lake Forest, Ill.-based Hospira Inc., now owned by Pfizer Inc., because of specific cybersecurity vulnerabilities associated with the device. The company later issued guidance on the topic to clarify how existing quality regulations apply to cybersecurity maintenance activities. The topic has also gained attention at industry events over the past year, including the annual meeting of the Advanced Medical Technology Association (Advamed). (See *Medical Device Daily*, Oct. 7, 2015.)

At a heavily-attended Advamed panel last year, Scott Rea, vice president of government and education relations at Digicert Inc., said device companies would be better off putting a plan in place for when a cybersecurity issue does happen, rather than focusing all the attention on preventing an attack. There is "no such thing" as a perfect solution that will solve all the industry's cybersecurity problems, Rea said.

It may be difficult to understand the motivation behind a cyberattack on an individual infusion pump, or other device, but cybersecurity firm Trapx suggested in a 2015 report that hackers may be trying to hijack medical data, which has become more valuable to cybercriminals than stolen credit card numbers. (See *Medical Device Daily*, June 10, 2015.)

Medtronic plc dealt with a similar issue with one of its infusion pumps back in 2011 after security software manufacturer Mcafee alerted the company to a flaw in some models of the Paradigm insulin pumps. Mcafee said at the time that such problems could exist with other drug pumps as well, given the devices' increasing use of wireless technology and software. //

Cybersecurity

Continued from page 1

The FDA said that cybersecurity and technological advances have led to increased vigilance from all in the medical industry, and an increasing need for the government to work closely with the private sector to get products to market.

This summer saw two medical device companies – Cyberdyne Inc. of Japan and St. Paul, Minn.-based St. Jude Medical Inc. – criticized by short sellers. In both cases, the crux of the criticism was related to technology.

St. Jude was brought into the firing line by Muddy Waters Research LLC, which accused the company of failing to make sure its technology was secure. At least three other companies in the short-selling sphere said Cyberdyne's future promises of a technological revolution were based on hype and little else.

Both incidents raise questions. With the pace of technological change accelerating, are our current regulatory systems adequate? And do we know that those systems said to be coming to market will be as safe, reliable or effective as the companies releasing them would have us believe?

Muddy Waters, a research firm that takes pride in finding overvalued companies, said in August that St. Jude device users were vulnerable to potentially fatal cyberattacks. Soon after, St. Jude sued the research company, claiming it had misled the public to profit from short selling. Security company Medsec, which partnered with Muddy Waters to profit from the release of the information, was also mentioned in the lawsuit. Other cybersecurity firms have since questioned the Medsec results.

An FDA representative acknowledged that cybersecurity risks are becoming more common as technology advances.

"Addressing cybersecurity and public health takes input and effort from many stakeholders — the FDA cannot do this alone," Angela Stark, a public affairs specialist at the FDA, told *Medical Device Daily*. She added that manufacturers, health care professionals, hospitals and security experts are all working together to ensure safety.

Critics, however, question whether the FDA is doing enough. A group called the Clinical Decision Support (CDS) Coalition points to the fact that after five years of attempting to get together a guidance document on the types of clinical decision support software that will be regulated, results are yet to be seen.

Bradley Merrill Thompson of Epstein Becker & Green, P.C., in Washington, D.C., who serves as counsel to the CDS Coalition, told *Medical Device Daily* the lack of guidance "suggests that the agency is having a very difficult time developing regulatory policy with regard to fast-moving technology. We are sympathetic to the challenges. It is difficult to write regulatory policy when you don't know exactly what the technology will look like, or even what it will do."

Cyberdyne expressed similar frustrations to *Medical Device Daily* in a July interview.

"It has been a struggle for us to separate ourselves from [other devices] in terms of the categories we are judged under," said CFO Shinji Uga.

The Japanese company's flagship Hybrid Assistive Limb robotic system connects to neurological pathways and helps people, through practice, to regain control of their limbs. However, it is considered a standard robotic device, which has led to delays in market release.

Three short-selling companies – Well Investment Research, Citron Research and Oasis Management Co., Ltd. – have all said Cyberdyne is grossly overvalued, citing the lack of FDA regulatory approval for any of its devices as one reason to be bearish on the company's stock.

Cyberdyne said it is making progress in getting products into the U.S. market, while the FDA declined to comment, citing protocol. However, if Cyberdyne is correct, and its systems cannot be categorized under current systems, then that points to a flaw in the current regulatory policy.

"Medical devices have always been evolving and by their inherent nature are subject to technological advances," said Stark. "All medical devices the FDA regulates have gone through technological changes. Our regulations account for that and our approach accounts for that."

Thompson disagrees. "The FDA's existing approach is based on the premise that new is risky," he said. "That's a problem. Because right now companies are coming up with plenty of technology that is new, but which a reasonable person would conclude is not risky."

He suggested replacing the top-down approach to rules with one that gives manufacturers more power to regulate themselves on a constant basis.

"We are not proposing that the FDA hire more experts or do anything else that would be expensive. Instead, we are recommending a new framework where manufacturers take the responsibility to use the unique capabilities of software to collect and analyze information, to in effect create a better safety net to identify problems with new software products and to continuously improve such software." **//**

St. Jude

Continued from page 1

access to the new therapy. Those who previously were implanted with upgradeable Protégé and Proclaim SCS systems soon will have the option to upgrade their systems to deliver Burstdr stimulation without additional surgery.

Although the approval came as expected in the second half of the year, analysts were surprised that the FDA granted a superiority claim, as it did with Nevro Corp.'s Senza system delivering HF10 therapy.

"Burstdr, which already is available in international markets has helped STJ take share in recent quarters outside the U.S. and we expect Burstdr to have meaningful adoption in the U.S. based on our physician checks," wrote Larry Biegelsen, senior analyst at Wells Fargo Securities.

He added that Burstdr should take from the 88 percent tonic portion of the market, affecting Medtronic and Boston Scientific.

In a presentation at the North American Neuromodulation Society (NANS) meeting last December, Timothy Deer, president and CEO of The Center for Pain Relief in Charleston, W. Va., compared tonic versus burst stimulation, saying the former is a "monotonous, chronic pacing mode." Meanwhile, burst stimulation may have an effect because of its ability to modulate the lateral and medial pathways.

Unlike other designs, Burstdr stimulation uses intermittent burst pulses intended to mimic the body's natural nerve impulse patterns. St. Jude said that Burstdr stimulation is the only approved form of burst stimulation to be evaluated in a large-scale, multicenter randomized controlled trial.

Chronic pain affects about 1.5 billion people worldwide, St. Jude said. While tonic SCS therapy has offered many patients pain relief, about 20 percent to 30 percent fail to respond to the therapy.

Prof. Dirk De Ridder, from the University of Otago in Dunedin, New Zealand, who developed Burstdr stimulation, said he initially set out to offer patients a new option. "I am very excited that patients across the United States will now have access to Burstdr stimulation, which has enjoyed strong success across other global markets," he added.

The company reported outcomes from the 100-patient Sunburst study backing the device at NANS, saying that results demonstrated that burst stimulation from St. Jude is superior to traditional tonic SCS in relieving chronic pain. (See *Medical Device Daily*, Dec. 16, 2015.)

Almost 70 percent of the first 85 patients to complete their 24-week visit said they preferred the company's burst stimulation to traditional treatment. More than 90 percent and experienced a great reduction in paresthesia — which is the tingling sensation common during traditional SCS — versus tonic SCS.

At the time, group president Eric Fain said chronic pain represents an underpenetrated market, particularly with the regulatory and congressional scrutiny of oral opioid use. He added that the worldwide SCS market would be about $1.6 billion this year.

When asked during a session about claims by a competitor that it was offering burst technology, company officials demurred. Keith Boettiger, senior vice president and general manager, Chronic Pain Therapies and Movement Disorders, said it seemed "to be more marketing than anything else."

Biegelsen noted that Marlborough, Mass.-based Boston Scientific Corp. offers Multiwave therapy that has its own form of Burst, St. Jude has the data from the multicenter, randomized control trial to back it up.

GOOD QUARTER

St. Paul-Minn.-based St. Jude's neuromodulation portfolio has been a bright spot for the company. Sales reached $140 million, a 20 percent increase on a constant currency basis versus the prior year quarter. The company credited the adoption of Burst technology in international markets, the U.S. launch of the Axium system and the introduction of the Infinity DBS system and direction lead in Europe.

During a call on second quarter results, St. Jude President and CEO Michael Rousseau touted neuromodulation's performance, saying it is above market rates. He added that it marked the seventh consecutive quarter in which the company had taken share. Further, the company expects the area "to remain [a share taker] for the foreseeable future."

In a note discussing quarterly results of Abbott, which is poised to pick up St. Jude by the end of the year, William Blair analysts labeled the neuromodulation business as one of the "particularly compelling assets within St. Jude that can grow in the high single to low double digits over time."

NEVRO HF10

Despite St. Jude's victory, Menlo Park, Calif.-based Nevro seems to have a winner with Senza. The SCS therapy provides electrical pulses delivered by electrodes on leads placed near the spinal cord and connected to a compact generator implanted under the skin.

Specifically, Senza is indicated as an in managing chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with failed back surgery syndrome, intractable low back pain, and leg pain.

Senza got a lot of buzz during July's Spine Intervention Society meeting in New Orleans. William Blair analysts Margaret Kaczor and Scott Schaper said they had expected more discussion of Burst therapy; however, based on feedback, Senza could prove very popular among clinicians.

"Overall, we believe there is significant interest in the treatment of chronic pain through novel waveforms such as HF10 and Burst, new stimulation areas such as DRG, and RF ablation that have all seen solid growth," Kaczor and Schaper wrote. "We expect the innovation to be a positive for the U.S. market," they added. //

OIG

Continued from page 1

that while spending for drug tests rose 19 percent between 2014 and 2015, spending for molecular pathology tests plummeted by 44 percent over the same period.

The gapfill issue has already cropped up into plain view as a test for heart transplant rejection is under a degree of price pressure that clinicians have argued is inappropriate. The Allomap test by Caredx of Brisbane, Calif., received a dose of bad news from several Medicare administrative contractors about their proposed pricing for CPT code 81595, which the company said would further damage its attempts to recoup research and development costs. (See *Medical Device Daily*, Oct. 4, 2016.)

Despite the consternation over the recently completed gapfill process, the OIG reports – one each for the revamp of the CLFS and for recent trends in spending – give at best a lukewarm assessment of CMS's now-suspended efforts to overhaul the methodology for determining rates under the lab fee schedule. Nonetheless, OIG observed that Medicare paid $7 billion for lab tests in 2015, a number that is flat over the prior year (OIG pointed out that its numbers do not include billings for lab tests paid under other Medicare fee schedules, including the physician fee and outpatient fee schedules).

The spending report stated that CMS paid $4.1 billion in claims for the "top 25 lab tests" in 2015, down from $4.2 billion for the top 25 in 2014. OIG said billings for these top 25 tests accounted for nearly 60 percent of the fees paid under the CLFS, and blamed much of the up-tick in drug testing on efforts to monitor drug abuse. However, the agency also stated that medically unnecessary testing could represent a significant portion of that increase. Payments made for testing for opiates was up 20 percent last year, but drug confirmation testing payments skyrocketed by nearly 550 percent in 2015, representing an increase in spending of $63 million.

The 44 percent hit absorbed by molecular testing represented a drop from $466 million in 2014 to $259 million last year, and OIG said this reduction was "largely concentrated in payments for three tests," without elaborating other than to note that payments to testing company Renaissance Rx of New Orleans came to a halt in late 2014 over allegations that the DNA tests performed by Renaissance were medically unnecessary.

CMS announced in June that it would suspend implementation of the new pay rates for lab tests until calendar year 2018 after considerable pushback from industry, but several members of the U.S. House of Representatives also wrote the agency to suggest CMS apply the brakes to the overhaul, given the presumed risk that adherence to the January 2017 deadline might create as many problems as it would solve. Among the issues cited by stakeholders was the type of tests CMS had proposed to include in its definition of advanced lab tests, and the use of a six-month private payer fee reporting period, which some stakeholders argued could fail to capture some of the seasonal variation in the volume of tests ordered. (See *Medical Device Daily*, June 21, 2016.)

The Protecting Access to Medicare Act of 2014, the bill that mandated the overhaul of the lab fee schedule, requires that CMS survey applicable labs for the private-sector fees they receive for a given test, but the OIG report said that CMS has its work cut out for it on several points. One of the issues is whether CMS will be able to ensure the quality of the data it receives from labs, and OIG said the absence of a system for ensuring the quality of those data could lead to overpayment. The report also said CMS has no mechanism by which non-compliant labs would be referred to OIG for enforcement.

In a passage that seems to corroborate the notion that the 2017 implementation deadline was too aggressive, the OIG report made reference to the "limited amount of time" CMS has to deal with data quality issues. Another potential source of drag is the fact that CMS will have to draft and finalize sub-regulatory guidances that will deal with the question of whether a test qualifies as an advanced lab test. The OIG also mentioned several conditions that it said call for ongoing monitoring of the rates paid by Medicare, including regional variations in fees that could raise rates in areas where payment is less than a national figure that would be paid under the overhauled lab fee schedule.

Alan Mertz, president of the American Clinical Laboratory Association (ACLA), told *Medical Device Daily* that the association "has advocated for a system that bases Medicare reimbursement on the broad scope of the laboratory market, encourages innovation, and protects access to laboratory services for Medicare patients" since Congress began examining the idea of reforming the CLFS.

Mertz confirmed that many labs will not be required to report data, which in some instances has been seen as problematic, and that CMS has little time to deal with the issue of whether a test qualifies as an advanced diagnostic test. Nonetheless, he said ACLA "takes exception to the suggestion by the OIG that 'ongoing monitoring' may be necessary in cases where payment rates increase," stating that Congress's intent with the language of PAMA was that Medicare reimbursement for laboratory testing services "are to reflect true market rates." //

Owlstone

Continued from page 1

branch of the company is already well along in parallel clinical trials for detecting lung and colorectal cancer and in October 2016, announced a CE mark for pediatric asthma patients.

All of which is based upon a novel, non-invasive diagnostic tool that no other medical device company is close to developing based on a technology that few have even heard about. Unless you are with the U.S. Department of Defense that has advanced some $25 million in funding for Owlstone products that include an explosives detector, a battlefield chemical detector or the upcoming next-generation handheld chemical detector that will be embedded into a smartphone.

The parent company has also raised $28 million in financing for an ever-expanding line of products based on the Field Asymmetric Ion Mobility Spectrometer (FAIMS) sensor platform that was spun out of Cambridge University in 2004.

Owlstone Medical was created to bring the same technology into a medical device that has taken the form of the CE marked Respiration Collector for In Vitro Analysis (ReCIVA), an oxygen mask hooked to a device for capturing volatile organic compounds (VOCs) that was designed as an open-source program with dozens of academic institutions.

Both an adult and a pediatric version of ReCIVA are currently being used in the £2.5 million (US$3.2 million) East Midlands Breathomics Pathology Node project, funded by the U.K.'s National Health Service (NHS) with the goal of testing this breath-based system for molecular pathology of disease in order to clinically validate breathomics as a new diagnostic modality.

In February 2016, Owlstone won a £1 million (US$1.4 million) NHS contract for Stratification of Asthma Treatment by Breath Analysis (STRATA) to adapt the breathalyzer technology for precision medicine and companion diagnostic for asthma drugs.

The validity of this modality is also being tested in the Lung Cancer Indicator Detection (LuCID) clinical trial that successfully passed a first phase and, in September 2016, was extended to include up to 3,000 patients at a high risk for lung cancer across 21 international sites.

And the Owlstone technology is also being used to sniff out the signature of compounds linked to colorectal cancer from urine samples in the Intercept project, building on the publication of results showing a sensitivity of 88 percent.

Meanwhile, the Rochester, Minn.-based Mayo Clinic is running a high-throughput trial analyzing fecal effluent to determine the efficacy of bowel preparation ahead of colonoscopies using the FAIMS technology, which Owlstone estimates to be a $2 billion opportunity in the U.S.

Owlstone Medical formally intends to become the global leader in non-invasive diagnostics for cancer, infectious disease and inflammatory disease. It estimates the global potential in colorectal cancer alone to be $12 billion.

AKIN TO A BLOOD TEST

There is an unmet medical need in the U.S. for early detection of lung cancer in a high-risk population of nine million people that Owlstone estimated could be screened by simply breathing for several minutes into a plastic face mask, creating a $3 billion annual opportunity.

"Every time you breathe out there are about a thousand chemicals on your breath, and some of these are specific markers for everything from cancer to infectious and inflammatory disease," CEO Boyle told *Medical Device Daily*.

Lungs exchange chemicals between blood and the air, he explained, and as blood circulates completely through the body every minute, capturing VOCs from a person's breathing over several minutes "is like performing a massive blood test."

"We built a microchip technology that is able to pick out these markers and a platform that can report out the analysis so that we can sample these chemicals in a completely non-invasive way that is comfortable for patients, as easy as going to a GP surgery [general practitioner's office]," he said.

Tumors have a distinctly altered metabolism shedding unique metabolites that breath analysis can pick out sooner, at an earlier stage, than technologies for liquid biopsy where blood or urine samples as analyzed as a non-invasive screening alternative to CT for lung cancer and colonoscopies for colorectal cancer, Boyle explained. (*Medical Device Daily*, Apr. 14 and June 29, 2016.)

The VOCs are trapped, concentrated and stored in metal tubes loaded with an absorbent material, and then shipped to Owlstone for analysis.

He said Owlstone prefers metal over plastic for shipping as "plastics are super smelly. If we are looking for tiny concentrations of chemicals in breath, the sample container needs to be super clean," he said.

Centralizing analysis in Cambridge may be fine for 3,000 patients in a clinical trial, but what happens with 300,000 or even three million breath tests?

"This is one of the more straight-forward bits of our future journey," said Boyle, noting that the Owlstone Lonestar platform for anaylsis has already been installed at the Mayo Clinic and that other such placements are possible.

He said work in breath analysis has advanced over many years with hundreds of publications identifying chemical markers for various disease conditions.

See Owlstone, page 8

PRODUCT BRIEFS

Carecentrix Inc., of Hartford, Conn., reported the launch of Homebridge, a cloud-based platform that enables patients to heal and age in their homes, and avoid unnecessary hospitalizations and readmissions. Built on Salesforce Health Cloud, Homebridge connects patients to the providers and care they need on their paths home. Carecentrix developed Homebridge to provide a complete view of a patient's data, track clinical events over time, and collaborate to provide exceptional care.

Ekso Bionics Holdings Inc.,of Richmond, Calif., said it has shipped the first device incorporating Smartassist, its next generation gait therapy software, allowing the company to expand the range of patients who can participate in robotic therapy. The Smartassist technology, which is currently available for Ekso Gt devices in Europe, offers new options to therapists for customizing training in gait and balance.

Personal Genome Diagnostics Inc., of Baltimore, reported the launch of its Plasmaselect 64 targeted panel for pan-cancer tumor profiling. PlasmaSelect 64 identifies clinically actionable and functionally important sequence mutations and structural alterations across multiple cancer types without the need for invasive biopsies. The assay incorporates proprietary Pgdx technologies and bioinformatics to identify sequence mutations with exceptional accuracy.

Royal Philips N.V., of Amsterdam, the Netherlands, reported the latest version of the Intellivue Guardian software, designed to aid clinicians in the early recognition of subtle signs of patient deterioration in the general care ward. This software can notify caregivers to early signs of potential degradation.

DAILY M&A

Becton, Dickinson and Co. (BD) and **Apax Partners LLP** launched a joint venture – Vyaire Medical – as a standalone respiratory solutions company. The launch of the new company finalizes the sale of 50.1 percent interest in BD's respiratory solutions business to funds advised by Apax, which has been in the works since March. Vyaire Medical will have all business lines within BD's respiratory business – including Ventilation, Respiratory Diagnostics, Vital Signs and Airlife – and all of BD's respiratory solutions facilities will transfer to the new company. Franklin Lakes, N.J.-based BD will retain a 49.9 percent minority interest in Vyaire, which is expected to make more than $800 million in annual revenue. The transaction valued BD's respiratory business at about $500 million. J.P. Morgan Securities LLC was BD's financial advisor on the deal, and Skadden, Arps, Slate, Meagher & Flom was the company's legal advisor. (See *Medical Device Daily*, March 9, 2016.)

Owlstone

Continued from page 7

"The challenge everyone faces is what technology will be used to translate the findings to routine clinical use? This is what we have addressed successfully, a high-performance miniaturized technology deployed in other military and industrial markets that we can bring to bridge the gap between an academic curiosity to a test with real clinical utility and patient benefit," said Boyle.

"When we need to develop a new diagnostic application, it is a matter of developing the classification software for that disease. Everything else stays the same, the hardware always stays the same," he said.

"We are getting a lot of interest from big pharmaceutical companies that want better biomarkers for their drugs because it improve the chance of approval where they have a companion test once the drug is commercialized," he added.

"We have ambitious goals, we want to scale up, we are growing fast," Boyle said. //

ONCOLOGY EXTRA

Keeping you up to date on recent developments in oncology

By Mark McCarty, Regulatory Editor, Shyama Ghosh, IPD Editor, and Anette Breindl, Senior Science Editor

LYN expression a potential target for cervical cancer

Tyrosine kinases fostered by the LYN gene have been known to medical science for nearly three decades, but an article appearing recently in *Oncotarget* suggests that these kinases play a significant role in cervical cancer. Researchers at mainland China's Second Affiliated Hospital of Chongqing Medical University sorted through roughly 3,300 proteins via isobaric tags for relative and absolute quantitation (iTRAQ), which was followed by 2-dimensional liquid chromatography and tandem mass spectrometry, leading to expression of the LYN gene as a target of interest. The abstract stated that immunohistochemistry indicated that LYN expression was "significantly increased in cervical cancer tissues" compared to normal tissues, regardless of whether those normal tissues were adjacent to the cancerous tissue. The authors stated that increased LYN expression was associated with cancer differentiation and disease stage, adding that any silencing of LYN expression "inhibited cell proliferation, migration and invasion," while overexpression increased all three behaviors. The authors said LYN may promote metastasis by means of activation of the IL-6/STAT3 pathway, and they concluded that LYN tyrosine kinase "is an oncogenic gene and can serve as a novel target for cervical cancer research and therapy." The title of the article is, "Tyrosine kinase LYN is an oncotarget in human cervical cancer: A quantitative proteomic based study."

Changing demographics of cervical cancer in the U.S. (1973-2008)

Incidence trends by histology and stage: A retrospective cohort study, evaluating the analysis of 25 years of data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program, confirmed that the overall incidence of invasive cervical cancer has declined, with an estimated annual percent change (EAPC) of -2.3, due to a decreasing incidence of squamous cell carcinoma (SCC) (EAPC, -3.0), while the incidence of adenocarcinoma (ACA) has risen (EAPC, 0.6). From 1973 to 1989, 86.0 percent of patients had squamous histology as compared to 75.8 percent from 1990 to 2008. The odds ratio (OR) of a newly diagnosed cervical cancer patient having ACA is 1.95 times higher in the second time period than in the first.

Age and Race: Overall, the EAPC for age 50 or older was -3.0, and was -1.7 for those below the age of 50. During the first years of the study 47.7 percent of patients were younger than 50 while 55.5 percent were younger than 50 in the second half of the study. The odds of a newly diagnosed cervical cancer patient being less than age 50 years of age were 37 percent higher in the second time period (OR 1.37). Between 1973 and 1989, the mean age of diagnosis was 51.8, while the mean age from 1990 to 2007 was 50.1 years of age.

Stratifying by race showed that the EAPC was -3.8 for black women, -2.1 for white women, and -2.9 for women of other races. The odds of a newly diagnosed cervical cancer patient being Asian or Pacific Islander were 68 percent higher in the second time period (OR 1.68) than in the first.

A woman presenting with cervical cancer in 2008 will have 3.6 times higher odds of having ACA, 2.1 times higher odds of being Asian or Pacific Islander, 1.6 times higher odds of having advanced disease and 1.4 times higher odds of being younger than age 50 compared to a woman who presented in 1973. Declining incidence of cervical cancer indicates great progress in screening and treatment of pre-invasive disease. However, the increasing incidence of ACA is consistent with the observation that there is relatively less success in diagnosing and treating pre-invasive ACA compared to SCC. For more information, see the Incidence and Prevalence Database.

Cancer stem cells need to chew the fat

Relapsed and metastatic cancer, which is currently largely incurable, likely is seeded by cancer stem cells that can survive chemotherapy. Why cancer stem cells can resist most therapies and how they manage to lie dormant for long periods of time before causing relapse is not well understood. Researchers from the National Institutes of Health had previously used genetic interaction screening in drosophila to show that knocking out certain fat metabolism genes could selectively kill normal and tumor stem cells while sparing differentiated cells. In follow-up studies, they have shown that knocking down the Golgi transport protein Arf1 in drosophila killed cancer stem cells, and Arf1 inhibitors killed human cancer stem cell lines. The researchers concluded that "normal or cancer stem cells may rely primarily on lipid reserves for energy, in such a way that blocking lipolysis starves them to death. This finding may lead to new therapies that could help to eliminate CSCs in human cancers." Their findings appeared in the Sept. 28, 2016, online issue of *Nature*.

Iron and nanotech bad combo for cancer cells

Ferumoxytol, an FDA-approved iron oxide nanoparticle, prevented tumor growth and metastasis in preclinical models of several different tumor types. Iron oxide nanoparticles are used to treat anemia, as well as for imaging purposes and as drug carriers. They can be used to image macrophage immune cells because macrophages take up the nanoparticles, and

Continues on next page

Continued from previous page

researchers from Stanford University wanted to understand the effects of the particles on macrophage physiology. Macrophages, like T cells, can have either activating or suppressive effects on the immune response depending on their subtype. The team discovered that iron nanoparticles nudged the macrophages from an inhibitory state into a pro-inflammatory cancer-fighting state. The authors said that "potential clinical applications of ferumoxytol-mediated pro-inflammatory immune responses could entail potentiating the efficacy of other [macrophage]-activating cancer immunotherapies." Their research was published in the Sept. 26, 2016, issue of *Nature Nanotechnology*.

...In many ways

Another study combined cancer, nanotechnology, and iron in a different manner. Researchers have shown that Cornell dots or C-dots, ultrasmall nanoparticles, could induce an iron-dependent form of programmed cell death known as ferroptosis in starved cancer cells and tumor-bearing animals when they were attached to melanoma-targeting peptides. Ferroptosis is a recently discovered cell death mechanism that is mediated through iron and lipid reactive free radicals. Ferroptosis is initiated by cell starvation, and a team from Memorial Sloan-Kettering Cancer Center showed that combining starvation and high-dose treatment with C-dots synergized to kill cells in mice with subcutaneous melanoma. The team acknowledged that "the concentration of nanoparticles used here to either induce in vitro cell death or inhibit in vivo tumor growth is at least four orders of magnitude higher than what is used currently in human subjects for single-dose imaging-based studies," but argued that "local concentrations could be driven to much higher levels at tumor sites as part of a multidosing strategy, combinatorial treatment regimen and/or by direct catheter infusion at the target site." Their research appeared in the Sept. 26, 2016, issue of *Nature Nanotechnology*.

Tumor suppressor for lymphoma

Chimeric antigen receptor (CAR) T cells could be engineered to produce a soluble tumor suppressor, slowing down the growth of germinal center lymphomas. Authors from Memorial Sloan-Kettering Cancer Center and the French University of Rennes investigated the role of HVEM, a gene that is frequently mutated in B cell cancers that arise in germinal centers. They found that HVEM loss promoted tumor formation via several mechanisms, including the creation of a supportive microenvironment. HVEM normally binds to the protein B and T lymphocyte attenuator (BTLA), and when the authors treated mice with CAR T cells engineered to produce and secrete soluble HVEM, the cells had stronger activity against xenografted lymphomas than regular CAR T cells. "Our study illustrates the use of CAR-T cells as "micro-pharmacies" able to deliver an anti-cancer protein," the authors concluded. Their work appeared in the Sept. 29, 2016, online issue of *Cell*.

Combo imaging and response to chemo

Payers want to know whether a treatment will work, and an article in the *Journal of Nuclear Medicine* suggests that the combination of CT and PET imaging with fludeoxyglucose can tell a clinician whether to proceed with induction chemotherapy for patients with stage III-IVa locally advanced head and neck squamous cell carcinoma (HNSCC). The researchers prospectively evaluated 20 patients via 18F-FDG-PET/CT and diffusion-weighted MRI (DW-MRI) prior to and two weeks after each cycle of induction chemotherapy. Treatment response was evaluated at three months after completion of therapy via with clinical examination, MRI and 18F-FDG-PET/CT. The authors say they saw no significant changes in metabolic tumor volume from baseline between the first and second rounds of chemotherapy among responders, and that most of the biological response to chemotherapy had occurred before the second round of treatment. Thus, the authors stated, the responses seen in the imaging procedures demonstrate that metabolic tumor volume and total lesion glycolysis are "early predictive biomarkers for ultimate response to subsequent chemoradiotherapy," which gives the clinician and patient a chance to consider alternative strategies to the standard chemotherapy dosing regime.

Xofigo wins again at NICE

The U.K.'s National Institute of Health and Care Excellence published a newly updated guidance for radium-223 dichloride, otherwise known as Xofigo, which the agency previously said is indicated for men whose prostate cancer is refractory to hormone-based therapies. The update includes men for whom treatment with docetaxel "is contraindicated or is otherwise not suitable," language that did not appear in the previous update. The agency had passed on Xofigo treatment for this population in 2014, but offered a limited recommendation the following year, pointing to men with symptomatic bone metastates, but no metastases to the viscera. NICE had initially rejected the drug because of a projected quality-adjusted life year cost of £57,000, but limiting the coverage to men who are refractory to docetaxel seems to have addressed the relative cost problem for the agency.